DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

November 2007

1) **CONVENING**
2) **ATTENDANCE**
3) **REVIEW MINUTES OF LAST MEETING**
4) **ITEMS FOR INFORMATION**
5) **REVIEW OF RECENTLY APPROVED AGENTS**

A. Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF) – The Pharmacy and Therapeutics (P&T) Committee was briefed on one new drug which was approved by the Food and Drug Administration (FDA) (see Appendix B). The Department of Defense (DoD) P&T Committee determined that this new drug fell into a drug class that has not yet been reviewed for UF status; therefore, UF consideration was deferred until the drug class review is completed. The P&T Committee discussed the need for a quantity limit (QL) for formoterol fumarate inhalation solution, based on existing QLs for other oral inhalation products and recommendations for use in product labeling. (See paragraph 5A on page 22 and Appendix B on page 73 of the P&T Committee minutes).

COMMITTEE ACTION: QL – The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend a QL for formoterol fumarate inhalation solution of 60 unit dose vials per 30 days, 180 unit dose vials per 90 days.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. Renin Angiotensin Antihypertensive (RAA) – Valsartan/Amlodipine (Exforge)

Background – Exforge is a fixed dose combination product containing valsartan (Diovan) with amlodipine (Norvasc, generics). It is the first combination product containing an ARB with a dihydropyridine (DHP) calcium channel blocker (CCB). Valsartan/amlodipine is solely indicated for treating hypertension.

Treatment with valsartan/amlodipine has been shown in two randomized trials to produce additive blood pressure (BP) lowering and superior BP control compared to placebo and the individual components administered alone. Valsartan/amlodipine showed similar BP lowering as the fixed dose combination of lisinopril/hydrochlorothiazide (HCTZ) in one trial.

The adverse event profile of valsartan/amlodipine reflects that of the individual angiotensin receptor blocker (ARB) and DHP CCB components. In clinical trials, the

incidence of peripheral edema with valsartan/amlodipine is less than that seen when amlodipine is administered alone.

Studies evaluating the effect of valsartan/amlodipine in terms of patient convenience have not been conducted. Potential benefits of fixed dose combination drugs include reduced tablet burdens, simplified medication regimens, and improved adherence.

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that, while valsartan/amlodipine offers a slight convenience to the patient in terms of decreased tablet burden and simplified medication regimen, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other anti-hypertensive agents included on the UF.

Relative Cost Effectiveness Conclusion – The P&T Committee concluded (13 for, 0 opposed, 3 abstained, 1 absent) that valsartan/amlodipine is not cost effective relative to the other agents in the RAA class. The weighted average cost of combined individual agents (UF ARBs and generic amlodipine) is more cost effective relative to Exforge.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 3 abstained, 2 absent) to recommend that valsartan/amlodipine be classified as non-formulary under the UF. (See paragraph 5B, pages 22-24 of the P&T Committee minutes).

   Director, TMA, Decision: ■ Approved □ Disapproved

   Approved, but modified as follows:

2) ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** – Based on the clinical evaluation of valsartan/amlodipine and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for valsartan/amlodipine. (See paragraph 5B, pages 24-25 of the P&T Committee minutes for the criteria).

   Director, TMA, Decision: ■ Approved □ Disapproved

   Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend: 1) an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Network Pharmacy (TRRx) programs, and at military treatment facilities (MTFs) no later than a 60-day implementation period; and 2) TMA letter to be sent to every

beneficiary affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TRICARE Management Activity (TMA). (See paragraph 5B, page 25 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. Attention Deficit Hyperactivity Disorder (ADHD)/Narcolepsy Agent – Lisdexamfetamine dimesylate (Vyvanse)

Background – Lisdexamfetamine is a pro-drug that is hydrolyzed in the gastro-intestinal tract to the stimulant dextroamphetamine and the amino acid l-lysine. It is approved for treating ADHD in children 6 to 12 years of age.

Lisdexamfetamine and a current UF product, mixed amphetamine salts extended release (ER) (Adderall XR), are manufactured by the same company; generic formulations of Adderall XR are anticipated in 2009.

With regard to efficacy, there is insufficient evidence to determine if there are clinically relevant differences between lisdexamfetamine and other ADHD stimulant products. With regard to safety, there is no evidence to suggest that the adverse event profile of lisdexamfetamine differs clinically from other amphetamine formulations, although no comparative trials are available. Up to 33% of patients report appetite suppression.

Lisdexamfetamine was designed to have less potential for abuse, diversion and overdose toxicity than amphetamine, as it requires activation in the gut. Two small manufacturer-sponsored studies in drug abusers reported that the doses of lisdexamfetamine used clinically produced similar "likeability" scores as placebo. However, lisdexamfetamine is a Schedule II controlled substance.

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that lisdexamfetamine does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other ADHD agents included on the UF.

Relative Cost Effectiveness Conclusion – The P&T Committee concluded (14 for, 0 opposed, 1 abstained, 2 absent) that lisdexamfetamine had similar relative cost effectiveness compared to the other UF once daily ADHD stimulants.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of lisdexamfetamine dimesylate and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 1 abstained, 2 absent) to recommend that lisdexamfetamine dimesylate be classified as non-formulary under the UF. This recommendation was primarily based upon the determination that lisdexamfetamine offers no significant, clinically meaningful therapeutic

advantage over other once daily ADHD stimulants. (See paragraph 5C on pages 25-27 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

2) ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation of lisdexamfetamine dimesylate and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for lisdexamfetamine dimesylate. (See paragraph 5C, page 27 of the P&T Committee minutes for the criteria).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend: 1) an effective date of the first Wednesday following a 60-day implementation period in TMOP and TRRx, and at MTFs no later than a 60- day implementation period; and 2) TMA letter to be sent to every beneficiary affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 5C, pages 27-28 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. Contraceptive – Ethinyl estradiol 20 mcg/levonorgestrel 0.09 mg (Lybrel)

Background – Ethinyl estradiol (EE) 20 mcg/levonorgestrel 90 mg is the first FDA-approved contraceptive formulation specifically packaged for continuous use. Active tablets are taken 365 days a year, with the intent of eliminating cyclical bleeding periods.

Conventionally packaged contraceptives are commonly used on a continuous or extended cycle basis. Four conventional contraceptive packs are dispensed every 90 days, and the patient is instructed to discard the unneeded placebo tablets. This practice also provides access to the full array of oral contraceptive products, with varying estrogen levels and types of progestins.

Contraceptives containing 20 mcg of EE with 100 mcg of levonorgestrel are included on the Basic Core Formulary (BCF). The EE 20 mcg/levonorgestrel 0.09 mg product cannot be exactly duplicated by using conventional packages of EE 20 mcg/ levonorgestrel 0.1 mg or its equivalents, due to the 10 mcg difference in the levonorgestrel component; however, this difference in the progestin content is of questionable clinical relevance.

With respect to efficacy, there is no evidence to suggest that EE 20 mcg/ levonorgestrel 0.09 mg would differ from other similar contraceptives containing low-dose estrogen. With respect to safety, as with other continuous regimens, break-through bleeding is common with EE 20 mcg/levonorgestrel 0.09 mg, but decreases over time.

Relative Clinical Effectiveness Conclusion – The Committee voted (15 for, 0 opposed, 0 abstained, 0 absent) that EE 20 mcg/levonorgestrel 0.09 mg did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness or clinical outcome over other oral contraceptives included on the UF.

Relative Cost Effectiveness Conclusion – The Committee voted (13 for, 1 opposed, 0 abstained, 3 absent) that the weighted average cost per day of treatment for EE 20 mcg/levonorgestrel 0.09 mg is significantly higher than other UF monophasic 20 mcg EE agents used on a continuous cycle basis.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of EE 20 mcg/levonorgestrel 0.09 mg and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that Lybrel be designated as non-formulary under the UF. (See paragraph 5D, page 29 of the P&T Committee minutes).

   Director, TMA, Decision: ■ Approved □ Disapproved

   Approved, but modified as follows:

2) ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation of EE 20 mcg/levonorgestrel 0.09 mg and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for Lybrel. (See paragraph 5D, pages 29-30 of the P&T Committee minutes for the criteria).

   Director, TMA, Decision: ■ Approved □ Disapproved

   Approved, but modified as follows:

   COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (12 for, 2 opposed, 1 abstained, 2 absent): 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and no later than a 60-day implementation period at MTFs; and 2) TMA letter to be sent to every beneficiary affected by this UF decision. The implementation period will begin immediately following approval by Director, TMA. (See paragraph 5D, page 30 of the P&T Committee minutes.)

   Director, TMA, Decision: ■ Approved □ Disapproved

   Approved, but modified as follows:

6) DRUG CLASS REVIEW – ADRENERGIC BETA-BLOCKING AGENTS (ABAs)

The P&T Committee evaluated the relative clinical effectiveness of the 22 ABAs marketed in the US (see Table 1). The ABA drug class was subdivided into three categories: ABAs evaluated (but not necessarily FDA-approved) for treating chronic heart failure (HF); ABAs not evaluated for HF (older ABAs used primarily for hypertension); and ABA/diuretic combinations (one combination product, timolol/ hydrochlorothiazide (HCTZ), has now been discontinued). The current BCF ABAs are metoprolol tartrate and atenolol.

The ABAs are all available in generic formulations, with the exception of carvedilol ER (Coreg CR), which was introduced to the market in March 2007. Generic formulations of carvedilol immediate release (IR) and metoprolol succinate ER were launched in mid- to late-2007.

Expenditures for the ABAs exceeded $140 million in FY 07, ranking them in the top 15 drug class expenditures for the Military Health System (MHS). In terms of 30-day equivalent prescriptions dispensed in FY 07, atenolol is the highest utilized ABA in the MHS (~225,000/month), followed by branded metoprolol succinate ER, and metoprolol tartrate (~100,000/month). Generic formulations of metoprolol succinate ER have exceeded 50,000 30-day equivalent prescriptions since August 2007. Since market introduction, carvedilol ER has seen a steady increase in utilization, which exceeded 12,000 30-day equivalent prescriptions dispensed in October 2007.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the following clinical effectiveness conclusion:

a) Labetolol was not clinically comparable to carvedilol, despite exhibiting alpha blocking properties, as it has not been evaluated for chronic HF.

b) Sotalol was not clinically comparable to the other ABAs, as it is not FDA-approved for treating chronic HF.

c) For treating hypertension, there is no evidence of clinically relevant differences in efficacy between the ABAs, when titrated to effect.

d) For treating chronic HF, metoprolol succinate ER, carvedilol IR and ER, and bisoprolol have been shown to reduce mortality. Bisoprolol is not FDA-approved for this indication. Based on the available evidence, there is no data to suggest that there are differences in the reduction in mortality between carvedilol, metoprolol succinate ER, or bisoprolol.

e) Clinically relevant differences in the safety and tolerability profile of the ABAs are not apparent. There is insufficient evidence to determine if there are clinically relevant differences in the adverse event profile between carvedilol IR and carvedilol ER.

f) Despite the convenience of once daily dosing of carvedilol ER, there is no compelling clinical evidence to suggest a benefit of carvedilol ER over carvedilol IR.

Relative Cost Effectiveness Conclusion: the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that:

a) All ABAs used primarily to treat hypertension are cost-effective, with atenolol, metoprolol tartrate, and propranolol IR being the most effective.

b) All of the ABAs with clinical evidence for heart failure are effective, with carvedilol IR being the most cost effective agent.

c) Sotalol, sotalol AF, and labetalol are cost-effective.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend the following: that atenolol, atenolol-chlorthalidone, metoprolol tartrate, metoprolol succinate ER, propranolol, propranolol/HCTZ, propranolol ER, timolol, timolol/HCTZ, bisoprolol, bisoprolol/HCTZ, nadolol, nadolol/bendroflumethiazide, acebutolol, betaxolol, penbutolol, carvedilol IR, and carvedilol ER be designated formulary on the UF. (See paragraphs 6A, 6B and 6C on pages 30-36 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that atenolol and metoprolol tartrate be maintained on the BCF, and that generic formulations of metoprolol succinate ER and carvedilol IR be added to the BCF. (See paragraph 6D on pages 36-37 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

7) DRUG CLASS REVIEW – ALPHA BLOCKERS (ABs) FOR BENIGN PROSTATIC HYPERTROPHY (BPH)

The P&T Committee evaluated the relative clinical effectiveness of the ABs used for BPH currently marketed in the US. The BPH ABs comprise the non-uroselective agents terazosin and doxazosin (both available in generic formulations), and the uroselective agents alfuzosin (Uroxatral) and tamsulosin (Flomax). The BPH AB class was first reviewed by the DoD P&T Committee in August 2005.

Relative Clinical Effectiveness Conclusion: The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that:

a) Based on randomized placebo-controlled trials, terazosin, doxazosin, tamsulosin, and alfuzosin were found to produce clinically significant and comparable symptom improvements when compared to placebo.

b) Based on limited head-to-head trials and indirect comparisons between the agents, existing evidence does not support clinically significant differences in efficacy between alfuzosin and tamsulosin.

c) There appear to be few differences in the incidence of adverse effects with alfuzosin and tamsulosin, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated. The most common adverse events are vasodilatory effects.

d) There appear to be major differences in withdrawal rates due to adverse events between non-uroselective and the uroselective agents. Withdrawal rates reported in clinical trials were low overall for alfuzosin and tamsulosin.

e) The package labeling for alfuzosin contains cautions for QT prolongation effects. The effect of tamsulosin on the QT interval has not been studied.

f) Alfuzosin is contraindicated for use with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, and ritonavir. Tamsulosin has potential drug interactions with cimetidine and warfarin.

g) Doxazosin should be used with caution in men with hepatic failure. Alfuzosin is contraindicated in men with moderate to severe hepatic impairment (Child-Pugh categories B and C). Tamsulosin does not require dosage adjustment in men with moderate hepatic dysfunction.

h) Package labeling for all four ABs contains information regarding the potential for IFIS. For patients receiving alfuzosin and tamsulosin consultation with an ophthalmologist is recommended prior to cataract surgery.

i) Terazosin and doxazosin have a low degree of therapeutic interchangeability with alfuzosin and tamsulosin in terms of safety/tolerability due to the higher incidence of discontinuation rates and vasodilatory effects seen with the non-uroselective ABs.

j) Alfuzosin and tamsulosin have a high degree of therapeutic interchangeability; either drug could be expected to meet the needs of the majority of MHS BPH patients requiring an uroselective agent.

k) Review of the clinical literature since 2005 does not add substantial new information or support changes in current clinical practice for the treatment of LUTS in men with BPH, or for safety profiles between the uroselective ABs.

l) Based on clinical issues alone, there are no compelling reasons to classify any of the AB agents as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that:

a) UF scenario, under condition set #1, with alfuzosin as the one uroselective agent on the UF and BCF in conjunction with Step Therapy to be the most cost effective UF scenario considered.

b) UF scenario, under condition set #2, with alfuzosin as the one uroselective agent on the UF and BCF without Step Therapy was the next most cost effective UF scenario considered. However, under this UF scenario, without Step Therapy, the weighted average cost per day of therapy increased by 53% over the most cost effective UF scenario.

c) Any condition set that included tamsulosin on the UF was more costly compared to the baseline (what DoD pays today) weighted average cost per day of therapy.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 2 absent) to recommend that: 1) alfuzosin be maintained as the uroselective formulary AB, and that terazosin and doxazosin be maintained as the non-uroselective formulary ABs; and; and 2) tamsulosin be classified as non-formulary under the UF with a PA requiring a trial of alfuzosin for new patients. (See paragraphs 7A, 7B and 7C on pages 37-43 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: PA CRITERIA – The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that the following PA criteria should apply for tamsulosin. Coverage would be approved if a patient met any of the following criteria (See paragraph 7D on pages 43-44 of the P&T Committee minutes):

1) Automated PA criteria:

   a) The patient has received a prescription for either tamsulosin or alfuzosin at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2) PA criteria if automated criteria are not met:

   a) The patient has tried alfuzosin and had an inadequate response or was unable to tolerate treatment due to adverse effects.

   b) Treatment with alfuzosin is contraindicated.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for tamsulosin and the conditions for establishing medical necessity for a non-formulary

medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) MN criteria for tamsulosin. (See paragraph 7E on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: IMPLEMENTATION PERIOD –The P&T Committee recommended (14 for, 1 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 7F on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: BCF RECOMMENDATION – The P&T Committee considered the BCF status of the AB agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that the current BCF listing for this class be maintained, requiring each MTF to carry terazosin and alfuzosin. (See paragraph 7G on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

8) DRUG CLASS REVIEW – TARGETED IMMUNOMODULATORY BIOLOGICS (TIBs)

The P&T Committee evaluated the relative clinical effectiveness of the targeted immunomodulatory biologics (TIBs) currently marketed in the United States. The TIB class comprises five medications covered as part of the TRICARE pharmacy benefit: adalimumab (Humira), anakinra (Kineret), etanercept (Enbrel), efalizumab (Raptiva), and alefacept (Amevive). Three similar biologic agents are not part of the pharmacy benefit due to their intravenous (IV) route of administration. Abatacept (Orencia), infliximab (Remicade), and rituximab (Rituxan). Like adalimumab and etanercept, infliximab is approved for multiple indications and in many respects directly competes with these two self-administered multiple indication agents. The IV agents were included in the review for comparative purposes only.

Since the FDA lacks regulatory authority to approve generic versions of biologic medications, generic formulations for the TIBs are not likely to appear in the near future. The TIB class accounted for approximately $136 million dollars in MHS expenditures in

FY 2007, primarily at the retail point of service (66%), followed by MTFs (19%) and mail order (15%). This estimate does not accurately represent utilization of the IV agents (e.g., infliximab), since these medications are commonly administered in clinic or office settings and are included on outpatient pharmacy profiles only in MTFs that choose to maintain such a record. The cost of treatment with these agents is high (on the order of $10,000 to $20,000 annually). There were approximately 11,500 unique TIB utilizers in the MHS in the most recent quarter (June to August 2007), not including patients receiving IV agents.

The majority of use of TIBs in DoD is for the two multi-indication agents (adalimumab and etanercept), not including patients receiving IV agents. Fewer than 4% of DoD TIB utilizers are receiving other TIBs. Over the entire patient population, adalimumab and etanercept are consistently used in about a 2:1 ratio, although utilization in the last quarter (June to August 2007) shows increased uptake of adalimumab among new users (new users only: 44% use of adalimumab vs. 54% use of etanercept, 2% other TIBs).

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept that

a) Across all disease states reviewed, all of the TIBs FDA-indicated for a particular condition have sufficient evidence from placebo-controlled randomized controlled trials (RCTs) to demonstrate efficacy. TIBs are typically added to standard therapy in patients with moderate to severe disease. In general, combination treatment of rheumatologic conditions with TIBs plus methotrexate (MTX) offers better efficacy than TIBs or MTX alone. Beneficial effects on quality of life and productivity are associated with improvements in clinical response.

b) There is a lack of direct comparative evidence (head-to-head RCTs) across all disease states. In all disease states except rheumatoid arthritis (RA), trials were too small in number or too heterogeneous to make indirect comparisons based on meta-analysis of placebo-controlled trials feasible. With two exceptions, treatment effect across agents appeared similar.

c) In RA, anakinra appears to be less efficacious than the TNF inhibitors (adalimumab, etanercept, and infliximab) with respect to effects on symptoms (American College of Rheumatology response), based on indirect comparison of data from placebo-controlled trials.

d) In psoriasis, PASI 75 scores for infliximab appeared consistently higher than with other TIBs used for psoriasis (etanercept, alefacept, and efalizumab), although there is insufficient comparative evidence to draw a definitive conclusion. Some evidence suggests diminishing effect with infliximab as continuous use approaches 1 year. PASI 75 response rates for alefacept, efalizumab, and etanercept appear similar in 12- to 24-week trials. An indication for adalimumab for the treatment of plaque psoriasis is under consideration by the FDA; one published trial and additional unpublished data available from the manufacturer support its efficacy for this condition.

e) The multi-indication self-administered TIBs (adalimumab and etanercept) compare favorably to one another. Etanercept did not appear to be efficacious in

Crohn's disease, for which adalimumab is indicated. Adalimumab lacks published evidence in juvenile rheumatoid arthritis (JRA) and has limited published evidence in psoriasis; however, the manufacturer has unpublished data suggesting efficacy in both disease states and both are under consideration by the FDA. For disease states in which both are indicated, there is little evidence to suggest any clinically relevant difference in treatment effect.

f) Alefacept and efalizumab are FDA-indicated only for psoriasis; they appear to compare favorably to etanercept in terms of treatment effect. Their place in therapy relative to etanercept and infliximab (and potentially adalimumab) in the treatment of psoriasis is probably dependent on factors such as intramuscular administration of alefacept, recommended lab monitoring with both agents, and greater familiarity of providers with the TNF inhibitors.

g) Overall, TIBs were well-tolerated during clinical trials; the most common and consistently reported AEs are injection site or infusion reactions (depending on route). Anakinra may cause more injection reactions than adalimumab and etanercept based on the mean crude incidence of injection reactions calculated by Oregon Health & Science University's Drug Effectiveness Review Program reviewers from clinical trials included in that review: 17.5% for adalimumab (95% CI 7.1-27.9); 22.4% for etanercept (95% CI 8.5-36.3); but 67.2% for anakinra (95% CI 38.7-95.7). In addition, anakinra is given once daily, as opposed to weekly or every other week dosing for adalimumab and etanercept.

h) The primary safety concerns with TIBs are related to the potential for increased risk of serious adverse events (e.g., infections, malignancies, autoimmune disorders, etc), most of which are associated with the drugs' effects on the immune system. These effects are rare and cannot be assessed reliably during clinical trials, although the overall incidence of serious adverse events tends to be higher with TIBs compared to placebo, and trends in large RCTs approach statistical significance. There is insufficient evidence to draw conclusions about comparative risk of any of these serious adverse events.

   i) There is fair evidence of an increased risk of serious infections (including tuberculosis) for TIBs compared to placebo.

   ii) Observational evidence indicates a higher risk of lymphoma for patients treated with infliximab or etanercept. Results of studies addressing other malignancies are mixed.

   iii) Evidence concerning the safety of TIBs in patients with chronic HF and the effects of TIBs on the development of chronic HF is mixed. Data from etanercept and infliximab RCTs evaluating these TIBs for the treatment of chronic HF suggested higher rates of mortality compared to placebo. However, observational studies have reported lower rates of cardiovascular events in RA patients on TNF inhibitors compared to those on conventional therapy.

   iv) All TNF inhibitors appear to cause the development of autoantibodies to some extent. Cases of drug-induced lupus, lupus-like syndromes and other

autoimmune disorders have been reported with etanercept, adalimumab, and infliximab.

v) Adalimumab, etanercept, and infliximab may be associated with demyelination. Hepatotoxicity has been reported with infliximab and alefacept.

vi) Laboratory monitoring is required or recommended for anakinra (neutrophil counts), alefacept (CD4+ T lymphocyte counts), and efalizumab (platelet counts) due to reports of hematologic abnormalities.

i) There is little substantive information concerning potential drug interactions with the TIBs, which are in general considered safe for use with the large number of drugs used concomitantly in clinical trials. Based on two combination trials (one with anakinra plus etanercept and one with abatacept plus etanercept), additive effects on the immune system appear to preclude concomitant treatment with more than one TIB.

j) Overall, TIBs do not appear to have major differences in terms of efficacy or safety/tolerability in specific subsets of patients (e.g., based on age, gender, race, or comorbid conditions), with the exception of a reported higher risk of mortality among chronic HF patients treated with etanercept or infliximab. Potential differences include varying pregnancy categories (B vs. C) across drugs (alefacept, abatacept, and rituximab are Category C); the need for dose reduction of anakinra in patients with impaired renal function; and availability of data in pediatric patients (etanercept for JRA; infliximab for pediatric Crohn's disease).

Relative Cost Effectiveness Conclusion: the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that:

a) For RA, the clinical effectiveness evaluation concluded that anakinra appears to be less effective for the treatment of RA than the multi-indication TIBs. A cost effectiveness analysis comparing the expected cost per year of treatment across all three points of service for etanercept, adalimumab, and anakinra showed that adalimumab was the most cost effective TIB for treatment of RA. Etanercept was more costly than adalimumab with similar effectiveness, while anakinra was both more costly and less effective.

b) For psoriasis, there was insufficient evidence to definitely conclude that treatment effectiveness differed among agents. A cost analysis comparing the expected cost per year of treatment across all three points of service for efalizumab, etanercept, and alefacept showed similar cost effectiveness profiles for all three agents.

c) The UF scenario that placed adalimumab as the sole multi-indication TIB on the UF was the most cost effective scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the TIBs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 2 opposed, 1 abstained, 1 absent) to recommend that adalimumab, alefacept, and efalizumab be maintained as formulary on the UF and that etanercept and anakinra be classified as non-formulary

under the UF. (See paragraphs 8A, 8B, and 8C on pages 45-59 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for etanercept and anakinra. (See paragraph 8D on page 60 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (15 for, 0 opposed, 1abstained, 1 absent): 1) an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision.. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 8E on pages 60-61 of the P&T Committee minutes.)

Director, TMA, Decision: □ Approved □ Disapproved

Approved, but modified as follows: *Approved as 120 days.*

D. COMMITTEE ACTION: PA REQUIREMENTS AND CRITERIA – Currently, PA criteria apply to four of the five TIBs: adalimumab, anakinra, efalizumab, and etanercept. The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) that 1) no changes be made to the PA criteria for etanercept, adalimumab, anakinra, and efalizumab, as outlined in Appendix C; 2) that a PA be required for alefacept under the PA criteria outline above; and 3) that the effective date for the alefacept PA be timed to coincide with that established for the UF decision in this class. (See paragraph 8F on page 61 and Appendix C on page 76 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: QLs – Currently, QLs apply to three of the five TIBs. adalimumab, anakinra, and etanercept. The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) that 1) no changes be made to existing QL/days

supply limits for etanercept, adalimumab, and anakinra. (See paragraph 8G on page 61 and Appendix C on page 74 of the P&T Commit\tee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

F. COMMITTEE ACTION: EXTENDED CORE FORMULARY (ECF) RECOMMENDATION – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend that adalimumab be added to the ECF. (See paragraph 8H on page 62 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

9) BCF STATUS OF ROSIGLITAZONE

The Pharmacoeconomic Center (PEC) updated the P&T Committee on the latest news/ evidence regarding the safety of the thiazolidinediones (TZD), particularly that of rosiglitazone, the DoD's BCF TZD. The P&T Committee discussed the advantages and disadvantages of removing rosiglitazone and rosiglitazone/metformin from the BCF. Ultimately, the P&T Committee determined that there was sufficient clinical evidence to justify removal of rosiglitazone and rosiglitazone/metformin from the BCF. (See paragraph 9 on page 62 of the P&T Committee minutes).

COMMITTEE ACTION: The Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to remove rosiglitazone and rosiglitazone/metformin from the BCF.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

10) BCF / ECF REVIEW

As part of an ongoing plan to systematically review drug classes represented on the BCF, the P&T Committee made recommendations for clarifying BCF listings in two current BCF drug classes, analgesics (meloxicam, cyclobenzaprine, and oxycodone/ acetaminophen) and ADHD and narcolepsy agents (methylphenidate IR).

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) the following changes to BCF / ECF listings. (See paragraph 10 on page 62 of the P&T Committee minutes and Appendix D on page 75):

Drug class or potential drug class	Current BCF/ECF listing	Recommendation	Vote			
			For	Opposed	Abstained	Absent
Analgesics	BCF – Meloxicam (Mobic) oral	Clarify BCF listing to "meloxicam tablets only"	14	0	1	2
	BCF – Cyclobenzaprine (Flexeril) oral; does not include 5 mg strength	Clarify BCF listing to "cyclobenzaprine IR tablets, 5 and 10 mg"	14	0	1	2
	BCF – Oxycodone 5 mg / acetaminophen 325 mg	Clarify BCF listing to "oxycodone 5 mg / acetaminophen 325 mg tablets"	14	0	1	2
ADHD and Narcolepsy Agents	BCF – methylphenidate IR; methylphenidate ER (specific brand is Concerta); mixed amphetamine salts ER (Adderall XR)	Clarify BCF listing to "methylphenidate IR (excludes Methylin oral solution and chewable tablets), methylphenidate ER (specific brand name is Concerta); mixed amphetamine salts ER (Adderall XR)"	14	0	1	2

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

11) STATUS OF AMLODIPINE ON THE UF

On an ongoing basis, the DoD PEC monitors changes in the clinical information, current costs, and utilization trends to evaluate whether the UF status of agents designated as non-formulary needs to be readdressed. At this meeting, the UF status of amlodipine (Norvasc, generics) was re-evaluated due to a significant decrease in cost across all three points of service.

Clinical Effectiveness Conclusion - At the August 2005 P&T Committee meeting, the Committee concluded that, in general, amlodipine had similar clinical effectiveness relative to other DHP CCBs in regards to efficacy, safety, and tolerability.

Cost Effectiveness Conclusion – The Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) that amlodipine was the most cost effectiveness DHP CCB.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the DHP CCB, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that amlodipine be reclassified as generic on the UF. (See paragraph 11A on page 63 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: UF IMPLEMENTATION PERIOD – The P&T Committee recommend immediate implementation upon signing of the November 2007 DoD P&T Committee minutes by the Director, TMA. (See paragraph 11B on page 63 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: BCF REVIEW AND IMPLEMENTATION - The P&T Committee considered the BCF status of the DHP CCB agents. Based on the results of the clinical and economic evaluations presented, the Committee voted (15 for, 0 opposed, 1 abstained and 1 absent) to add amlodipine to the BCF. (See paragraph 11C on page 63 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

12) RE-EVALUATION OF NON-FORMULARY AGENTS

The P&T Committee's process for the re-evaluation of non-formulary agents established at the May 2007 meeting was approved by the Director, TMA on 24 June 2007. For this meeting, the PEC applied the appropriate criteria and defined a list of non-formulary drugs for re-evaluation of UF status (Table 3) for the P&T Committee's consideration. Accordingly, the P&T Committee reviewed a list of non-formulary drug agents identified that were: 1) from drug classes in which UF status was NOT awarded based on condition sets that specified the number of similar agents on the UF (i.e., agents in the same class or subclass); and 2) determined to have similar relative clinical effectiveness (i.e., similar efficacy, safety, and tolerability) compared to similar agents on the UF and not excluded from the UF based on clinical issues alone.

Accordingly, the PEC recommended that the following pre-established criteria be applied to each non-formulary agent for re-evaluation of UF status.

1) The non-formulary agent becomes generically available and:
   a) The generic product is "A-rated" as therapeutically equivalent to the brand name product according to the FDA's classification system
   b) The generic market supply is stable and sufficient to meet DoD MHS supply demands.
2) The non-formulary agent is cost effective relative to similar agents on the UF. A non-formulary agent becomes cost effective when:
   a) The non-formulary agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the UF class to which they were compared.
   b) The non-formulary agent's total weighted average cost based on an alternate measure used during the previous review is less than or equal to that for the UF class to which they were compared. For example, antibiotics may be compared on the cost per course of therapy used to treat a particular condition.

The PEC reminded the DoD P&T Committee that when the pre-established criteria for reclassification are met, the Chairperson of the P&T Committee will call for an electronic vote by the members of the P&T Committee on the matter.

1) Upon a majority vote affirming that the non-formulary drug should be reclassified as generic, that agent will be changed from non-formulary status to formulary status as a generic.

2) Committee members will be briefed on any reclassification of a non-formulary agent at the next meeting of the P&T Committee. This information will be recorded as an information-only item in the meeting minutes. The item will be included in information provided for the BAP's next meeting; however, since the BAP will have already made any comments on the subject, the item will normally not be subject to further BAP comment.

COMMITTEE ACTION: The P&T Committee voted (15 for, 1 against, 0 abstained, 1 absent) to recommend that the following list of non-formulary drug agents be re-evaluated for UF status when pre-established criteria are met. (See paragraph 12 on pages 63-65 of the P&T Committee minutes).

Generic Name	Brand Name	UF Class	Generics Shipping?
EE 30 mcg; 0.15 mg levonorgestrel	Seasonale	BCs (M30)	Y
EE 30/10 mcg; 0.15 mg levonorgestrel	Seasonique	BCs (M20)	N
EE 35 mcg; 0.4 mg norethindrone	Ovcon-35	BCs (M35)	Y
EE 50 mcg; 1 mg norethindrone	Ovcon-50	BCs (M50)	N
EE 20 mcg; 0.1 mg norethindrone	Loestrin 24 FE	BCs (M20)	N
ciclopirox	Loprox	AF-DERMs	Y
econazole	Spectazole	AF-DERMs	Y
moexipril	Univasc	ACEs	Y
quinapril	Accupril	ACEs	Y
amlodipine	Norvasc	CCBs	Y
nicardipine	Cardene	CCBs	Y
nicardipine SR	Cardene SR	CCBs	N
isradipine IR	Dynacirc	CCBs	Y
isradipine CR	Dynacirc CR	CCBs	N
diltiazem ER HS	Cardizem LA	CCBs	N
verapamil ER HS	Verelan	CCBs	N
verapamil ER HS	Covera HS	CCBs	N
bupropion XL	Wellbutrin XL	AD1s	Y (300mg only)
paroxetine CR	Paxil CR	AD1s	N
escitalopram	Lexapro	AD1s	N
verapamil ER / trandolapril	Tarka	Misc HTNs	N
tramadol ER	Ultram ER	Narcotic analgesics	N
timolol maleate	Istalol	EYE-1s	N
timolol hemihydrate	Betimol	EYE-1s	N
tolterodine IR	Detrol IR	OABs	N

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

Appendix A – Implementation Status of UF Recommendations/Decisions
Appendix B – Newly Approved Drugs
Appendix C – Existing Prior Authorization Criteria and Quantity Limits for TIBs
Appendix D - BCF Review
Appendix E – Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

signed 13 Feb 08

S. Ward Casscells, M.D.

Department of Defense
Pharmacy and Therapeutics Committee Minutes
November 2007

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 14-15 Nov 2007 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
LTC Brett Kelly, MSC, USA	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Capt Jeremy King, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Lt Col Charlene Reith, BSC *for* Col Everett McAllister, BSC	Air Force, Pharmacy Officer
CDR Walter Downs, MC *for* LCDR Michelle Perelló, MC	Navy, Internal Medicine Physician
LCDR Ronnie Garcia, MC *for* LCDR Scott Akins, MC	Navy, Pediatrics Physician
CDR David Tanen, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Ted Cieslak, MC	Army, Physician at Large
LTC (P) Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino, RPh.	Department of Veterans Affairs

B. Voting Members Absent

To be determined	Air Force, Internal Medicine Physician

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CDR Kim Lefebvre, MSC	Defense Supply Center Philadelphia
Mr. Howard Altschwager	Deputy General Counsel, TMA
LT Thomas Jenkins, MSC, USN	TMA Aurora

D. Non-Voting Members Absent

Martha Taft	Health Plan Operations, TMA

E. Others Present

CDR Matthew Carlberg, MC, USN	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
LTC Chris Conrad, MC, USA	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
Angela Allerman, Pharm.D.	DoD Pharmacoeconomic Center
Julie Liss, Pharm.D.	DoD Pharmacoeconomic Center
David Meade, Pharm.D.	DoD Pharmacoeconomic Center
Harsha Mistry, Pharm.D.	DoD Pharmacoeconomic Center
Eugene Moore, Pharm.D.	DoD Pharmacoeconomic Center
Shana Trice, Pharm.D.	DoD Pharmacoeconomic Center
Nancy Misel, RPh	Director, Air Force High Dollar Program
LCDR James Ellzy, MC, USN	Prospective DoD P&T Committee Chair
Lt Col Thom Bacon	TMA Pharmaceutical Operations Directorate
CDR Rob Hayes	USPHS/IHS
Melinda Neuhauser	VA PBM

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – August 2007 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. Approval of August Minutes – Dr. Samuel Ward Casscells, III., M.D., approved the minutes of the August 2007 DoD P&T Committee meeting on October 17, 2007.

4. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss, CAPT Blanche and LTC Kelly briefed the members of the P&T Committee regarding the August 2007 BAP meeting. The P&T Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions – The PEC briefed the members of the P&T Committee on the progress of implementation for drug classes reviewed for UF status since February 2005.

5. REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on one new drug which was approved by the FDA (see Appendix B). The P&T Committee determined that this new drug fell into a drug class that has not yet been reviewed for UF status; therefore, UF consideration was deferred until the drug class review is completed. The P&T Committee discussed the need for a quantity limit (QL) for formoterol fumarate inhalation solution (Perforomist), based on existing QLs for other oral inhalation products and recommendations for use in product labeling.

COMMITTEE ACTION: QL – The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1absent) to recommend a QL for formoterol fumarate inhalation solution of 60 unit dose vials per 30 days, 180 unit dose vials per 90 days**.**

B. Renin Angiotensin Antihypertensive (RAA) – Valsartan/Amlodipine (Exforge)

1) Valsartan/Amlodipine Relative Clinical Effectiveness –The proprietary product Exforge contains the combination of valsartan (Diovan) with amlodipine (Norvasc). It is the first fixed-dose combination product containing an angiotensin receptor blocker (ARB) with a dihydropyridine (DHP) calcium channel blocker (CCB). Generic formulations of amlodipine are now commercially available.

The DoD P&T Committee previously reviewed several subclasses of the RAA drug class, including the angiotensin converting enzyme (ACE) inhibitors and ACE/diuretic combinations in August 2005, the ACE/CCB combinations in February 2006, the ARBs and ARB/diuretic combinations in February 2005 and May 2007, and the direct renin inhibitor aliskiren (Tekturna) in August 2007.

Fixed-dose combination RAA agents designated as UF are benazepril/amlodipine (Lotrel, generics), telmisartan/ hydrochlorothiazide (HCTZ) (Micardis HCT), candesartan/HCTZ (Atacand HCT), losartan/HCTZ (Hyzaar), lisinopril/HCTZ (Prinzide, Zestoretic, generics), captopril/HCTZ (Capozide, generics), benazepril/ HCTZ (Lotensin HCT, generics), enalapril/ HCTZ (Vaseretic, generics), and fosinopril/HCTZ (Monopril HCT, generics).

Valsartan/amlodipine is approved for treating hypertension in patients whose blood pressure (BP) is not adequately controlled with an ARB or DHP CCB administered as monotherapy. Although Exforge is not approved for the initial treatment of hypertension, there is no evidence to suggest that it would not be effective when used in that manner clinically.

With regard to efficacy, combining an ARB with a DHP CCB provides two differing mechanisms to reduce BP. Two randomized controlled trials (RCTs) in over 2,000 patients showed superior BP reduction and control with Exforge compared to valsartan and amlodipine administered as monotherapy, and compared to placebo. A trial in 130 patients with Stage 2 hypertension (>160/>100 mm Hg) found similar BP reductions when valsartan/amlodipine was compared to the fixed dose combination of lisinopril/HCTZ.

There are no clinical trials with valsartan/amlodipine that have evaluated clinical outcomes of reducing mortality, stroke, heart failure (HF) hospitalization, or need for renal dialysis/transplantation. However, valsartan and amlodipine individually have shown benefits in these areas, and there is no evidence to suggest that valsartan/amlodipine would not be beneficial here.

With regard to safety, the package labeling for Exforge reflects that of the individual components for adverse events, drug interactions, and black box warnings (e.g., teratogenicity concerns with ARBs). In clinical trials, the incidence of peripheral edema with valsartan/amlodipine was lower than that observed with amlodipine monotherapy.

Although not specifically evaluated in a controlled clinical trial with valsartan/ amlodipine, potential benefits to fixed dose combination drugs include reduced tablet burden, simplified drug regimens, increased patient convenience, and improved adherence to therapy.

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded that, while valsartan/amlodipine offers a slight convenience to the patient in terms of decreased tablet burden and simplified medication regimen, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other antihypertensive agents included on the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusion stated above.

2) Valsartan/Amlodipine Relative Cost Effectiveness – The P&T Committee evaluated the relative cost effectiveness of valsartan/amlodipine in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly the ARBs. Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2).

A cost minimization analysis (CMA) was employed to evaluate the cost effectiveness of valsartan/amlodipine. The cost effectiveness of Exforge was evaluated relative to the following pairings of single ingredient agents (ARB plus amlodipine): telmisartan (the most cost effective UF ARB) plus amlodipine; candesartan (chronic HF indication UF ARB) plus amlodipine; valsartan plus amlodipine (single ingredient agents of Exforge).

The results of the CMA showed that the projected weighted average daily cost of Exforge was significantly higher than the weighted average daily cost of the pairings of UF ARBs with amlodipine.

Cost Effectiveness Conclusion – The P&T Committee concluded that valsartan/ amlodipine is not cost effective relative to the other agents in the RAA class. The weighted average cost of combined individual agents (UF ARBs and generic amlodipine) is more cost effective relative to Exforge.

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 3 abstained, 1 absent) to accept the valsartan/amlodipine relative cost effectiveness analysis as presented by the PEC.

3) *Valsartan/Amlodipine UF Recommendation*

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of valsartan/amlodipine, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 3 abstained, 2 absent) to recommend that Exforge be designated as non-formulary on the UF.

4) *Valsartan/Amlodipine MN Criteria* - Based on the clinical evaluation of valsartan/amlodipine, and the conditions for establishing medical necessity (MN) for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for Exforge:

   1) Use of the formulary alternatives is contraindicated.
   2) The patient has experienced significant adverse effects from formulary alternatives.
   3) The patient previously responded to the non-formulary agent, and changing to the formulary alternatives would incur unacceptable risk.

   The P&T Committee specifically noted circumstances under which criterion #3 might be considered: 1) post-myocardial infarction (MI) patients with previous angioedema or other intolerance to ACE inhibitors who are stabilized on valsartan/amlodipine and in whom changes in therapy to a formulary ARB plus amlodipine might result in destabilization or 2) chronic HF patients who are stabilized on valsartan/ amlodipine and in whom changes in therapy to a formulary ARB plus amlodipine might result in destabilization.

   COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

5) *Valsartan/Amlodipine Implementation Plan* – The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRICARE Retail Pharmacy Network (TRRx), and no later than a 60-day implementation period at military treatment facilities (MTFs). The implementation period will begin immediately following approval by the Director, TMA.

   As part of the implementation plan, the P&T Committee also recommended that the TRICARE Management Activity (TMA) send a letter to beneficiaries affected by this UF decision to inform them about the change in formulary status for valsartan/amlodipine. A retrospective pharmacy claims analysis revealed that

approximately 2,400 DoD beneficiaries have filled a prescription for valsartan/ amlodipine in the previous quarter.

MTFs will not be allowed to have valsartan/amlodipine on their local formularies. MTFs will be able to fill non-formulary requests for this agent only if both of the following conditions are met: 1) the prescription must be written by a MTF provider; MTFs may (but are not required to) fill a prescription for valsartan/amlodipine written by a non-MTF provider to whom the patient was referred, and 2) MN is established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent): 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TMA.

C. Attention Deficit Hyperactivity Disorder/Narcolepsy Agent – Lisdexamfetamine dimesylate (Vyvanse)

1) Lisdexamfetamine Relative Clinical Effectiveness –Lisdexamfetamine (Vyvanse) is a new stimulant drug approved for treating attention deficit/hyperactivity disorder (ADHD) in children 6 to 12 years of age. In contrast to methylphenidate extended release (ER) (Concerta), mixed amphetamine salts ER (Adderall XR), and atomoxetine (Strattera), lisdexamfetamine is not currently indicated for treating adolescents and adults. Vyvanse and Adderall XR are manufactured by the same company; generic formulations of Adderall XR are anticipated in 2009.

The ADHD and narcolepsy drugs were evaluated at the November 2006 DoD P&T Committee meeting. The UF designated ADHD drugs include the non-stimulant atomoxetine, and the stimulants dextroamphetamine (Dexedrine, generics), methamphetamine (Desoxyn), mixed amphetamines salts (Adderall, and generics; Adderall XR), and all oral formulations of methylphenidate (Concerta, all Metadate products, all Methylin products, all Ritalin products, and generics). Methylphenidate transdermal system (Daytrana) and dexmethyl-phenidate (Focalin and Focalin XR) were classified as non-formulary.

With regard to efficacy, there is insufficient evidence to suggest that clinically relevant differences exist between lisdexamfetamine and other ADHD stimulant products. One randomized published trial in 290 children showed significant improvements in ADHD rating scales with lisdexamfetamine compared to placebo. A double-blind, placebo-controlled crossover study available only in abstract form showed significant reductions in observer ratings of ADHD behaviors (e.g., improved ADHD control) with either lisdexamfetamine or mixed amphetamine salts (Adderall XR) in 52 children compared to placebo; outcomes with Vyvanse were not directly compared to Adderall XR.

With regard to safety, there is no evidence to suggest that the adverse event profile of lisdexamfetamine differs clinically from other amphetamine formulations, although no comparative trials are available. Up to 33% of patients

report appetite suppression. The package labeling for lisdexamfetamine carries the same black box warning as the other stimulants for tolerance, dependence, abuse potential and sudden cardiac death in children with pre-existing structural cardiovascular abnormalities. The drug interaction profile is the same as other ADHD stimulants, and lisdexamfetamine should not be used concurrently with monoamine oxidase inhibitors, due to the risk of hypertensive crisis.

With regard to abuse potential, lisdexamfetamine is a Schedule II controlled substance, as are the other ADHD stimulants (e.g., methylphenidate and amphetamines). Lisdexamfetamine is a pro-drug that is hydrolyzed in the gastrointestinal tract to dextroamphetamine and the amino acid l-lysine, and was thus designed to have less potential for abuse, diversion and overdose toxicity than amphetamine. Two unpublished studies reported the preference of lisdexamfetamine in a total of 50 drug abusers. At lisdexamfetamine doses less than 100 mg "likeability" scores on a Drug Rating Questionnaire scale were similar to placebo, while doses exceeding 100 mg showed similar likeability as with dextroamphetamine (the maximum recommended lisdexamfetamine dose currently marketed is 70 mg).

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded that lisdexamfetamine does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other ADHD agents included on the UF.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the clinical effectiveness conclusion stated above.

2) *Lisdexamfetamine Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of lisdexamfetamine in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly the other once-daily ADHD stimulant medications. Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2).

   The ADHD stimulants include methylphenidate immediate release (IR) and ER and various immediate and ER formulations of amphetamines (dextroamphetamine, methamphetamine, mixed salts of amphetamine, and lisdexamfetamine). The comparators for the cost effectiveness analysis of lisdexamfetamine included the UF once daily formulations ADHD stimulants: methylphenidate (Concerta, Metadate CD, Ritalin LA), and mixed salts of amphetamine ER (Adderall XR).

   The relative clinical effectiveness evaluation concluded that there is insufficient evidence of a clinically meaningful difference between once daily stimulants for the treatment of ADHD. As a result, a CMA was employed to determine the cost effectiveness of lisdexamfetamine relative to the UF once daily ADHD stimulants.

   Results from the CMA revealed that the weighted average cost per day of therapy for lisdexamfetamine was similar to the other UF once daily ADHD stimulants.

Cost Effectiveness Conclusion – The P&T Committee concluded that lisdexamfetamine had similar relative cost effectiveness compared to the other UF once daily ADHD stimulants.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to accept the lisdexamfetamine relative cost effectiveness analysis as presented by the PEC.

3) *Lisdexamfetamine UF Recommendation*

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of lisdexamfetamine, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 1 abstained, 2 absent) to recommend that lisdexamfetamine be designated as non-formulary on the UF. This recommendation was primarily based upon the determination that lisdexamfetamine offers no significant, clinically meaningful therapeutic advantage over other once daily ADHD stimulants.

4) *Lisdexamfetamine MN Criteria* – Based on the clinical evaluation of lisdexamfetamine and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for lisdexamfetamine.

   1) Use of the formulary alternatives is contraindicated.
   2) The patient has experienced significant adverse events from formulary alternatives.
   3) Use of formulary alternatives has resulted in therapeutic failure.

   COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

5) *Lisdexamfetamine Implementation Plan* – The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at MTFs no later than a 60-day implementation period.

   As part of the implementation plan, the P&T Committee also recommended that TMA send a letter to beneficiaries affected by this UF decision to inform them about the change in formulary status for lisdexamfetamine. A retrospective pharmacy claims analysis revealed that approximately 2,800 DoD beneficiaries have filled a prescription for lisdexamfetamine in the previous quarter.

   MTFs will not be allowed to have lisdexamfetamine on their local formularies. MTFs will be able to fill non-formulary requests for this agent only if both of the following conditions are met: 1) the prescription must be written by a MTF provider; MTFs may (but are not required to) fill a prescription for lisdexamfetamine written by a non-MTF provider to whom the patient was referred, and 2) MN is established.

   COMMITTEE ACTION*:* The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent): 1) an effective date of the first Wednesday

following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TMA.

D. Contraceptive – Ethinyl estradiol 20 mcg/levonorgestrel 0.09 mg (Lybrel)

1) Lybrel Relative Clinical Effectiveness – The contraceptive drug class was reviewed in May 2006. Lybrel is a new contraceptive marketed in July 2007 that contains 20 mcg of ethinyl estradiol (EE) and 90 mcg of levonorgestrel. It is the first FDA-approved contraceptive formulation specifically packaged for continuous use. Active tablets are taken 365 days a year, with the intent of eliminating cyclical bleeding periods.

Contraceptives containing 20 mcg of EE with 100 mcg of levonorgestrel (Lutera, Levlite or equivalent) are included on the Basic Core Formulary (BCF). The Lybrel product cannot be exactly duplicated by using conventional packages of Lutera or its equivalents, due to the 10 mcg difference in the levonorgestrel component; however this difference in the progestin content is of questionable clinical relevance.

Contraceptives are traditionally available in conventional 28-day packaging containing 21 days of active tablets followed by seven days of placebo tablets, which leads to 13 cycles of withdrawal bleeding yearly. Some recently introduced oral contraceptives reduce the number of placebo tablets to four (Yaz, Loestrin-24 Fe), thus shorting the bleeding period, or extend the number of active tablets to 84, resulting in only four withdrawal bleeding periods per year (e.g., Seasonique, Seasonale). Continuous use of oral contraceptives may be beneficial in women with symptoms related to fluctuations in hormone levels (e.g., endometriosis or menstrual migraines) and in women desiring cessation of cyclical bleeding. Conventionally packaged contraceptives are commonly used on a continuous or extended cycle basis. Four conventional contraceptive packs are dispensed every 90 days, and the patient is instructed to discard the unneeded placebo tablets. This practice also provides access to the full array of oral contraceptive products, with varying estrogen levels and types of progestins.

With respect to efficacy, there is no evidence to suggest that Lybrel would differ from other similar contraceptives. One head-to-head, open-label trial in 641 women that compared Lybrel with a traditional regimen of 20 mcg EE/100 mg levonorgestrel (Lutera, Levlite or equivalents) reported no difference in pregnancy rates after one year (zero vs. three, respectively). A non-comparative trial in over 2,000 women reported 23 pregnancies after one year (a rate of 1.55 per 100 user years), which is similar to pregnancy rates reported with other contraceptives containing 20 mcg EE.

With respect to safety, breakthrough bleeding/spotting is common with all extended-cycle or continuous regimens, particularly in the first few months of use. In the non-comparative trial, 18.6% of women discontinued therapy because of uterine bleeding. However, this decreased over time (48% incidence of breakthrough bleeding at pack 3 vs. 21% at pack 13), and approximately 60% of

women achieved amenorrhea after one year. In the head-to-head trial mentioned previously, the incidence of common adverse effects (dysmenorrhea, nausea, and headache) was similar between Lybrel and the comparator (Lutera, Levlite or equivalents). The safety profile of Lybrel has not been evaluated for longer than two years.

Relative Clinical Effectiveness Conclusion: The Committee concluded that Lybrel did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness or clinical outcome over other oral contraceptives included on the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusion stated above.

2) *Lybrel Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of ethinyl estradiol 20/levonorgestrel 0.09 (Lybrel) in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly other monophasic ethinyl estradiol 20 mcg (M20 EE) contraceptives. Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2).

   The relative clinical effectiveness evaluation concluded that Lybrel does not show compelling clinical superiority over currently available contraceptives on the UF in the M20 EE subclass. As a result, a CMA was employed to determine the cost effectiveness of Lybrel relative to other UF M20 EE agents (Sronyx, Lutera, Levlite-28, Aviane, and Lessina-28) used on a continuous cycle basis.

   The results from the CMA revealed that the weighted average cost per day for treatment for Lybrel is significantly higher than other UF M20 EE agents used on a continuous cycle basis.

   Cost Effectiveness Conclusion. The P&T Committee concluded that Lybrel is not cost effective relative to other UF M20 EE agents used on a continuous cycle basis.

   COMMITTEE ACTION: The P&T Committee voted (14 for, 1 opposed, 1 abstained, 2 absent) to accept the ethinyl estradiol 20/levonorgestrel 0.09 (Lybrel) relative cost effectiveness analysis as presented by the PEC.

3) *Lybrel UF Recommendation*

   COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the M20 EE contraceptive agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that. Lybrel be designated non-formulary on the UF.

4) *Lybrel MN Criteria* – Based on the clinical evaluation of Lybrel, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for Lybrel:

1) The patient has experienced significant adverse effects from formulary alternatives.

2) Use of formulary alternatives has resulted in therapeutic failure.

The P&T Committee commented that these MN criteria could be expected to apply to Lybrel only rarely, given the wide variety of formulary oral contraceptives—including oral contraceptives containing 20 mcg of EE and 100 mcg of levonorgestrel—all of which can be used on a continuous basis by discarding unneeded placebo tablets. Both criteria would likely only apply to patients who have encountered difficulty with the process of discarding unneeded placebo tablets. The P&T Committee did not expect that the difference between 100 and 90 mcg of levonorgestrel was likely to result in any clinically predictable reduction in adverse effects.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

5) *Lybrel Implementation Plan* – The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in TMOP and TRRx, and no longer than a 60-day implementation period at MTFs. The implementation period will begin immediately following approval by the Director, TMA.

As part of the implementation plan, the P&T Committee also recommended that TMA send a letter to beneficiaries affected by this UF decision to inform them about the change in formulary status for Lybrel. A retrospective pharmacy claims analysis revealed that approximately 273 DoD beneficiaries have filled a prescription for Lybrel in the previous quarter.

MTFs will not be allowed to have ethinyl estradiol 20/levonorgestrel 0.09 (Lybrel) on their local formularies. MTFs will be able to fill non-formulary requests for this agent only if both of the following conditions are met: 1) the prescription must be written by a MTF provider; MTFs may (but are not required to) fill a prescription for Lybrel written by a non-MTF provider to whom the patient was referred, and 2) MN is established.

COMMITTEE ACTION*:* The P&T Committee recommended (12 for, 2 opposed, 1 abstained, 2 absent): 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following the approval by the Director, TMA.

6. DRUG CLASS REVIEW – ADRENERGIC BETA-BLOCKING AGENTS (ABAs)

The P&T Committee evaluated the relative clinical effectiveness of the 22 adrenergic beta-blocking agents (ABA) marketed in the US (see Table 1). The ABA drug class was subdivided into three categories; ABAs evaluated (but not necessarily FDA-approved) for treating chronic HF; ABAs not evaluated for HF (older ABAs used primarily for hypertension), and ABA/diuretic combinations (one combination product, timolol/HCTZ

(Timozide) has now been discontinued). The current BCF ABAs are metoprolol tartrate (Lopressor, generics) and atenolol (Tenormin, generics).

The ABAs are all available in generic formulations, with the exception of carvedilol extended/controlled release (Coreg CR), which was introduced to the market in March 2007. Generic formulations of carvedilol IR (Coreg) and metoprolol succinate ER (Toprol XL) were launched in mid- to late-2007.

Table 1 ABAs evaluated by the DoD P&T Committee

Generic	Brand	Generic	Brand
ABAs evaluated for chronic heart failure (but not necessarily FDA-approved)		**Older Adrenergic Blocking Agents not evaluated for chronic heart failure; used primarily for hypertension**	
bisoprolol	Zebeta	acebutolol	Sectral
carvedilol	Coreg CR (controlled release) (GlaxoSmithKline)	atenolol	Tenormin
	Coreg (immediate release)	betaxolol	Kerlone
metoprolol tartrate	Lopressor	labetalol	Trandate (Prometheus) Normodyne (Schering; D/C'd)
metoprolol succinate	Toprol XL (Astra Zeneca)	nadolol	Corgard
ABA/ diuretic combinations		penbutolol	Levatol
atenolol / chlorthalidone	Tenoretic	pindolol	Visken
bisoprolol /HCTZ	Ziac	propranolol	Inderal
metoprolol / HCTZ	Lopressor HCT	propranolol extended release	Inderal LA
nadolol / bendroflumethiazide	Corzide	sotalol	Betapace
propranolol / HCTZ	Inderide	sotalol for atrial fibrillation	Betapace AF
timolol / HCTZ	Timozide (discontinued)	timolol	Blockadren

Expenditures for the ABAs exceeded $140 million in FY 07, ranking them in the top 15 drug class expenditures for the Military Health System (MHS). In terms of 30-day equivalent prescriptions dispensed in FY 07, atenolol (Tenormin, generics) is the highest utilized ABA in the MHS (~225,000/month), followed by branded metoprolol succinate (Toprol XL; ~150,000/month), and metoprolol tartrate (Lopressor, generics; ~100,000/ month). Generic formulations of metoprolol succinate (Toprol XL) have exceeded 50,000 30-day equivalent prescriptions since August 2007. Since market introduction, carvedilol ER (Coreg CR) has seen a steady increase in utilization, which exceeded 12,000 30-day equivalent prescriptions dispensed in October 2007.

A. ABAs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the ABAs marketed in the U.S. by considering information regarding their safety, effectiveness, and clinical outcomes. The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 CFR 199.21(e)(1).

The P&T Committee focused on the clinical effectiveness of the ABAs for treating cardiovascular disorders, in particular chronic HF; non-cardiovascular uses were not

evaluated. Use of the ABAs for hypertension and acute MI was only briefly discussed, since all of the older ABAs are available in generic formulations and have been commercially available for decades. Additionally other antihypertensive drug classes are now available that are widely used (e.g., ACE inhibitors, ARBs, calcium channel blockers).

1) *Pharmacology* - With respect to pharmacology, the ABAs differ in their selectivity for the beta (β) and alpha (α) receptors. ABAs with β1-selectivity include atenolol (Tenormin, generics), metoprolol succinate (Toprol XL, generics), metoprolol tartrate (Lopressor, generics) and bisoprolol (Zebeta). Cardioselectivity is postulated to reduce adverse pulmonary effects, however selectivity is dose dependent. Carvedilol (Coreg IR and generics; Coreg CR) and labetolol (Trandate, generics) are non-selective ABAs that have equal affinity for β1 and β2 receptor, and also exhibit α-blocking properties, which decreases peripheral vascular resistance via vasodilation.

2) *FDA-Approved Indications* – All of the ABAs and the ABA/diuretic combinations are approved for treating hypertension, with the exception of sotalol (Betapace, Betapace AF, generics). Both metoprolol tartrate and metoprolol succinate are approved for angina. With regards to chronic HF, carvedilol (Coreg, Coreg CR) and metoprolol succinate are indicated for use to reduce the risk of death; however, there are slight differences in the package labeling. Both Coreg IR and Coreg CR are approved for use in patients with mild to severe HF and to reduce the risk of death following MI in patients with left ventricular systolic dysfunction (LVSD). Metoprolol succinate is approved for treating patients with mild to moderately severe HF. Bisoprolol (Zebeta) is not approved for treating HF, but has evidence of a mortality benefit from one clinical trial (see efficacy section).

3) *Labetolol* – Labetolol is similar to carvedilol in that it is a non-selective ABA that also exhibits α receptor blocking properties. However the Committee agreed that clinical comparisons to carvedilol (Coreg, Coreg CR) would not be considered, since labetolol has not been evaluated in the treatment of chronic HF. Niche uses for labetolol include intravenous use for hypertensive urgency/emergency, and use for pregnancy.

4) *Sotalol* – Unlike the other ABAs, sotalol is the only ABA that is not approved for treating hypertension. Two branded formulations are available; Betapace is FDA-approved for treating ventricular arrhythmias, while Betapace AF is specifically labeled for use in maintaining normal sinus rhythm (NSR) in atrial fibrillation and contains instructions for initiating therapy. The Committee did not further evaluate sotalol, as both Betapace and Betapace AF are available in generic formulations.

5) *Carvedilol ER* – The Committee evaluated the pharmacokinetic and pharmacodynamic differences between carvedilol ER and carvedilol IR. Coreg CR is a capsule containing beads with differing release mechanisms. The Committee agreed that with the exception of the time to max concentration (which is delayed with carvedilol extended release), Coreg CR and carvedilol IR show similar kinetic profiles.

6) *Efficacy for hypertension* – The Oregon Health & Science University's Drug Effectiveness Review Program (DERP) first reviewed the beta blockers in 2005, with an update published in 2007. DERP concluded that the ABAs are equally effective at controlling BP in patients with hypertension. No ABA has been shown to be more efficacious than another, either as initial therapy or when added on to a diuretic, ACE inhibitor or ARB.

7) *Efficacy for chronic HF* – The P&T Committee focused on the use of metoprolol succinate, metoprolol tartrate, carvedilol (Coreg, Coreg CR) and bisoprolol for chronic HF. Both formulations of carvedilol are FDA-approved for HF, but the Coreg CR indication was granted solely based on data from carvedilol IR clinical trials.

   a) *Placebo controlled trials* – Placebo controlled trials conducted with bisoprolol (CIBIS-II, metoprolol succinate (MERIT-HF), and carvedilol IR (US Carvedilol Trial) showed reductions in mortality of approximately 30%. Treatment with carvedilol IR showed a 35% reduction in mortality in patients with severe HF (left ventricular ejection fraction <20%) in the COPERNICUS trial. The CAPRICORN trial supported the use of carvedilol IR as it reduced the risk of death by 23% in post-MI patients with LVSD. FDA-approval for carvedilol ER was based on the clinical trial data with carvedilol IR; Coreg CR has not been evaluated in a clinical trial for HF.

   b) *Head-to-head trials* – Clinical outcomes were evaluated with carvedilol IR vs. metoprolol tartrate in the COMET trial, which enrolled over 3,000 patients with mild to moderate HF. After 58 months, treatment with carvedilol resulted in a significant 17% reduction in mortality and a significant 29% reduction in fatal and non-fatal MI. The superiority of carvedilol over metoprolol tartrate seen in this trial has generated controversy, due to concerns of potential non-equivalent dosage comparisons. Metoprolol succinate was not available to the COMET investigators, and has not been evaluated directly with carvedilol.

   c) *National Guidelines* – The 2005 American College of Cardiology/American Heart Association guidelines specifically mention that three ABAs, metoprolol succinate, carvedilol (Coreg, Coreg CR), and bisoprolol, have shown a benefit in reducing mortality in patient with chronic HF. Patients with Stage C HF should receive one of these three ABAs.

8) *Safety and tolerability* - With respect to safety and tolerability, the adverse event profile of the ABAs is well known, and generally recognized as a class effect. In a retrospective study conducted in 268 patients enrolled in a HF clinic, no difference was seen in the percentage of patients started on either carvedilol IR or metoprolol succinate who were switched to the other drug due to tolerability problems with dizziness, fatigue, or dyspnea.

   With respect to safety differences between carvedilol IR and carvedilol ER, conflicting results have been seen. In one comparative trial in patients with hypertension, the overall incidence of adverse events was lower with carvedilol ER than carvedilol IR. However a higher incidence of adverse events with

carvedilol ER was seen at the 80 mg dose vs. 25 mg carvedilol IR in patients with HF.

9) *Other Factors* – Differences in adherence between carvedilol IR and carvedilol ER were evaluated by the P&T Committee. Carvedilol IR requires twice daily (BID) dosing, while carvedilol ER is dosed once daily (QD), which theoretically should improve patient adherence. Systematic reviews conduced with several drug classes other than the ABAs report adherence rates of 79% +/- 14% with QD dosing, vs. 69% +/- 15% with BID dosing. Whether this increase in adherence translates into improved outcomes for the ABAs used for chronic HF remains unclear.

   One manufacturer-sponsored study evaluating differences in compliance rates between carvedilol ER and carvedilol IR found no difference between the two drugs in 269 patients with HF after 5 months of therapy (Coreg CR: 89.3% +/- 20.8 vs. Coreg: 88.1% +/- 24.1%). The clinical applicability of these results is difficult to determine, due to the open-label design of the Coreg CR arm, and the supervised setting of a HF clinic.

10) *Clinical Coverage* – In order to meet the needs of the majority of patients in DoD, the P&T Committee agreed that an ABA with evidence of a mortality benefit in chronic HF must be included on the BCF. The DoD P&T Committee also agreed that an ABA/diuretic combination need not be included on the BCF.

11) *Therapeutic Interchangeability* – With respect to treating hypertension, the ABAs have a high degree of therapeutic interchangeability. With respect to treating chronic HF, there is a high degree of therapeutic interchangeability between carvedilol, metoprolol succinate, and bisoprolol, which have been shown to reduce mortality.

12) *ABA overall clinical effectiveness conclusion* - The DoD P&T Committee concluded that:

   a) Labetolol was not clinically comparable to carvedilol (Coreg; Coreg CR) despite exhibiting alpha blocking properties, as it has not been evaluated for chronic HF.

   b) Sotalol (Betapace, Betapace AF) was not clinically comparable to the other ABAs, as it is not FDA-approved for treating chronic HF.

   c) For treating hypertension, there is no evidence of clinically relevant differences in efficacy between the ABAs, when titrated to effect.

   d) For treating chronic HF, metoprolol succinate, carvedilol (Coreg, Coreg CR), and bisoprolol have been shown to reduce mortality. Bisoprolol is not FDA-approved for this indication. Based on the available evidence, there is no data to suggest that there are differences in the reduction in mortality between carvedilol, metoprolol succinate, or bisoprolol.

   e) Clinically relevant differences in the safety and tolerability profile of the ABAs are not apparent. There is insufficient evidence to determine if there

are clinically relevant differences in the adverse event profile between carvedilol IR and carvedilol extended release.

f) Despite the convenience of once daily dosing of carvedilol ER, there is no compelling clinical evidence to suggest a benefit of Coreg CR over carvedilol IR.

g) Based on clinical issues alone, there are no compelling reasons to classify any of the ARBs as non-formulary on the UF.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the conclusions stated above.

B. ABAs – Relative Cost Effectiveness - The P&T Committee evaluated the relative cost effectiveness of the ABAs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

For the economic evaluation, the ABAs were functionally divided into three groups, based on predominant use: 1) ABAs for hypertension, 2) ABAs for chronic HF, and 3) ABAs used for other conditions (e.g., severe hypertension; arrhythmias).

The ABAs for hypertension include acebutolol, atenolol, betaxolol, metoprolol tartrate, nadolol, penbutolol, pindolol, propranolol IR and ER, timolol, and their diuretic combinations of atenolol chlorthalidone, bisoprolol/HCTZ, metoprolol tartrate/HCTZ, nadolol/bendroflumethiazide, propranolol/HCTZ, and timolol/HCTZ (which has now been discontinued).

The ABAs for heart failure include bisoprolol, metoprolol succinate, carvedilol IR, and carvedilol ER.

Lastly, the ABA group for other conditions includes sotalol (Betapace, Betapace AF) for ventricular arrhythmias and maintenance of normal science rhythm in patients with atrial fibrillation/flutter and labetolol for hypertension and severe hypertension.

The relative clinical effectiveness evaluation concluded that: 1) for hypertension, ABAs are highly clinically interchangeable when titrated to effect, and 2) for chronic HF, there is insufficient evidence to suggest clinically significant differences between agents [e.g. metoprolol succinate vs. carvedilol (Coreg, Coreg CR) vs. bisoprolol] or between different dosage forms approved for chronic HF (e.g. carvedilol IR vs. carvedilol CR). As a result, CMAs were conducted for each subgroup to compare the relative cost effectiveness of these agents.

Results from the cost effectiveness analyses revealed:

For hypertension,

1) The three most cost effective agents are atenolol, metoprolol tartrate, and propranolol IR, which account for 90% of the hypertensive ABA utilization.

2) The other agents are more costly and have lower utilization relative to the top three, but all of these agents are generically available and are considered to be cost-effective.

For heart failure,

1) Carvedilol IR is the most cost effective ABA followed closely by (ranked from most to least cost effective) bisoprolol, metoprolol succinate, and carvedilol ER.

2) The system-wide weighted average cost per day for carvedilol ER was only slightly higher than that of carvedilol IR, and thus was determined to be cost effective relative to the other ABAs for chronic HF.

For other conditions,

1) Sotalol, sotalol AF, and labetalol are all available in generic formulations and are cost-effective.

A budget impact analysis (BIA) was performed to examine the potential budget impact of a UF scenario with carvedilol ER designated as formulary on the UF versus a one with carvedilol ER designated as non-formulary under the UF. The BIA showed that the scenario that designated carvedilol ER as formulary on the UF resulted in significantly lower MHS expenditures versus the scenario that designated carvedilol ER as non-formulary under the UF.

Cost Effectiveness Conclusion – The P&T Committee concluded for consideration of UF status that:

1) All ABAs used primarily to treat hypertension are cost-effective, with atenolol, metoprolol tartrate, and propranolol IR being the most cost-effective.

2) All of the ABAs with clinical evidence for heart failure are cost-effective, with carvedilol IR being the most effective agent.

3) The ABAs for other indications, sotalol, sotalol AF, and labetalol are cost-effective.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the cost effectiveness conclusion stated above.

C. ABAs – UF Recommendations

COMMITTEE ACTION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that. atenolol, atenolol-chlorthalidone, metoprolol tartrate, metoprolol succinate, propranolol, propranolol/HCTZ, propranolol ER, timolol, timolol/HCTZ, bisoprolol, bisoprolol/HCTZ, nadolol, nadolol/bendroflumethiazide, acebutolol, betaxolol, penbutolol, carvedilol IR, and carvedilol ER be designated formulary on the UF.

D. ABAs – BCF Review and Recommendations

COMMITTEE ACTION– The P&T Committee considered the BCF status of the ABA agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to

recommend that atenolol and metoprolol tartrate be maintained and to add generic formulations of carvedilol IR and metoprolol succinate to the BCF.

7. DRUG CLASS REVIEW – ALPHA BLOCKERS (ABs) FOR BENIGN PROSTATIC HYPERTROPHY (BPH)

A. BPH Alpha Blockers – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the ABs used for BPH that are currently marketed in the US. The BPH ABs comprises the non-uroselective agents terazosin (Hytrin, generics) and (Cardura, Cardura XL, generics), and the uroselective agents alfuzosin (Uroxatral) and tamsulosin (Flomax). The BPH AB class was first reviewed by the DoD P&T Committee in August 2005. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

1) *FDA-approved indications* – Terazosin, doxazosin, alfuzosin, and tamsulosin are FDA-approved for treating the signs and symptoms of BPH.

2) *Efficacy measures* - The primary outcome measures used to assess BPH AB efficacy are changes in symptom scores [e.g., American Urological Association Symptom Index (AUA-SI) or international prostate symptom score (IPSS)], and urinary flow rate (Qmax). In clinical trials, a decrease in symptom score of three or more points is generally considered clinically significant, although men self-rate decreases of one to two points as slightly improved symptoms. A change in urinary flow rate of 2 to 3 mL/sec is considered clinically significant.

3) *Efficacy*

   a) *Meta-analyses/systematic reviews* – A meta-analysis [AUA 2003], systematic reviews [Djavan 1999, Clifford & Farmer 2000, Wilt 2002,2003], and pooled analysis concluded that the ABs were effective, and consistently improved lower urinary tract symptoms (LUTS) and Qmax compared to placebo. The ABs produced comparable improvements in LUTS and Qmax.

   b) *Placebo-controlled studies* - Placebo-controlled studies have demonstrated improvements in total symptom score from baseline of about 30% to 50% for the ABs vs. about 10% to 30% for placebo. On average, terazosin reduced AUA-SI score by 3 points; tamsulosin by 3 points [Wilt 2002, 2003]; doxazosin by 3 points at 1 year [Kirby 2003] and 2 points at 4 years, [McConnell 2003]; and alfuzosin by 2 points short-term [MacDonald 2005], more than placebo. Improvements in Qmax for the ABs were about 5% to 15% greater than placebo [Djavan 1999, Clifford & Farmer 2000, Wilt 2002, 2003, Roehrborn 2001].

A rapid response (within 2 weeks) was seen with most ABs. Improvement with tamsulosin has been observed after the first dose, with peak effects occurring after one week [Djavan 1999, 2004]. Alfuzosin has also demonstrated improvement after the first-dose [Djavan 1999, Roehrborn 2001].

c) *Head-to-head trials* - Head-to-head trials and indirect comparative studies (e.g., meta-analysis and systematic reviews) between ABs when used at equivalent doses do not show clinically relevant difference in efficacy, in terms of symptom relief and urodynamic improvements. Overall, for the ABs, total symptom score improved by 30% to 40% relative to baseline and Qmax by 16% to 29%.

d) *Newly published clinical trials* - Since the prior August 2005 DoD P&T Committee review, only two randomized controlled trials and three quality of life (QoL) studies were identified.

- *Nordling 2005* – The first trial was a double-blind, placebo-controlled trial that indirectly compared alfuzosin10 mg or 15 mg or tamsulosin 0.4 mg to placebo. Although alfuzosin and tamsulosin were not directly compared to each other, significant symptoms improvement occurred when both treatments were administered at the recommended doses (i.e., alfuzosin 10 mg, tamsulosin 0.4 mg) compared to placebo. The IPSS change from baseline was similar with both agents.
- *Roehrborn 2006* - The second double-blinded, placebo-controlled study demonstrated that alfuzosin prevented/slowed the overall clinical progression of BPH after 2 years, but did not reduce the risk of acute urinary retention or need for surgery. Alfuzosin reduced AUA-SI score by 1 point, and improved QoL compared to placebo.
- *Elhilali 2006, Flannery 2006, Hartung 2006* - Three non controlled open-labeled studies conducted in the primary care setting suggested that both alfuzosin and tamsulosin improved QoL measures in addition to improving LUTS.
- *Conclusion for new information since 2005* - No newly published U.S. head-to-head trials were identified since the 2005 review was conducted. Review of the clinical literature since 2005 does not add substantial new information or support changes in current clinical practice for the treatment of LUTS in men with BPH.

e) *Efficacy conclusion*- Based on limited head-to-head trials and indirect comparisons between the agents the following conclusions can be made:

- The existing evidence does not support clinically significant differences in efficacy between terazosin, doxazosin, tamsulosin, and alfuzosin.
- All the ABs produce clinically significant symptom improvements when compared to placebo. Results of the AUA meta-analysis suggest terazosin, doxazosin, alfuzosin, and tamsulosin are similar in efficacy, based on partial relief of symptoms and improvement in the AUA-SI Score. Other systematic reviews, meta-analyses, and clinical trials agree with the AUA meta-analysis.

- There are no published head-to-head trials directly comparing alfuzosin with tamsulosin. One trial published since 2005 [Nordling] that indirectly compared alfuzosin or tamsulosin with placebo reported significant symptom improvement with both treatments. Existing evidence does not support clinically significant differences in efficacy between alfuzosin and tamsulosin.

4) Safety / Tolerability

a) Adverse reactions – The most commonly reported adverse events with the ABs during placebo controlled and open label uncontrolled studies are vasodilatory in nature (e.g., dizziness, asthenia/fatigue, headache, and hypotension). The incidence of vasodilatory effects with alfuzosin and tamsulosin are relatively low. Postural hypotension occurred in approximately 3% of patients treated with tamsulosin and in less than 1% of patients treated with alfuzosin. Asthenia and dizziness were reported in a higher percentage of tamsulosin (7-8%) and alfuzosin (3-4%) treated patients compared to placebo. Adverse events associated with ABs are dose dependent, with a higher incidence reported with higher doses compared to low dose or placebo.

b) Discontinuation rates – Discontinuation rates due to adverse events range between 4% to 10% for tamsulosin and alfuzosin, which is comparable to placebo. For terazosin and doxazosin, the percentage of patients who discontinued treatment due to adverse events was 8% to 20%.

c) Syncope and orthostatic hypotension **–** The package labeling for all four ABs contain a warning for syncope and orthostatic hypotension; however, these events are more prevalent with terazosin and doxazosin. As a result, terazosin and doxazosin require dose titration when treatment is initiated. In clinical trials, tamsulosin and alfuzosin either do not decrease BP to a clinically significant extent, or reduce BP similar to placebo. Tamsulosin and alfuzosin may be better options for patients with BPH who cannot tolerate a BP reductions, or orthostatic changes in BP, heart rate, or peripheral vascular responsiveness.

d) Sexual Dysfunction – The package labeling for tamsulosin carries a warning concerning the risk of priapism. Although alfuzosin labeling does not contain a warning for priapism, post-marketing cases have been reported. Data from the AUA meta-analysis estimated that the rate of ejaculatory dysfunction with tamsulosin was 10%. The incidence of ejaculatory dysfunction with alfuzosin, terazosin, and doxazosin were approximately 1% in placebo-controlled trials.

e) Drug-drug interactions – Drug interactions are more of an issue with alfuzosin and tamsulosin compared to doxazosin and terazosin. Alfuzosin is contra-indicated for concomitant use with potent cytochrome P450 (CYP) 3A4 inhibitors such as ketoconazole (Nizoral), itraconazole (Sporanox), and ritonavir (Norvir). Tamsulosin has potential drugs interactions with cimetidine and warfarin.

f) Drug-drug interactions with phosphodiesterase Type 5 (PDE-5) inhibitors – PDE-5 inhibitors (sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis)]

are mild vasodilators, which may decrease BP. Concomitant use of PDE-5 inhibitors with any AB may evoke orthostatic hypotension.

g) *Special populations* – Terazosin and doxazosin are rated pregnancy category C, while alfuzosin and tamsulosin are rated pregnancy category B. No AB is indicated for use in women. Doxazosin should be used with caution in patients with hepatic failure. Alfuzosin is contraindicated in patients with moderate or severe hepatic insufficiency (Child-Pugh categories B and C), and caution is recommended in patients with severe renal insufficiency. Alfuzosin should be used with caution in patients with a history of QT prolongation or who are receiving concomitant medications with the potential for QT prolongation. The effect of terazosin, doxazosin, and tamsulosin on the QT interval has not been studied. Allergic reactions with tamsulosin have been reported in patients with sulfa allergy.

h) *Dose titration* – Each time there is a period of noncompliance with terazosin or doxazosin, dosage titration from the lowest dose will be necessary to avoid potential problems with orthostatic hypotension. Dosage titration after non-compliance episodes is not necessary with alfuzosin or terazosin.

i) *Intraoperative Floppy Iris Syndrome (IFIS)* –Tamsulosin can cause a potential intraoperative complication, IFIS, during cataract surgery. IFIS was a recently described phenomenon affecting cataract surgery at the time of the 2005 review. To date, several case reports and observational studies have connected IFIS with tamsulosin use [Blouin 2007, Chang 2005, Chadha 2007, Cheung 2007, Parssinen 2006, Oshika 2007, Takmaz 2007]. The literature has a few anecdotal case reports of IFIS occurring with alfuzosin [Blouin 2007, Settas 2006], terazosin, and doxazosin [Chadha 2007, Parmar 2005]. Data from the FDA) Adverse Event Reporting System (AERS) identified isolated cases suggestive of IFIS with tamsulosin, doxazosin, terazosin, and the 5-alpha reductase inhibitor finasteride (Proscar), and has included this as a precaution in all AB package labeling.

j) *Safety and tolerability conclusion*- Vasodilatory adverse events were reported most commonly with the ABs during placebo-controlled and open label uncontrolled trials. Dizziness and asthenia most commonly lead to discontinuation of therapy. Alfuzosin and tamsulosin appear well-tolerated; there are only a few differences in safety considerations (e.g., drug interactions with CYP3A4 inhibitors; precautions for QT prolongation). Data from the clinical trials published since 2005 did not add substantial new information as to safety, tolerability or adverse events.

5) *Other Factors*

Provider Input: Results from a survey sent to MTF providers indicated that alfuzosin and tamsulosin had similar effectiveness, safety and tolerability profiles.

6) *Therapeutically Interchangeability*

Terazosin and doxazosin the non-uroselective ABs, have a low degree of therapeutic interchangeability with alfuzosin and tamsulosin, the uroselective AB, in terms of

safety/tolerability. The non-uroselective agents have a high incidence of discontinuation rates and vasodilatory effects than the non-uroselective agents.

For the uroselective ABs alfuzosin and tamsulosin, there is a high degree of therapeutic interchangeability with regards to efficacy, safety, and tolerability.

7) Clinical Coverage

Neither alfuzosin nor tamsulosin offers a unique benefit over the other. It is not likely that a patient who did not have an adequate response with one uroselective AB would have a better response with the other. Either alfuzosin or tamsulosin could be expected to meet the needs of the majority of the DoD patients requiring a uroselective agent.

There is no evidence to suggest switching between the four ABs would provide additional benefit to patients who fail treatment due to lack of effectiveness. Patients with an inadequate response to the ABs would be candidates for a 5-alpha reductase inhibitor or surgery. To meet the needs of the majority of the patients in DoD, one non-uroselective AB and one uroselective AB (for patients who can not tolerate a non-uroselective AB) is required.

8) Clinical Effectiveness Conclusion - The P&T Committee concluded that:

a) Based on randomized placebo-controlled trials, terazosin, doxazosin, tamsulosin, and alfuzosin were found to produce clinically significant and comparable symptom improvements when compared to placebo.

b) Based on limited head-to-head trials and indirect comparisons between the agents, existing evidence does not support clinically significant differences in efficacy between alfuzosin and tamsulosin.

c) There appear to be few differences in the incidence of adverse effects with alfuzosin and tamsulosin, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated. The most common adverse events are vasodilatory effects.

d) There appear to be major differences in withdrawal rates due to adverse events between non-uroselective (terazosin and doxazosin) and the uroselective agents (alfuzosin and tamsulosin). Withdrawal rates reported in clinical trials were low overall for alfuzosin and tamsulosin.

e) The package labeling for alfuzosin contains cautions for QT prolongation effects. The effect of tamsulosin on the QT interval has not been studied.

f) Alfuzosin is contraindicated for use with potent CYP3A4 inhibitors such as ketoconazole (Nizoral), itraconazole (Sporanox), and ritonavir (Norvir). Tamsulosin has potential drug interactions with cimetidine and warfarin.

g) Doxazosin should be used with caution in men with hepatic failure. Alfuzosin is contraindicated in men with moderate to severe hepatic impairment (Child-Pugh categories B and C). Tamsulosin does not require dosage adjustment in men with moderate hepatic dysfunction.

h) Package labeling for all four ABs contains information regarding the potential for IFIS. For patients receiving alfuzosin and tamsulosin consultation with an ophthalmologist is recommended prior to cataract surgery.

i) Terazosin and doxazosin have a low degree of therapeutic interchangeability with alfuzosin and tamsulosin in terms of safety/tolerability due to the higher incidence of discontinuation rates and vasodilatory effects seen with the non-uroselective ABs.

j) Alfuzosin and tamsulosin have a high degree of therapeutic interchangeability; either drug could be expected to meet the needs of the majority of DoD BPH patients requiring an uroselective agent.

k) Review of the clinical literature since 2005 does not add substantial new information or support changes in current clinical practice for the treatment of LUTS in men with BPH, or for safety profiles between the uroselective ABs.

l) Based on clinical issues alone, there are no compelling reasons to classify any of the AB agents as non-formulary under the UF.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the clinical effectiveness conclusions stated above.

B. BPH Alpha Blockers – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the BPH ABs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e) (2).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the uroselective AB medications differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of BPH. As a result, a CMA was performed to compare the relative cost effectiveness of potential UF uroselective ABs scenarios. The CMA compared the weighted average cost per day of treatment for each potential UF scenario across all three points of service. The potential UF uroselective ABs scenarios considered were derived from the following condition sets:

1) One selective BPH-AB will be selected to the UF and the BCF. In addition, a PA process would require all new selective BPH-AB users to complete an adequate trial of the UF selective BPH-AB before the non-formulary selective BPH-AB is provided to a new user through an MTF pharmacy, the TMOP, or a TRICARE retail network pharmacy. (1 UF, 1 BCF, with PA)

2) One selective BPH-AB will be selected to the UF and up to one selective BPH-AB will be included on the BCF. (1 UF, 0-1 BCF).

3) Two or more selective BPH-ABs will be selected to the UF and up to one selective BPH-AB will be included on the BCF. (2+ UF, 0-1 BCF)

Results from the AB CMA showed that: 1) UF scenario, under condition set #1, with alfuzosin as the one uroselective agent on the UF and BCF in conjunction with Step

Therapy to be the most cost effective UF scenario considered; 2) UF scenario, under condition set #2, with alfuzosin as the one uroselective agent on the UF and BCF without Step Therapy was the next most cost effective UF scenario considered. However, under this UF scenario, without Step Therapy, the weighted average cost per day of therapy increased by 53% over the most cost effective UF scenario; 3) any condition set that included tamsulosin on the UF was more costly compared to the baseline (what DoD pays today) weighted average cost per day of therapy.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the Committee in determining which uroselective AB best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS. The results of the BIA paralleled those of the cost effectiveness analysis. The UF scenario, under condition set #1, with alfuzosin as the one uroselective agent on the UF and BCF in conjunction with Step Therapy was the most cost effective UF scenario.

Cost Effectiveness Conclusion – The DoD P&T Committee accepted the conclusions from the cost effectiveness analyses stated above. In addition, the Committee concluded that the UF scenario that maintained alfuzosin as the only uroselective agent on the UF and BCF in conjunction with a step therapy/PA was the most cost effective scenario.

COMMITTEE ACTION: The P&T Committee concluded (16 for, 0 opposed, 0 abstained, and 1 absent) to accept the AB relative CEA as presented by the PEC.

C. BPH Alpha Blockers – UF Recommendations

COMMITTEE ACTION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 2 absent) to recommend that: 1) alfuzosin be maintained as the uroselective formulary AB, and that terazosin and doxazosin be maintained as the non-uroselective formulary ABs; and 2) tamsulosin be classified as non-formulary under the UF with a PA requiring a trial of alfuzosin for new patients.

D. BPH Alpha Blockers – PA Criteria

The P&T Committee agreed that the following PA criteria should apply to tamsulosin. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:

    c) The patient has received a prescription for either tamsulosin or alfuzosin at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2) PA criteria if automated criteria are not met:

    d) The patient has tried alfuzosin and had an inadequate response or was unable to tolerate treatment due to adverse effects.

e) Treatment with alfuzosin is contraindicated.

The P&T Committee noted that in order for a patient to receive tamsulosin at the formulary cost-share, both the PA and MN criteria must be met. If the PA criteria are met without an approved MN determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved PA for tamsulosin would NOT automatically receive it at the formulary cost-share.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend the PA criteria outlined above.

E. BPH Alpha Blockers – MN Criteria

Based on the clinical evaluation for tamsulosin and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for tamsulosin:

1) The use of formulary alternatives is contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.
3) Formulary alternatives have resulted in therapeutic failure.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to approve the MN criteria outlined above.

F. BPH Alpha Blockers – UF Implementation Period

The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in TMOP program and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have tamsulosin on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider; MTFs may (but are not required to) fill a prescription for non-formulary AB agent written by a non-MTF provider to whom the patient was referred, and 2) MN is established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 1 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

G. BPH Alpha Blockers – BCF Review and Recommendation

COMMITTEE ACTION: The P&T Committee considered the BCF status of the AB agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that the current BCF listing for this class be maintained, requiring each MTF to carry terazosin and alfuzosin.

8. DRUG CLASS REVIEW – TARGETED IMMUNOMODULATORY BIOLOGICS (TIBs)

A. TIBs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the TIBs currently marketed in the United States. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

The TIB class is comprised of five medications covered as part of the DoD pharmacy benefit: adalimumab (Humira), anakinra (Kineret), etanercept (Enbrel), efalizumab (Raptiva), and alefacept (Amevive). Three similar biologic agents are not part of the pharmacy benefit due to their intravenous (IV) route of administration: abatacept (Orencia), infliximab (Remicade), and rituximab (Rituxan). Like adalimumab and etanercept, infliximab is approved for multiple indications and in many respects directly competes with these two self-administered multiple indication agents. The IV agents were included in the review for comparative purposes only. (See Table 2.)

Table 2. FDA-Approved Indications for Targeted Immunomodulatory Biologics (TIBs)

Brand	Generic	Manufacturer	How Given	RA	JRA	PsA	AS	Plaque psoriasis	Crohn's Disease	UC
Enbrel	etanercept	Amgen/Wyeth	SQ	X	X	X	X	X		
Humira	adalimumab	Abbott	SQ	X	*	X	X	*	X	
Kineret	anakinra	Amgen	SQ	X						
Raptiva	efalizumab	Genentech	SQ					X		
Amevive	alefacept	Astellas	IM/IV					X		
Not part of outpatient pharmacy benefit										
Remicade	infliximab	Centocor	IV	X		X		X	X	X
Orencia	abatacept	BMS	IV	X						
Rituxan**	rituximab	Genentech	IV	X						

RA = rheumatoid arthritis; JRA = juvenile rheumatoid arthritis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; UC = ulcerative colitis; NHL =; SQ = subcutaneous; IM = intramuscular; IV = intravenous
* The Food and Drug Administration is currently considering adalimumab (Humira) for the treatment of JRA and plaque psoriasis.
** Rituxan is also approved for non-Hodgkin's lymphoma.

Since the FDA lacks regulatory authority to approve generic versions of biologic medications, generic formulations for the TIBs are not likely to appear in the near future. The TIB class accounted for approximately $136 million dollars in MHS expenditures in FY 2007, primarily at the retail point of service (66%), followed by MTFs (19%) and mail order (15%). This estimate does not accurately represent utilization of the IV agents (e.g., infliximab), since these medications are commonly administered in clinic or office settings and are included on outpatient pharmacy profiles only in MTFs that choose to maintain such a record. The cost of treatment with these agents is high (on the order of $10,000 to $20,000 annually). There were

approximately 11,500 unique TIB utilizers in the MHS in the most recent quarter (June to August 2007), not including patients receiving IV agents.

The majority of use of TIBs in DoD is for the two multi-indication agents (adalimumab and etanercept), not including patients receiving IV agents. Fewer than 4% of DoD TIB utilizers are receiving other TIBs. Over the entire patient population, adalimumab and etanercept are consistently used in about a 2:1 ratio, although utilization in the last quarter (June to August 2007) shows increased uptake of adalimumab among new users (new users only: 44% use of adalimumab vs. 54% use of etanercept, 2% other TIBs).

1) Pharmacology and Clinical Use

TIBs are used to treat a variety of serious disease states. Based on an analysis of TIB prescriptions for patients with relevant diagnosis codes in the MHS Mart (M2) over a six-month period (January through June 2007), the most commonly treated condition treated with TIBs in DoD is rheumatoid arthritis (RA). About 73% of TIB patients are being treated for RA. Other conditions include psoriasis (15%), psoriatic arthritis (PsA) (7%), ankylosing spondylitis (AS) (4%), as well as Crohn's disease, juvenile rheumatoid arthritis (JRA), and ulcerative colitis (UC) (all less than 1% each). In most cases the TIBs are indicated as treatment for moderate to severe cases of these conditions, usually following an inadequate response to initial therapy.

Table 3. Dosing and Administration of the TIBs

Brand	Generic	Dosing
Enbrel	etanercept	**RA, PsA, AS** – 25 mg twice weekly or 50 mg once weekly SQ **JRA** (4-17 years) – 0.8 mg/kg per week (maximum 50 mg per week), given once or twice per week SQ **Plaque psoriasis** – 50 mg twice weekly SQ for 3 months, then decrease to 50 mg SQ weekly
Humira	adalimumab	**RA** – 40 mg every other week SQ, may increase to 40 mg q week for monotherapy **PsA, AS** – 40 mg every other week SQ **Crohn's** – 160 mg at week 0, 80 mg at week 2, then 40 mg every other week beginning week 4
Kineret	anakinra	**RA** – 100 mg daily SQ (consider 100 mg every other day SQ in patients with severe renal insufficiency or end stage renal disease)
Raptiva	efalizumab	**Plaque psoriasis** – Initial 0.7 mg/kg SQ injection, then 1 mg/kg weekly SQ injections (not to exceed 200 mg)
Amevive	alefacept	**Plaque psoriasis** – 15 mg once weekly IM; continue for 12 weeks; after a 12-week interval, may retreat with an additional 12-week course if CD4+ T lymphocyte counts are >250 cells/µL
Not part of outpatient pharmacy benefit		
Remicade	infliximab	**RA (adult)** – 3 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks (may increase to maximum of 10 mg/kg every 4 weeks) **RA (pediatric; 6-17 years)** – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks **Crohn's** – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks (may increase to 10 mg/kg) **PsA -** 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks **AS** – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 6 weeks **UC, plaque psoriasis** – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks Doses > 5 mg/kg per day are contraindicated in patients with moderate to severe heart failure.
Orencia	abatacept	**RA** – IV based on body weight <60 kg = 500 mg; 60-100 kg = 750 mg; >100 kg = 1000 mg); initial dose at 0, 2, 4 weeks, then every 4 weeks
Rituxan	rituximab	**RA** – 1000 mg IV infusion on days 1 and 15 in combination with methotrexate. Safety and efficacy of retreatment not established.

RA = rheumatoid arthritis; JRA = juvenile rheumatoid arthritis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; UC = ulcerative colitis; NHL =; SQ = subcutaneous; IM = intramuscular; IV = intravenous

The TIBs target various mediators of the inflammation cascade, effectively retarding the extent and severity of inflammation at the local level. Etanercept,

adalimumab, and infliximab all act through inhibition of tumor necrosis factor-alpha (TNF-α). Adalimumab and infliximab are monoclonal antibodies; they bind specifically to TNF-α, blocking interaction with the p55 and p75 cell surface TNF receptors. Etanercept is a soluble receptor to TNF- α that binds circulating TNF-α and lymphotoxin-α, preventing interaction with cell surface receptors. Anakinra (which is FDA-indicated only for RA) is a human recombinant protein that competitively blocks the interleukin (IL)-1 receptor, blocking inflammatory and immunological responses.

The other TIBs affect T cell (alefacept, efalizumab, abatacept) or B cell (rituximab) involvement in autoimmune and inflammatory processes. Alefacept and efalizumab are FDA-indicated only for the treatment of plaque psoriasis, while the IV agents abatacept and rituximab are FDA-indicated only for RA.

Dosing of the various agents varies from every 8 weeks via IV infusion (infliximab) to daily subcutaneous dosing (anakinra) (See Table 3).

The two multi-indication self-administered TIBs, adalimumab and etanercept, are given every 1 or 2 weeks (see Table 2). Major areas of uncertainty about actual dosing of the TIBs (which may affect safety, tolerability, and efficacy as well as cost) are: 1) the percent of RA patients who receive weekly rather than every other week dosing with adalimumab; 2) the percent of plaque psoriasis patients who continue to receive twice weekly dosing with etanercept 50 mg following the 12-week induction phase; and 3) the percent of patients who receive higher or more frequent doses of infliximab for the treatment of RA and Crohn's disease.

2) Efficacy

A recent well-done systematic review of the drugs in this class is available from the Oregon Health & Science University's DERP. The January 2007 review included published clinical trials through August 2006. The review took a "best evidence" approach, with a primary focus on health outcomes (symptoms, QoL, functional capacity, hospitalizations, and mortality). Radiological changes were considered as a secondary, intermediate measure.

Many TIB trials, particularly in rheumatologic conditions, included treatment with disease-modifying antirheumatic drugs (DMARDs), particularly methotrexate (MTX), either as monotherapy or in combination with a TIB. (Although the term DMARD technically includes the TIBs, which slow disease progression in RA, it is used in this evaluation to refer solely to non-biologic agents that slow disease progression in RA, such as MTX, sulfasalazine, gold salts, and hydroxylchloroquine.) Since there are no head-to-head RCTs comparing two or more TIBs, comparisons between TIBs in any given disease state primarily rest on the results of placebo- and/or active-controlled RCTs.

As part of its evaluation of the TIB class, the P&T Committee considered summary efficacy and safety data and conclusions from the DERP review, along with more recently published clinical data following the same general approach. Unpublished data provided by pharmaceutical manufacturers as part of their Academy of Managed Care Pharmacy "dossiers" were also considered when little

published data were available (published trials have undergone peer review and are generally considered more reliable than unpublished data). Additional information (typically from open label extension trials or observational studies) was also considered to address questions concerning switching between the TIBs (e.g., in patients refractory to treatment), long-term efficacy and safety, and effects on QoL and productivity.

Few published guidelines to date attempt to establish the place of specific TIBs in the treatment of the disease states addressed in this evaluation.

a) Rheumatoid Arthritis

A prominent RA efficacy measure is the number of patients attaining a American College of Rheumatology (ACR) 20, 50 , or 70 response, based on at least a 20, 50, or 70% reduction compared to baseline in tender / swollen joint counts plus improvements in at least three other specified measures of pain, overall effect, or laboratory measures of inflammation. DERP reviewers chose an ACR 50 response as the outcome measure for adjusted indirect comparisons of randomized placebo controlled trials because it was felt to translate to a clinically significant improvement in health-related QoL.

Based both on trials included in the DERP review and more recently published trials, there is good-to-fair evidence from meta-analyses and large placebo-controlled RCTs supporting the efficacy of etanercept, adalimumab, and anakinra for the treatment of RA. The same is true for the IV agents infliximab, abatacept, and rituximab. Alefacept and efalizumab lack evidence for the treatment of RA. In general, combination treatment with TIBs plus MTX offered better efficacy than TIBs or MTX alone. The same was true of the DMARD sulfasalazine based on one trial. Beneficial effects on QoL and productivity were associated with improvements in clinical response.

Meta-analysis results from the DERP review suggested no significant difference in efficacy among etanercept, adalimumab, and infliximab for the treatment of RA. Point estimates favored the TNF inhibitors (etanercept, adalimumab, and infliximab) over the IL-1 inhibitor anakinra, although differences were statistically significant only for ACR 20 and not ACR 50 response. A recent high-quality meta-analysis [Nixon et al, 2007] similarly reported comparable efficacy among etanercept, adalimumab, and infliximab for the treatment of RA. An analysis comparing anakinra to the TNF inhibitors as a class concluded that the TNF inhibitors were statistically significantly more efficacious than anakinra (OR 1.96, 95% CI 1.03 to 4.01 for ACR 20; OR 1.93, 95% CI of 1.05 to 3.50 for ACR 50).

Numerous studies have shown clinical benefit in patients switching from one TIB to another, including patients switching from infliximab to etanercept, etanercept to infliximab, etanercept to adalimumab, infliximab to adalimumab, and TNF inhibitors to rituximab or abatacept. In general, clinical response was seen with the second TIB regardless of the reason for switching—albeit at lower rates than in TIB-naïve patients—with no increase in adverse events. This appeared to be true both for switches between TNF

inhibitors and from a TNF inhibitor to another TIB. Data on the efficacy of switching to a third TNF inhibitor are mixed.

Another important aspect of overall efficacy concerns the impact of TIBs and other DMARDs on delaying the progressive structural destruction of peripheral joints seen in RA. A common measure is the Total Sharp Score (TSS), which is based on evaluation of x-rays of hands and feet scored for joint erosions and joint space narrowing. Optimally, treatment would both control RA symptoms and delay (or even halt) radiographic disease progression.

Long-term data supporting maintenance of effects on clinical measures (e.g., ACR response) is available for all the TIBs used for the treatment of RA; however, the length of follow-up varies. The longest-term data are available for adalimumab and etanercept (4 to 7 years). Both of these TIBs have evidence supporting delay in radiographic progression for up to 2 years. Infliximab and abatacept have 1-year data supporting sustained effects on clinical measures and radiographic progression. Anakinra has data supporting sustained effects on clinical measures for up to 1 year, but radiographic data only out to 6 months; rituximab lacks radiographic data but has data supporting sustained effect on clinical measures for up to 2 years (following one course of therapy).

b) Juvenile Rheumatoid Arthritis

Etanercept is the only TIB with published evidence that demonstrates efficacy for the treatment of JRA and the only TIB indicated for this condition. Evidence is limited to a single placebo-controlled RCT; similar results are reported in a retrospective analysis of registry data from Germany in pediatric patients with various forms of arthritis. A small, uncontrolled open-label study provides insufficient evidence for infliximab.

Unpublished evidence suggesting efficacy for adalimumab in JRA is available from the manufacturer; FDA approval of adalimumab for this indication is pending.

There is some uncontrolled or observational evidence with infliximab, etanercept, and adalimumab for the treatment of JRA-associated uveitis.

c) Ankylosing Spondylitis

AS causes inflammation of the spine and large joints, resulting in stiffness and pain and often progressive disability. Clinical measures are based on improvement in symptoms such as pain, morning stiffness, fatigue, and mobility. Non-biologic DMARDs are not consistently helpful for the treatment of AS.

Based both on trials included in the DERP review and more recently published trials, sufficient evidence exists to support efficacy of adalimumab, etanercept, and infliximab for treatment of AS symptoms over a period of one to three years, compared to placebo. It is not known if long-term treatment with TNF inhibitors or other biologics can alter the progression of AS. There

is insufficient evidence to conclude that there are differences in comparative efficacy.

One trial provided evidence of successful switching from infliximab to etanercept in patients with loss of efficacy or adverse events on infliximab. There are insufficient data to generalize these results across all treatments.

d) Psoriatic Arthritis

PsA is a chronic inflammatory arthritis associated with psoriasis. Approximately 10 to 30% of psoriasis patients will develop PsA; the psoriasis usually predates the arthritis by many years. Many RA measures are also used in PsA.

Based both on trials included in the DERP review and more recently published trials, evidence from seven placebo-controlled trials supports efficacy of etanercept (two trials), infliximab (two trials), and adalimumab (three trials) in the treatment of PsA. There is insufficient evidence to conclude that there are differences in comparative efficacy among these three agents. A high-quality meta-analysis of placebo-controlled trials [Woolacott et al, 2007] showed very similar treatment effects between etanercept and infliximab.

Long-term data out to 2 years is available for all three agents, including evidence supporting sustained effects on clinical measures of response and radiographic progression.

One trial with efalizumab (which is FDA indicated only for the treatment of plaque psoriasis) reported negative results in PsA. No statistically significant difference in ACR 20 response was seen at 12 weeks, compared to placebo.

e) Plaque Psoriasis

In psoriasis, an environmental trigger is thought to evoke an inflammatory response and subsequent hyperproliferation of keratinocytes, associated with activation of T cells which migrate from the vasculature into the dermal tissues.

A prominent clinical measure of disease severity is the Psoriasis Area and Severity Index (PASI), which incorporates measures of scaling, erythema, and induration of the head, trunk, upper and lower limbs, weighted by severity and affected body surface area. PASI 50/75/90/100 scores represent improvements from baseline in PASI score and are typically reported as the percentages of patients achieving a certain PASI improvement. A PASI 75 response is considered to be the benchmark for current therapies, particularly the biologics.

Based both on trials included in the DERP review and more recently published trials, evidence from published placebo-controlled RCTs supports efficacy of adalimumab (one trial), alefacept (two trials), efalizumab (four trials), etanercept (four trials), and infliximab (three trials) in the treatment of plaque psoriasis.

Due to lack of direct comparative data, it is difficult to draw conclusions regarding comparative efficacy. However, PASI 75 response rates appear consistently higher for infliximab compared to the other TIBs used for the treatment of plaque psoriasis, although some evidence suggests diminishing effect with infliximab as continuous use approaches 1 year. PASI 75 response rates for alefacept, efalizumab, and etanercept appear similar in 12- to 24-week trials.

Evidence for adalimumab in psoriasis includes one published RCT [Gordon et al, 2006] and additional unpublished data available from the manufacturer. FDA approval of adalimumab for plaque psoriasis is pending.

f) Crohn's Disease

Crohn's disease is a chronic inflammatory disease primarily involving the small and large intestine. In its most severe form, it can be associated with the development of deep ulcers and fistulas that can penetrate into adjoining structures or even to the surface skin, leading to infection. The spread of inflammation and thickening of the bowel wall can lead to bowel obstruction. Symptoms may include diarrhea, abdominal pain, anemia, and weight loss. Treatments include 5-aminosalicylic acid, antibiotics, corticosteroids (for patients without fistulas or abscesses), metronidazole (fistulizing disease), immunosuppressives, methotrexate, and TIBs.

Based both on trials included in the DERP review and more recently published trials, there is fair to good evidence from placebo-controlled RCTs supporting efficacy of infliximab (seven trials) and adalimumab (four trials) for initial and maintenance treatment of Crohn's disease.

There is insufficient evidence to conclude that there are differences in comparative efficacy between infliximab and adalimumab for the treatment of Crohn's disease. Both biologics have published data demonstrating persistence of response for up to one year.

One difference is use in children. Infliximab, but not adalimumab, has published evidence and is indicated for the treatment of pediatric Crohn's disease (ages 6 to 17 years).

Etanercept does not appear to be efficacious for Crohn's disease based on one fair-quality placebo-controlled trial [Sandborn et al, 2001]. The manufacturer states that they have discontinued development of etanercept for this indication. The difference in effect compared to the other two TNF inhibitors may be due to mechanistic differences between the monoclonal antibody agents (adalimumab and infliximab) and the soluble receptor agent etanercept.

g) Ulcerative Colitis

UC is a chronic inflammatory and ulcerative disease arising in the colonic mucosa, characterized most often by bloody diarrhea; fistulas and abscesses do not occur. Treatment includes 5-aminosalicylic acid (enemas or oral), corticosteroids, immunosuppressives (azathioprine), and TIBs.

Infliximab is the only TIB currently FDA-indicated for UC, with evidence from three published placebo-controlled RCTs supporting efficacy. No published RCTs were found for other TIBs in the treatment of UC.

3) Safety and Tolerability

a) Overall Adverse Event Profile

Overall, TIBs were well-tolerated during clinical trials; the most common and consistently reported adverse events (AEs) are injection site or infusion reactions (depending on route). With the exception of injection reactions, the overall rate of AEs and the percentage of patients discontinuing treatment due to AEs (3-16%) were typically comparable to placebo. The incidence of AEs does not appear to increase over time.

Anakinra may cause more injection reactions than adalimumab and etanercept based on the mean crude incidence of injection reactions calculated by DERP reviewers from clinical trials included in that review: 17.5% for adalimumab (95% CI 7.1-27.9); 22.4% for etanercept (95% CI 8.5-36.3); but 67.2% for anakinra (95% CI 38.7-95.7).

Infusion reactions have the potential to be more serious than injection site reactions; severe acute reactions have been reported in a small percentage of patients (~1%) after infliximab infusions.

b) Rare but Serious Adverse Events

The primary safety concerns with TIBs are related to the potential for increased risk of serious AEs (e.g., infections, malignancies, autoimmune disorders, etc), most of which are associated with the drugs' effects on the immune system. These effects are rare and cannot be assessed reliably during clinical trials, although the overall incidence of serious AEs tends to be higher with TIBs compared to placebo, and trends in large RCTs approach statistical significance. Current evidence focusing on specific serious adverse events is primarily observational.

Black box warnings concerning the risk of serious infections and the need to test for latent tuberculosis (TB) prior to initiating TIB therapy are included in labeling for adalimumab and infliximab; similar information appears in labeling for other TIBs. In general, caution is indicated in patients with chronic infections or a history of recurrent infections, and TIBs should be stopped if the patient develops a serious infection.

Other black box warnings for TIBs include the risk of hepatosplenic T-cell lymphoma with infliximab (reported in young Crohn's disease patients on other immunomodulatory medications) and a list of potentially severe reactions primarily associated with the use of rituximab for conditions other than RA. There are relatively few absolute contraindications for the TIBs. Alefacept is contraindicated in patients with HIV; etanercept is contraindicated in sepsis; and doses of infliximab greater than 5 mg/kg are contraindicated in patients with moderate to severe heart failure.

(i) Serious Infections

The most common serious infection appears to be TB. Observational studies have also reported infections with coccidiomycosis, histoplasmosis, pneumocystis carinii, listeriosis, candida, and Legionella. Evidence from RCTs is limited.

- A meta-analysis [Bongartz et al, 2006] that pooled data from adalimumab and infliximab RA trials (total n >5000) reported a pooled odds ratio for serious infections of 2.0 (95% CI 1.3 to 3.1), with a number needed to harm of 59 (95% CI 39 to 125) over 3 to 12 months.
- A large RCT (n=1084) designed to assess the risk of serious infections with infliximab in RA patients [Westhovens et al, 2006] reported similar rates of serious infections in patients treated with 3 mg/kg infliximab vs. placebo (RR: 1.0; 95% CI 0.3 to 3.1). However, patients treated with 10mg/kg infliximab had a significantly higher rate of serious infections vs. placebo (RR: 3.1 95% CI 1.2 to 7.9).

The DERP review also included five retrospective database analyses and a prospective cohort study that in general supported a higher risk of TB or granulomatous infection in patients treated with etanercept or infliximab compared to unexposed patients; more recently published studies do not add substantial evidence.

When all data are considered, the P&T Committee agreed that there is fair evidence of an increased risk of serious infections (including TB) for TIBs compared to placebo. There is insufficient evidence to draw conclusions about the comparative risk of serious infection.

(ii) Malignancies

The P&T Committee agreed that largely observational evidence indicates a higher risk of lymphoma for patients treated with infliximab or etanercept. Results of studies addressing other malignancies are mixed. There is insufficient evidence to draw conclusions about comparative risk.

(iii)Chronic Heart Failure

Evidence concerning the safety of TIBs in patients with chronic heart HF and the effects of TIBs on the development of chronic HF is mixed. Data from two unpublished etanercept RCTs and one published infliximab RCT evaluating these TIBs for the *treatment* of chronic HF suggested higher rates of mortality among chronic HF patients treated with etanercept or infliximab, compared to placebo. However, observational studies have reported *lower* rates of cardiovascular events in RA patients receiving TNF inhibitors compared to those receiving conventional therapy. Caution is indicated.

(iv) Other

All TNF inhibitors appear to cause the development of autoantibodies to some extent. Cases of drug-induced lupus, lupus-like syndromes and

other autoimmune disorders have been reported with etanercept, adalimumab, and infliximab. The relationship among auto-antibody levels, the likelihood of infusion reactions, degree and durability of clinical response, and the development of autoimmune disorders is unclear.

Based on case reports and product labeling, adalimumab, etanercept, and Infliximab may be associated with demyelination. Hepatotoxicity has been reported with infliximab and alefacept. Potential effects on hematologic parameters requiring laboratory monitoring include neutropenia with anakinra (neutrophil counts monthly for 3 months, then quarterly for 1 year); dose-dependent reductions in CD4+ T lymphocytes reported with alefacept (CD4+ T lymphocyte counts every 2 weeks during the 12-week treatment period); and periodic assessment of platelet counts with efalizumab (monthly to quarterly).

c) Drug Interactions

There is little substantive information concerning potential drug interactions with the TIBs. They are in general considered safe for use with the large number of drugs used concomitantly in clinical trials.

In general, additive effects on the immune system appear to preclude concomitant treatment with more than one TIB. A trial assessing a combination of anakinra and etanercept (plus MTX) appeared to offer no additional clinical benefit compared to etanercept plus MTX, but resulted in a substantially higher rate of pancytopenia and serious infections. Similarly, a trial assessing the addition of abatacept to etanercept appeared to offer minimal additional clinical benefit compared to etanercept alone, but resulted in a substantially higher rate of adverse events (including serious adverse events and serious infections).

4) Use in Special Populations

Overall, TIBs do not appear to have major differences in terms of efficacy or safety/tolerability in specific subsets of patients (e.g., based on age, gender, race, or comorbid conditions), although this has not been extensively studied. A higher risk of mortality among chronic HF patients treated with etanercept or infliximab has been previously discussed. Caution is in general indicated in elderly patients due to a higher background risk for serious infections and malignancy.

Other differences include varying pregnancy categories (B vs. C) across drugs (alefacept, abatacept, and rituximab are Category C due either to complete lack of data or some evidence of harm in animal studies); the potential for a higher risk of AEs with anakinra in patients with impaired renal function (anakinra is known to be substantially excreted by the kidney; dose reduction is recommended); and the availability of safety and efficacy data in pediatric patients (etanercept is the only TIB FDA-indicated for JRA; infliximab is the only TIB indicated for pediatric Crohn's disease [age 6-17]).

5) Provider Opinion

Opinions of MTF providers familiar with the use of TIBs were solicited through the Army, Navy, and Air Force specialty leaders for the three specialties in which these agents are primarily used (rheumatology, dermatology, and gastroenterology).

- *Rheumatology* – Factors influencing the decision to choose between adalimumab and etanercept were frequency of dosing and the shorter half-life of etanercept, which was considered useful in patients in whom there was a fear of infectious complications. Responders considered the two equally efficacious, and almost universally reported efficacy with a second TIB in patients who had had an inadequate response to the first TIB. They tended to use abatacept, then rituximab, in patients failing TNF agents, usually after a trial of two agents. Anakinra was not considered useful in RA; responders cited anecdotal use in Still's disease (pediatric and adult).
- *Dermatology* – Responders stated that they usually started with etanercept for psoriasis (with which they had the most experience) or adalimumab; many would consider adalimumab after a 4- to 6-month trial of etanercept. Some do use adalimumab as first line. Based on the published data (PASI 75 scores), providers thought that adalimumab might have greater efficacy, although they also theorized that it might have a higher risk of infection based on its binding of both tissue-bound and soluble TNF. Comments about dosing of etanercept (i.e., patients staying on the twice-weekly 50 mg dose after the initial treatment period) included a perception that many patients require the higher dose and that many also require additional therapy (phototherapy, MTX), the possibility that etanercept may need to be weight-based due to higher TNF production in patients with a high BMI; and the perception that effects of etanercept may wane over time, requiring that the dose be increased back to 50 mg twice weekly.

  Survey responders typically placed efalizumab before alefacept in patients with a contraindication to TNF inhibitors or who had failed etanercept or adalimumab. Efalizumab was noted to be helpful when treating very heavy or light-weight individuals, since dosing is weight-based; it was also noted as having a potential role in some off-label uses. Infliximab was typically reserved for severe or refractory disease or for patients in whom a more rapid onset of improvement is necessary (pustular psoriasis); responders noted that cyclosporine and infliximab are really the only options for acute cases.
- *Gastroenterology* – Responders commented that most are now using adalimumab for Crohn's disease to some extent (instead of infliximab); some prefer adalimumab as the first choice because of easier administration. They perceived that many providers will continue to use infliximab due to lack of guidelines. They noted that the factors affecting their choice of biologic agent for Crohn's disease were concerns about infusion reactions, antibody formation, need for a concomitant immunosuppressant, and type of disease

(with more literature and experience with infliximab for the treatment of fistulizing disease).

Responders did not perceive that there was much (off-label) use of adalimumab for Crohn's disease at present, although some providers have commented that they would try it before cyclosporine or colectomy in patients who cannot take infliximab.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the following clinical effectiveness conclusion:

a) Across all disease states reviewed, all of the TIBs FDA-indicated for a particular condition have sufficient evidence from placebo-controlled RCTs to demonstrate efficacy. TIBs are typically added to standard therapy in patients with moderate to severe disease. In general, combination treatment of rheumatologic conditions with TIBs plus MTX offers better efficacy than TIBs or MTX alone. Beneficial effects on QoL and productivity are associated with improvements in clinical response.

b) There is a lack of direct comparative evidence (head-to-head RCTs) across all disease states. In all disease states except RA, trials were too small in number or too heterogeneous to make indirect comparisons based on meta-analysis of placebo-controlled trials feasible. With two exceptions, treatment effect across agents appeared similar.

c) In RA, anakinra appears to be less efficacious than the TNF inhibitors (etanercept, adalimumab, and infliximab) with respect to effects on symptoms (ACR response), based on indirect comparison of data from placebo-controlled trials.

d) In psoriasis, PASI 75 scores for infliximab appeared consistently higher than with other TIBs used for psoriasis (etanercept, alefacept, and efalizumab), although there is insufficient comparative evidence to draw a definitive conclusion. Some evidence suggests diminishing effect with infliximab as continuous use approaches 1 year. PASI 75 response rates for alefacept, efalizumab, and etanercept appear similar in 12- to 24-week trials. An indication for adalimumab for the treatment of plaque psoriasis is under consideration by the FDA; one published trial and additional unpublished data available from the manufacturer supports its efficacy for this condition.

e) The multi-indication self-administered TIBs (adalimumab and etanercept) compare favorably to one another. Etanercept did not appear to be efficacious in Crohn's disease, for which adalimumab is indicated. Adalimumab lacks published evidence in JRA and has limited published evidence in psoriasis; however, the manufacturer has unpublished data suggesting efficacy in both disease states and both are under consideration by the FDA. For disease states in which both are indicated, there is little evidence to suggest any clinically relevant difference in treatment effect.

f) Alefacept and efalizumab are FDA-indicated only for psoriasis; they appear to compare favorably to etanercept in terms of treatment effect. Their place in therapy relative to etanercept and infliximab (and potentially adalimumab) in the treatment of psoriasis is probably dependent on factors such as intramuscular administration of alefacept, recommended lab monitoring with both agents, and greater familiarity of providers with the TNF inhibitors.

g) Overall, TIBs were well-tolerated during clinical trials; the most common and consistently reported AEs are injection site or infusion reactions (depending on route). Anakinra may cause more injection reactions than adalimumab and etanercept based on the mean crude incidence of injection reactions calculated by DERP reviewers from clinical trials included in that review: 17.5% for adalimumab (95% CI 7.1-27.9); 22.4% for etanercept (95% CI 8.5-36.3); but 67.2% for anakinra (95% CI 38.7-95.7). In addition, anakinra is given once daily, as opposed to weekly or every other week dosing for adalimumab and etanercept.

h) The primary safety concerns with TIBs are related to the potential for increased risk of serious AEs (e.g., infections, malignancies, autoimmune disorders, etc), most of which are associated with the drugs' effects on the immune system. These effects are rare and cannot be assessed reliably during clinical trials, although the overall incidence of serious AEs tends to be higher with TIBs compared to placebo, and trends in large RCTs approach statistical significance. There is insufficient evidence to draw conclusions about comparative risk of any of these serious AEs.

   i) There is fair evidence of an increased risk of serious infections (including TB) for TIBs compared to placebo.

   ii) Observational evidence indicates a higher risk of lymphoma for patients treated with infliximab or etanercept. Results of studies addressing other malignancies are mixed.

   iii) Evidence concerning the safety of TIBs in patients with chronic HF and the effects of TIBs on the development of chronic HF is mixed. Data from etanercept and infliximab RCTs evaluating these TIBs for the *treatment* of chronic HF suggested higher rates of mortality compared to placebo. However, observational studies have reported *lower* rates of cardio-vascular events in RA patients on TNF inhibitors compared to those on conventional therapy.

   iv) All TNF inhibitors appear to cause the development of autoantibodies to some extent. Cases of drug-induced lupus, lupus-like syndromes and other autoimmune disorders have been reported with etanercept, adalimumab, and infliximab.

   v) Adalimumab, etanercept, and infliximab may be associated with demyelination. Hepatotoxicity has been reported with infliximab and alefacept.

vi) Laboratory monitoring is required or recommended for anakinra (neutrophil counts), alefacept (CD4+ T lymphocyte counts), and efalizumab (platelet counts) due to reports of hematologic abnormalities.

i) There is little substantive information concerning potential drug interactions with the TIBs, which are in general considered safe for use with the large number of drugs used concomitantly in clinical trials. Based on two combination trials (one with anakinra plus etanercept and one with abatacept plus etanercept), additive effects on the immune system appear to preclude concomitant treatment with more than one TIB.

j) Overall, TIBs do not appear to have major differences in terms of efficacy or safety/tolerability in specific subsets of patients (e.g., based on age, gender, race, or comorbid conditions), with the exception of a reported higher risk of mortality among chronic HF patients treated with etanercept or infliximab. Potential differences include varying pregnancy categories (B vs. C) across drugs (alefacept, abatacept, and rituximab are Category C); the need for dose reduction of anakinra in patients with impaired renal function; and availability of data in pediatric patients (etanercept for JRA; infliximab for pediatric Crohn's disease).

B. TIBs – Relative Cost Effectiveness –The P&T Committee evaluated the relative cost effectiveness of the TIBs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The TIBs were grouped into sub-groups according to the number of indications for treatment that each agent possessed. The multi-indication agents included etanercept and adalimumab, and the single-indication agents consisted of anakinra, efalizumab, and alefacept. The cost effectiveness review compared the estimated cost of treatment by disease state for RA and plaque psoriasis. For RA, the analysis compared etanercept, adalimumab, anakinra, and infliximab, while the analysis of plaque psoriasis compared efalizumab, etanercept, and alefacept. Although infliximab is not part of the pharmacy benefit (it is covered under the TRICARE medical benefit), it was included in the analysis because it has indications for treatment that are similar to the products evaluated for the TIBs cost effectiveness review.

The relative clinical effectiveness evaluation concluded that the TIBs are effective for the treatment of RA and plaque psoriasis. Moreover, there was insufficient evidence to suggest that the TIBs' treatment effectiveness differed for RA and plaque psoriasis with one exception: Anakinra appeared to be less effective for the treatment of RA than the multi-indication TIBs, based on the available evidence.

With this information, a cost analysis for RA was conducted to compare the expected cost per year of treatment for each drug product by indication across all three points of service. Results from the analysis showed that adalimumab was the most cost effective TIB for treatment of RA. Etanercept was more costly than adalimumab with similar clinical effectiveness, while anakinra was the most costly agent evaluated and

was less effective than the multi-indication TIBs. The results showed that neither etanercept nor anakinra were cost effective when compared to adalimumab for the treatment of RA, and the conclusions were robust to assumptions about dose escalation with adalimumab. In the analysis of plaque psoriasis, all three products evaluated had comparable cost effectiveness profiles.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., condition sets, market share migration, switch costs, non-formulary cost shares). The goal of the BIA was to aid the Committee in determining which group of multi-indication TIBs best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS. The results showed that the scenario where adalimumab was the sole multi-indication TIB on the UF was the most cost effective scenario evaluated in the BIA.

Cost Effectiveness Conclusion – The P&T Committee concluded that:

1) For RA, the clinical effectiveness evaluation concluded that anakinra appears to be less effective for the treatment of RA than the multi-indication TIBs. A cost effectiveness analysis comparing the expected cost per year of treatment across all three points of service for etanercept, adalimumab, and anakinra showed that adalimumab was the most cost effective TIB for treatment of RA. Etanercept was more costly than adalimumab with similar effectiveness, while anakinra was both more costly and less effective.
2) For psoriasis, there was insufficient evidence to definitely conclude that treatment effectiveness differed among agents. A cost analysis comparing the expected cost per year of treatment across all three points of service for efalizumab, etanercept, and alefacept showed similar cost effectiveness profiles for all three agents.
3) The UF scenario that placed adalimumab as the sole multi-indication TIB on the UF was the most cost effective scenario.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, and 1 absent) to accept the TIB relative cost effectiveness analysis as presented by the PEC. The Committee concluded that the UF scenario that placed adalimumab as the sole multi-indication TIB on the UF was the most cost effective UF scenario.

C. TIBs – UF Recommendation

COMMITTEE ACTION: Taking into consideration the relative clinical effectiveness and relative cost effectiveness conclusions for the TIBs and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 2 opposed, 1 abstained, and 1 absent) to recommend that adalimumab, efalizumab, and alefacept be maintained as formulary on the UF and that etanercept and anakinra be classified as non-formulary under the UF.

D. TIBs – MN Criteria

Based on the clinical evaluation for etanercept and anakinra, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for etanercept and anakinra:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Formulary agents have resulted or are likely to result in therapeutic failure.
4) Patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.
5) (Etanercept only) There is no formulary alternative.

With respect to criterion #4, the P&T Committee's primary concern was for patients stabilized on treatment with etanercept or anakinra.

With respect to criterion #5, the P&T Committee agreed that this in general applies only to etanercept, as multiple formulary alternatives are available for anakinra, which is FDA-indicated only for RA. Etanercept is currently the only TIB indicated for JRA; the other self-administered multi-indication TIB, adalimumab, lacks an indication for plaque psoriasis.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. TIBs – UF Implementation Period

The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

As part of the implementation plan, the P&T Committee also recommended that TMA send a letter to beneficiaries affected by this UF decision to inform them about the change in formulary status for their TIB. A retrospective pharmacy claims analysis revealed that approximately 11,500 DoD beneficiaries have filled a prescription for a non-formulary TIB in the previous quarter.

MTFs will not be allowed to have etanercept or anakinra on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider; MTFs may (but are not required to) fill a prescription for non-formulary TIB written by a non-MTF provider to whom the patient was referred, and 2) MN is established.

COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately

following the approval by the Director, TMA. The P&T Committee also recommended that letters be sent to educate patients receiving non-formulary TIBs about the change in formulary status.

F. TIBs – PA Requirements, Criteria, and Implementation Period

Currently PA requirements apply to etanercept, adalimumab, anakinra, and efalizumab. A PA is not currently required for alefacept. The P&T Committee agreed that the following PA criteria should apply to alefacept, consistent with FDA-approved labeling and PA requirements for the other TIBs, and with an implementation period consistent with that established for the UF decision in this class.

1) Coverage would be approved for the treatment of:

- Adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy

2) Coverage would NOT be approved for:

- Patients with HIV, patients with a CD4+ T lymphocyte count below normal at start of treatment, immunocompromised patients or those receiving other immunosuppressive agents or phototherapy
- Children (age < 18 years)

Current PA criteria for etanercept, adalimumab, anakinra, and efalizumab are outlined in Appendix C. The P&T Committee agreed that the PA criteria reflect current FDA labeling and published clinical literature and require no substantive changes. Minor changes to clarify wording and increase consistency, as well as possible future changes to accommodate new FDA indications, will be accomplished on an administrative basis.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) to recommend 1) that no changes be made to PA criteria for etanercept, adalimumab, anakinra, and efalizumab as outlined in Appendix C; 2) that a PA be required for alefacept under the PA criteria outlined above; and 3) that the effective date for the alefacept PA be timed to coincide with that established for the UF decision in this class.

G. TIBs – QLs

Currently, quantity and/or days supply limits apply to etanercept, adalimumab, and anakinra, as outlined in Appendix C. In general, patients are limited to a 4-week supply of these medications at retail network pharmacies at any one time (no multiple fills for multiple copays) and a 6- to 8-week supply at the TMOP, based on product labeling and packaging. The intent is to limit potential wastage if medications are discontinued or changed.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) to recommend 1) that no changes be made to existing quantity / days supply limits for etanercept, adalimumab, and anakinra.

H. TIBs – Extended Core Formulary (ECF) Review and Recommendations – Based on the results of the clinical and economic evaluations presented, the P&T Committee

voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that adalimumab be added to the ECF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that adalimumab be added to the ECF.

9. BCF STATUS OF ROSIGLITAZONE

At the P&T Committee's request, the PEC updated the Committee on the latest news/evidence regarding the safety of thiazolidinedione (TZD) agents, particularly that of rosiglitazone (Avandia), the DoD's BCF TZD. The PEC informed the Committee about recent changes in DoD TZD utilization, evidence (meta-analyses, systematic reviews, and clinical studies) that has emerged in the clinical literature since the last meeting, and a revision to an FDA Alert for rosiglitazone issued 21 May 2007.

The P&T Committee discussed the advantages and disadvantages of removing rosiglitazone and rosiglitazone/metformin (Avandamet) from the BCF. Ultimately, the P&T Committee determined that there was sufficient clinical evidence to justify removal of rosiglitazone and rosiglitazone/metformin from the BCF.

COMMITTEE ACTION: The Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to remove rosiglitazone and rosiglitazone/metformin from the BCF at this time.

10. BCF / ECF REVIEW

As part of an ongoing plan to systematically review drug classes represented on the BCF, the P&T Committee made recommendations for clarifying BCF listings in two current BCF drug classes, analgesics (meloxicam , cyclobenzaprine, and oxycodone/acetaminophen) and ADHD and narcolepsy agents (methylphenidate IR). Details are outlined in Appendix D.

COMMITTEE ACTION: The P&T Committee recommended the following changes to BCF / ECF listings as outlined in Table 4 (see Appendix D for rationale):

Table 4. Recommended BCF / ECF Changes

Drug class or potential drug class	Current BCF/ECF listing	Recommendation	Vote			
			For	Opposed	Abstained	Absent
Analgesics	BCF – Meloxicam (Mobic) oral	Clarify BCF listing to "meloxicam tablets only"	14	0	1	2
	BCF – Cyclobenzaprine (Flexeril) oral; does not include 5 mg strength	Clarify BCF listing to "cyclobenzaprine IR tablets, 5 and 10 mg"	14	0	1	2
	BCF – Oxycodone 5 mg / acetaminophen 325 mg	Clarify BCF listing to "oxycodone 5 mg / acetaminophen 325 mg tablets"	14	0	1	2
ADHD and Narcolepsy Agents	BCF – methylphenidate IR; methylphenidate ER (specific brand is Concerta); mixed amphetamine salts ER (Adderall XR)	Clarify BCF listing to "methylphenidate IR (excludes Methylin oral solution and chewable tablets), methylphenidate ER (specific brand name is Concerta); mixed amphetamine salts ER (Adderall XR)"	14	0	1	2

11. RE-EVALUATION OF AMLODIPINE'S UF STATUS

On an ongoing basis, the DoD PEC monitors changes in the clinical information, current costs, and utilization trends to evaluate whether the UF status of agents designated as non-formulary needs to be readdressed. At this meeting, the UF status of amlodipine (Norvasc, generics) was re-evaluated due to a significant decrease in cost across all three points of service.

In early 2007, the FDA approved Mylan Pharmaceutical's first-time generic for Norvasc. Until recently, the price for amlodipine, even though available generically, was similar to the price for brand name Norvasc and did not support a change in its UF status.

At the August 2005 P&T Committee meeting, the Committee concluded that in general, amlodipine had similar clinical effectiveness relative to other DHP CCBs in regards to efficacy, safety, and tolerability. In consideration of the Committee's previous relative clinical effectiveness conclusion, a CMA was performed to determine the cost effectiveness of amlodipine relative to the other DHP CCBs included on the UF. The results of the CMA showed amlodipine to be the most-cost effective DHP CCB.

Cost Effectiveness Conclusion – The P&T Committee accepted the conclusions from the cost effectiveness analyses stated above.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, and 1 absent) to accept the relative CEA as presented by the PEC.

A. Amlodipine – UF Recommendation

COMMITTEE ACTION: In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the DHP CCB, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that amlodipine be reclassified as formulary on the UF.

B. Amlodipine – UF Implementation Period

The P&T Committee recommend immediate implementation upon signing of the November 2007 DoD P&T Committee minutes by the Director, TMA.

COMMITTEE ACTION: The P&T Committee recommend (15 for, 0 opposed, 1 abstained and 1 absent) an effective date as the date the Director, TMA signs the minutes.

C. Amlodipine – BCF Review and Recommendation

COMMITTEE ACTION: The P&T Committee considered the BCF status of the DHP CCB agents. Based on the results of the clinical and economic evaluations presented, the Committee voted (15 for, 0 opposed, 1 abstained and 1 absent) to add amlodipine to the BCF.

12. RE-EVALUATION OF NON-FORMULARY AGENTS

The P&T Committee's process for the re-evaluation of non-formulary agents established at the May 2007 meeting was approved by the Director, TMA on 24 June 2007. For this meeting, the PEC applied the appropriate criteria and defined a list of non-formulary drug agents for re-evaluation of UF status (Table 5) for the P&T Committee's consideration. More specifically, the non-formulary agents identified for re-evaluation were: 1) from

drug classes in which UF status was NOT awarded based on condition sets that specified the number of similar agents on the UF (i.e., agents in the same class or subclass); and 2) determined to have similar relative clinical effectiveness (i.e., similar efficacy, safety, and tolerability) compared to similar agents on the UF and not excluded from the UF based on clinical issues alone.

Table 5 – Non-Formulary Agents for Re-Evaluation

Generic Name	Brand Name	UF Class	Generics Shipping
EE 30 mcg; 0.15 mg levonorgestrel	Seasonale	BCs (M30)	Y
EE 30/10 mcg; 0.15 mg levonorgestrel	Seasonique	BCs (M20)	N
EE 35 mcg; 0.4 mg norethindrone	Ovcon-35	BCs (M35)	Y
EE 50 mcg; 1 mg norethindrone	Ovcon-50	BCs (M50)	N
EE 20 mcg; 0.1 mg norethindrone	Loestrin 24 FE	BCs (M20)	N
ciclopirox	Loprox	AF-DERMs	Y
econazole	Spectazole	AF-DERMs	Y
moexipril	Univasc	ACEs	Y
quinapril	Accupril	ACEs	Y
amlodipine	Norvasc	CCBs	Y
nicardipine	Cardene	CCBs	Y
nicardipine SR	Cardene SR	CCBs	N
isradipine IR	Dynacirc	CCBs	Y
isradipine CR	Dynacirc CR	CCBs	N
diltiazem ER HS	Cardizem LA	CCBs	N
verapamil ER HS	Verelan /Covera HS	CCBs	N
bupropion XL	Wellbutrin XL	AD1s	Y (300mg only)
paroxetine CR	Paxil CR	AD1s	N
escitalopram	Lexapro	AD1s	N
verapamil ER / trandolapril	Tarka	Misc HTNs	N
tramadol ER	Ultram ER	Narcotic analgesics	N
timolol maleate	Istalol	EYE-1s	N
timolol hemihydrate	Betimol	EYE-1s	N
tolterodine IR	Detrol IR	OABs	N

Accordingly, the PEC recommended that the following pre-established criteria be applied to each non-formulary agent for re-evaluation of UF status.

1) The non-formulary agent becomes generically available and:

   a) The generic product is “A-rated” as therapeutically equivalent to the brand name product according to the FDA’s classification system

   b) The generic market supply is stable and sufficient to meet MHS supply demands.

2) The non-formulary agent is cost effective relative to similar agents on the UF. A non-formulary agent becomes cost effective when:

   c) The non-formulary agent’s total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the UF class to which they were compared.

   d) The non-formulary agent’s total weighted average cost based on an alternate measure used during the previous review is less than or equal to that for the UF

class to which they were compared. For example, antibiotics may be compared on the cost per course of therapy used to treat a particular condition.

The PEC reminded the DoD P&T Committee that when the pre-established criteria for reclassification are met, the Chairperson of the P&T Committee will call for an electronic vote by the members of the P&T Committee on the matter.

1) Upon a majority vote affirming that the non-formulary drug should be reclassified as generic, that agent will be changed from non-formulary status to formulary status as a generic.
2) Committee members will be briefed on any reclassification of a non-formulary agent at the next meeting of the P&T Committee. This information will be recorded as an information-only item in the meeting minutes. The item will be included in information provided for the BAP's next meeting; however, since the BAP will have already made any comments on the subject, the item will normally not be subject to further BAP comment.

The P&T Committee developed the process for the re-evaluation of non-formulary agents for UF status because it recognized that there are situations in which it would be helpful if a procedure were in place that allowed reclassification of a drug from non-formulary to generic in a more expeditious manner than can be accomplished through the normal quarterly P&T Committee cycle. Such a procedure would be advantageous for both the MHS and its beneficiaries.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 against, 1 abstained, 1 absent) to recommend that the above list of non-formulary drug agents be re-evaluated for UF status when pre-established criteria are met.

13. CLASS OVERVIEWS

The class overview for the Pulmonary-1 Agents was presented to the P&T Committee. This drug class comprises the short-acting beta agonists, long-acting beta agonists (LABA), inhaled corticosteroids, and corticosteroid/LABA combinations.

The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the relative clinical effectiveness evaluation and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed for a future meeting; no action is necessary.

14. ADJOURNMENT

The second day of the meeting adjourned at 1530 hours on 15 Nov 2007. The next meeting will be 12-13 Feb 2008.

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Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

Appendix A – Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	**Effective Date for Non-Formulary Medications** (Implementation period)
Nov 07	Targeted Immunomodulatory Biologics	▪ etanercept (Enbrel) ▪ anakinra (Kineret)	ECF	▪ adalimumab (Humira) injection	Pending approval	Pending approval
Nov 07 re-review (Aug 05 original)	BPH Alpha Blockers	▪ tamsulosin (Flomax) Automated PA requiring trial of alfuzosin (Uroxatral) applies to new users of tamsulosin (no use of uroselective alpha blockers in last 180 days)	BCF	▪ terazosin tablets or capsules ▪ alfuzosin ER tablets (Uroxatral)	Pending approval	Pending approval
Nov 07	Adrenergic Beta-Blocking Agents	-	BCF	▪ atenolol tablets ▪ metoprolol tartrate IR tablets ▪ carvedilol IR tablets ▪ metoprolol succinate ER tablets	Pending approval	Pending approval
Nov 07 (update, original review Aug 05)	Calcium Channel Blockers	**Currently non-formulary, recommended for UF status Nov 07** ▪ amlodipine (Norvasc generic)	BCF	**Recommended for addition to BCF Nov 07** ▪ amlodipine besylate tablets	Pending approval	-
		To Remain Non-Formulary ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)		Currently on the BCF ▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Nov 07 (update, original review Nov 06)	ADHD / Narcolepsy Agents	**Recommended for non-formulary status Nov 07** ▪ lisdexamfetamine (Vyvanse)	BCF	-	Pending approval	Pending approval
		To remain NF ▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)		Currently on the BCF ▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07
Nov 07 (update, original review May 06)	Contraceptives	**Recommended for non-formulary status Nov 07** ▪ EE 20 mcg/levonorgestrel 0.09 mg in special packaging for continuous use (Lybrel)	BCF	-	Pending approval	Pending approval

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
		To remain NF ▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)		Currently on the BCF ▪ EE 20 mcg / 3 mg drospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07
		▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	18 Mar 07
Nov 07 (update) Original reviews ▪ ACE inhibitors: Aug 05 ▪ Miscellaneous antihypertensives, including ACE/CCB combos. Feb 06 ▪ ARBs: May 07 ▪ Renin inhibitors. Aug 07	Renin Angiotensin Antihypertensives	**Recommended for non-formulary status Nov 07** ▪ valsartan/amlodipine (Exforge)	BCF	-	Pending approval	Pending approval
		To remain NF ACE inhibitors ▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace) ACE/CCB combos ▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka) ARBs ▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)		Currently on the BCF ACE inhibitors ▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ ACE/CCB combos ▪ amlodipine/benazepril (Lotrel) ARBs ▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	ACE inhibitors ▪ 13 Oct 05 ACE/CCB combos ▪ 26 Apr 06 ARBs ▪ 24 July 07	ACE inhibitors ▪ 15 Feb 06 ACE/CCB combos ▪ 26 Jul 06 ARBs ▪ 21 Nov 07

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 07	Newer Antihistamines	▪ desloratadine (Clarinex) ▪ desloratadine/pseudoephedrine (Clarinex D)	BCF	▪ MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	17 Oct 07	16 Jan 08 (90 days)
Aug 07	Leukotriene Modifiers	▪ zileuton (Zyflo)	BCF	▪ montelukast (Singulair)	17 Oct 07	16 Jan 08 (90 days)
Aug 07	Growth Stimulating Agents	▪ somatropin (Genotropin, Genotropin Miniquick) ▪ somatropin (Humatrope) ▪ somatropin (Omnitrope) ▪ somatropin (Saizen)	ECF	▪ somatropin (Norditropin)	17 Oct 07	19 Dec 07 (60 days)
Aug 07 (new drug update, original review Nov 05)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone propionate (Flonase)	19 Jan 06	19 Apr 06 (90 days)
		Recommended for non-formulary status Aug 07 ▪ fluticasone furoate (Veramyst)			17 Oct 07	19 Dec 07 (60 days)
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex) Automated PA requiring trial of omeprazole OR esomeprazole (Nexium) applies to new users of non-formulary PPIs (no use of PPIs in last 180 days)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)
May 07	Antilipidemic Agents II	▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	▪ gemfibrozil ▪ fenofibrate IDD-P (Triglide)	24 July 07	21 Nov 07 (120 days)
May 07 re-review (Feb 05 original)	ARBs	▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	24 July 07	21 Nov 07 (120 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	24 July 07	24 Oct 07 (90 days)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem) Automated PA requiring trial of zolpidem IR applies to new users of eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) (new users = no use of newer sedative hypnotics in last 180 days)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	-
Nov 06 (updated Nov 07)	ADHD / Narcolepsy Agents	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07 (90 days)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	-
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	-

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06 (updated Nov 06, Nov 07)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended for non-formulary status Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)		-	17 Jan 07	18 Mar 07 (60 days)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	**Effective Date for Non-Formulary Medications** (Implementation period)
Nov 05 (updated Aug 07)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05 (re-review Nov 07)	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05 (updated Nov 07)	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications, NF to UF changes)	**Effective Date for Non-Formulary Medications** (Implementation period)
		Recommended for non-formulary status Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			17 Jan 07	18 Mar 07 (60 days)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-
Feb 05	ARBs – see May 07 for re-review	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs – see May 07 for re-review	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary
ER = extended release; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle
ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs= Thiazolidinediones
*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Newly Approved Drugs. November 2007 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Formoterol fumarate inhalation solution (Perforomist, Dey) inhaled LABA	May 07 (launched Oct 07) Long term twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. Not intended to treat asthma or acute deterioration of COPD	No UF recommendation at this meeting. Consideration of UF status deferred until inhalational Pulmonary I drugs are reviewed; UF review anticipated within the next 12 months. Quantity limits recommended: ▪ TMOP o #180 unit dose vials per 90 days ▪ Retail Network o #60 unit dose vials per 30 days

Appendix C – Existing Prior Authorization Criteria and Quantity Limits for Targeted Immunomodulatory Biologics

	Adalimumab (Humira)	Etanercept (Enbrel)	Anakinra (Kineret)	Alefacept (Amevive)	Efalizumab (Raptiva)
Prior Authorization (approved PAs are good indefinitely)	Coverage provided for the treatment of: ▪ Moderately to severely active RA in patients 18 years of age or older. ▪ Active arthritis in patients with PsA 18 years of age or older. ▪ Active AS in patients 18 years of age or older. ▪ Moderately to severely active Crohn's disease following an inadequate response to conventional therapy, loss of response to infliximab, or an inability to tolerate infliximab in patients 18 years of age or older. ▪ Coverage NOT provided for concomitant use with anakinra, etanercept, or infliximab	Coverage provided for the treatment of: ▪ Moderately to severely active RA ▪ Active PsA ▪ Active AS ▪ JRA when the patient has an inadequate response to at least one DMARD ▪ Chronic moderate to severe plaque psoriasis when the patient has tried and failed traditional therapy, such as phototherapy (e.g. UVB, PUVA) or systemic therapy (e.g., methotrexate, acitretin or cyclosporine) OR is not a candidate for phototherapy or systemic therapy ▪ Coverage NOT provided for concomitant use with anakinra, etanercept, or infliximab	Coverage provided for the treatment of: ▪ Moderately to severely active RA in patients 18 years of age or older when the patient has had an inadequate response to at least one disease-modifying antirheumatic drug (DMARD). ▪ Coverage NOT provided for concomitant use with anakinra, etanercept, or infliximab	none	Coverage provided for the treatment of: ▪ Adults (age = 18 years) with chronic moderate to severe plaque psoriasis, defined as a minimum body surface area involvement of 10% OR a body surface area involvement of less than 10%, but in critical areas (e.g. palms, soles or face) and interfering with day-to-day activities AND ▪ who have tried and failed traditional therapy, such as phototherapy (e.g. UVB, PUVA) or systemic therapy (e.g., methotrexate, acitretin or cyclosporine) OR are not candidates for phototherapy or systemic therapy AND ▪ for whom a dermatologist recommends treatment. Coverage NOT provided for: ▪ Immunocompromised patients or those receiving immunosuppressive agents. ▪ Children (age < 18 years) ▪ Patients with PsA without plaque psoriasis
Quantity Limits	Maximum quantity dispensed at any one time: 4 weeks supply (2 packs of 2 syringes) in retail and 6 weeks supply (3 packs of 2 syringes) in mail order. Does not apply to the Crohn's Disease starter pack (6 pens for the first 4 weeks of treatment), which is limited to 1 package (6 pens), with no refills.	4-week supply in retail and a 6-week supply in mail order (based on instructions for use on the prescription)	Maximum quantity dispensed at any one time is 4 weeks supply (1 package of 28 syringes) in retail and 8 weeks supply (2 packages of 28 syringes) in mail order		

Appendix D– Basic / Extended Core Formulary (BCF/ECF) Review

Drug Class or Potential Drug Class	BCF / ECF listing	Recommendation/ Rationale
Analgesics	BCF – meloxicam (Mobic) oral	• In Aug 2002, meloxicam (Mobic) tablets were added to the BCF • All tablets are now available in generic formulations • In June 2004 the FDA approved Mobic suspension 7.5 mg/ 5 ml (no generics available) • In the last year, there have been 30 Rxs across all Points of Service • Recommendation: • Clarify BCF listing to “meloxicam tablets only”
	BCF – cyclobenzaprine (Flexeril) oral; does not include 5 mg strength	• In Nov 2003, cyclobenzaprine was clarified to exclude the 5 mg strength due to high cost and availability solely as proprietary Flexeril • All IR products are now available in generic formulations at a cost of ~$0.02/tab • A new cyclobenzaprine ER capsule, Amrix (Cephalon), entered the market in Feb 2007 • Recommendation: • Clarify BCF listing to “cyclobenzaprine IR tablets, 5 and 10 mg”
	BCF – oxycodone 5 mg / acetaminophen 325 mg	• The BCF listing does not clarify tablets or capsules and does not specify the 5 mg / 325 mg product • No capsules are available in this strength • Recommendation • Clarify BCF listing to “oxycodone 5 mg / acetaminophen 325 mg tablets”
ADHD and Narcolepsy Agents	BCF – methylphenidate IR; methylphenidate ER (specific brand is Concerta); mixed amphetamine salts ER (Adderall XR)	• The methylphenidate IR oral tablets are available in generic formulations, and are listed on the PEC website as a BCF item. • The Nov 06 P&T Committee minutes for the ADHD BCF drugs were ambiguous for methylphenidate IR oral solution and chewable tablets, available under the brand name Methylin. These Methylin formulations are the only IR products available for the oral solution and chewable tablets. • The Uniform Formulary search tool BCF listing was erroneous, and the manufacturer of Methylin solution and chewable tablets concluded their products were BCF items. • Since Oct 06, MHS utilization for Methylin has been low, at 7 Rx’s dispensed monthly for the solution and 4 Rx’s dispensed monthly for the chewable tablets. • A CMA found that Methylin solution and chewable tablets were less cost effective than other methylphenidate IR formulations. • Recommendation: • Clarify BCF listing for ADHD drugs to exclude Methylin oral solution and chewable tablets.

Appendix E – Table of Abbreviations

AB	Alpha Blocker (drug class)
ABA	Adrenergic Beta Blocker (drug class)
ACE	angiotensin converting enzyme
ACR	American College of Rheumatology
ADHD	Attention Deficit Hyperactivity Disorder
AE	adverse event
AS	ankylosing spondylitis
ARB	angiotensin receptor blocker
AUA-SI	American Urological Association Symptom Index
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BP	blood pressure
BPH	benign prostatic hypertrophy
CCB	calcium channel blocker
CEA	cost effectiveness analysis
CFR	Code of Federal Regulations
CI	confidence interval
CMA	cost minimization analysis
CR	controlled release (extended release)
DERP	Drug Effectiveness Review Project (State of Oregon)
DHP	dihydropyridine
DMARD	disease-modifying antirheumatic drugs
DoD	Department of Defense
EE	ethinyl estradiol
ER	extended release
FDA	Food and Drug Administration
FY	fiscal year
HCTZ	hydrochlorothiazide
HF	heart failure
IFIS	intraoperative floppy iris syndrome
IPSS	international prostate symptom score
IL	interleukin
IR	immediate release
JRA	juvenile rheumatoid arthritis
LABA	long-acting beta agonists
LUTS	lower urinary tract symptoms
M20 EE	monophasic contraceptive with 20 mcg ethinyl estradiol
MHS	Military Health System
MI	myocardial infarction
MN	medical necessity
MTF	military treatment facility
MTX	methotrexate
NSR	normal sinus rhythm
PA	prior authorization
PASI	Psoriasis Area and Severity Index
P&T	Pharmacy and Therapeutics
PEC	Pharmacoeconomic Center
PDE-5	Phosphodiesterase type 5
PsA	psoriatic arthritis
Pulm I	Pulmonary I (drug class)
QD	once daily

Appendix E – Table of Abbreviations (continued)

Qmax	urinary flow rate
QoL	quality of life
RAAs	renin-angiotensin antihypertensive (drug class)
RCT	randomized controlled trial
RR	relative risk
TB	tuberculosis
TIBs	Targeted Immunomodulatory Biologics
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TNF-α	Tumor Necrosis Factor alpha
TRRx	TRICARE Retail Pharmacy Network
UC	ulcerative colitis
UF	Uniform Formulary
XR	extended release

DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

August 2007

1) **CONVENING**
2) **ATTENDANCE**
3) **REVIEW MINUTES OF LAST MEETING**
4) **ITEMS FOR INFORMATION**
5) **REVIEW OF RECENTLY APPROVED AGENTS**

A. Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF) – The P&T Committee was briefed on four new drugs which were approved by the U.S Food and Drug Administration (FDA) (see Appendix B). The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee determined that these four new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed. The P&T Committee discussed the need for quantity limits (QLs) requirements for budesonide/formoterol (Symbicort) oral inhaler. (See paragraph 5A on page 20 of the P&T Committee minutes).

COMMITTEE ACTION: QUANTITY LIMITS – The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend QLs for budesonide/ formoterol of 1 inhaler per 30 days, 3 inhalers per 90 days.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. Renin Angiotensin Antihypertensive – Aliskiren (Tekturna)

Background – In May 2007, the P&T Committee re-classified the angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), ARB/calcium channel blockers combinations and any newly approved antihypertensive drugs affecting the renin system into a single drug class, the Renin-Angiotensin Antihypertensives (RAAs). Aliskiren is the first new drug in the RAA class.

Relative Clinical Effectiveness Conclusion – the P&T Committee voted (14 for, 1 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated below. The one opposing vote was due to the opinion that there was insufficient clinical experience with aliskiren.

a) Aliskiren is a new antihypertensive agent with a novel mechanism of action as a direct renin inhibitor.

b) Aliskiren's blood pressure (BP) lowering effects are similar to those achieved with other antihypertensives, but it does not show improved efficacy compared to other classes of antihypertensive agents.

c) Combination therapy of aliskiren with ACE inhibitors, diuretics and ARBs has shown additive BP lowering effects compared to monotherapy with other antihypertensive agents.

d) Several other safe, once-daily, less costly antihypertensive drugs are available that have proven clinical outcomes (e.g., ACE inhibitors, ARBs, diuretics).

e) The long-term adverse event profile of aliskiren is unknown; diarrhea is the most commonly reported adverse event and the discontinuation rate is similar to placebo.

f) Clinical outcomes of aliskiren are unknown. Trials are underway, with initial results anticipated in November 2007.

Relative Cost Effectiveness Conclusion – the P&T Committee concluded (14 for, 0 opposed, 1 abstained, 2 absent) that:

Although aliskiren was somewhat more costly relative to the ARBs designated as formulary on the UF, the P&T Committee was reluctant to designate aliskiren non-formulary at this time given its novel mechanism of action and the anticipated availability of clinical outcomes data that would enable the P&T Committee to more definitively assess its value relative to other anti-hypertensives.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** –Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (10 for, 4 opposed, 1 abstained, 2 absent) to recommend that aliskiren be classified as formulary on the UF. The four opposing votes were cast due to the opinion that there was insufficient evidence to recommend formulary placement; the one abstaining vote was due to the opinion that there was a lack of sufficient cost effectiveness compared to the ARBs. (See paragraph 5B on pages 20-23 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows: "On condition that active surveillance be initiated."

C. Nasal Corticosteroid – Fluticasone Furoate (Veramyst)

Background – The P&T Committee reviewed the nasal corticosteroid drug class in November 2005; fluticasone propionate (Flonase, generics), mometasone furoate (Nasonex), and flunisolide (Nasarel) were designated as formulary on the UF, while beclomethasone dipropionate (Beconase AQ, Vancenase AQ), budesonide (Rhinocort AQ), and triamcinolone (Nasacort AQ, Nasacort HFA) were classified as non-formulary. Fluticasone furoate is a new nasal corticosteroid that replaces the

propionate ester of fluticasone propionate with a furoate ester. *In vitro* claims of enhanced glucocorticoid receptor binding *in-vitro* have not translated into enhanced clinical effectiveness.

There is insufficient evidence to determine if there are clinically relevant differences between Veramyst and Flonase; one head-to-head trial in patients older than 12 years of age with SAR showed that Veramyst was not inferior to Flonase in terms of changes from baseline in Total Nasal Symptom Score. Veramyst's adverse effect profile appears similar to other nasal corticosteroids. The P&T Committee also evaluated differences in the delivery device, ease of administration, and particle size of Veramyst compared to other nasal corticosteroids, but did not find a unique advantage or disadvantage relative to fluticasone propionate or mometasone furoate.

Relative Clinical Effectiveness Conclusion: The DoD P&T Committee concluded (12 for, 0 opposed, 1 abstained, 4 absent) that:

> Fluticasone furoate has no clinically significant differences with respect to safety, efficacy, or tolerability, when compared to other nasal corticosteroids included on the UF.

Relative Cost Effectiveness Conclusion: The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that:

> Fluticasone furoate was not cost effective relative to the UF nasal corticosteroids.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of fluticasone furoate, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 1 abstained, 4 absent) to recommend that fluticasone furoate be classified as non-formulary under the UF. (See paragraph 5C on pages 23-25 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

2) ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** – Based on the clinical evaluation of fluticasone furoate and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) medical necessity criteria for the nasal corticosteroids. (See paragraph 5C on page 26 of the P&T Committee minutes for the criteria).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an

effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy (TRRx) network, and at military treatment facilities (MTFs) no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TRICARE Management Activity (TMA). Committee members directed that if operationally feasible, the $22 co-pay should start immediately upon signing of the minutes for new users; the $22 co-pay would go into effect after the 60-day implementation date for current fluticasone furoate users. (See paragraph 5C on page 26 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

4) ***COMMITTEE ACTION: QUANTITY LIMITS*** **-** The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend a QL for fluticasone furoate in the TRRx of 1 inhaler device per 30 days and a QL in the TMOP of 3 inhaler devices per 90 days. (See paragraph 5C on page 26 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

6) DRUG CLASS REVIEW – NEWER ANTIHISTAMINE (NA) DRUG CLASS

The P&T Committee evaluated the relative clinical effectiveness of the NA agents. The NA drug class includes the following agents: loratadine (Claritin, generics), acrivastine/ pseudoephedrine (Semprex-D), fexofenadine (Allegra, generics), cetirizine (Zyrtec), and desloratadine (Clarinex). The class also includes combinations of all of the single agent products with pseudoephedrine. As of June 2007, about three million Military Health System (MHS) prescriptions for these agents were filled annually. The NA drug class was ranked #5 in terms of expenditures ($178 million) in FY 2006 .

The brand-only agents in this class are desloratadine, acrivastine/pseudoephedrine and cetirizine. Loratadine and fexofenadine are available as generics. Loratadine is only available over-the-counter (OTC). Cetirizine is expected to become available OTC by the end of 2007 and generic cetirizine OTC products are expected to be marketed in the first quarter of calendar year 2008. Marketing for a very recently approved product, levocetirizine (Xyzal), is expected to begin in September/October of 2007.

Relative Clinical Effectiveness Conclusion **–** The P&T Committee concluded (14 for, 0 opposed, 1 abstained, 2 absent) that:

1) Based on randomized placebo-controlled trials, cetirizine, desloratadine and loratadine are more efficacious than placebo for the symptomatic relief of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU). Fexofenadine is more efficacious than placebo for the

symptomatic relief of SAR and CIU. Acrivastine/pseudoephedrine is more efficacious than placebo for the symptomatic relief of SAR.

2) Based on six comparative trials in adults with SAR, there is insufficient evidence to suggest that there are clinically significant differences between cetirizine, fexofenadine, and loratadine, or desloratadine and fexofenadine. There is insufficient evidence to compare any of the agents in children less than 12 years old with this condition.

3) For the treatment of PAR in adults, there is insufficient evidence to suggest clinically significant differences between the agents. In children 2 to 6 years old, limited evidence based on one fair/poor quality comparative trial suggests that cetirizine may be more efficacious than loratadine with PAR.

4) For the treatment of CIU in adults, limited evidence based on two poor quality comparative trial suggests suggest that loratadine may be more efficacious than cetirizine for total symptom score reductions (but not response time), and cetirizine may be more efficacious than fexofenadine. In children, only cetirizine has evidence of efficacy for the treatment of CIU in children, based on both an active- and placebo-controlled trial.

5) The NAs appear to have similar adverse effect profiles and to result in similar low rates of discontinuation due to adverse events in clinical trials. There do not appear to be any major disadvantages for any one agent with respect to drug-drug interactions.

6) No NA appears preferable in hepatic impaired, renal impaired and pediatric patients. Loratadine, cetirizine and acrivastine/pseudoephedrine are FDA pregnancy category B, while desloratadine, fexofenadine and the combination products containing pseudoephedrine are FDA pregnancy category C.

7) All the parent products have multiple dosage forms and a pseudoephedrine-containing combination product.

8) It is likely that at least one NA is needed for adequate clinical coverage, based on provider responses regarding prescribing practices and likely patient response.

9) Loratadine has been identified as a candidate drug for the DoD OTC Demonstration Program.

Cost Effectiveness Conclusion – The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) Desloratadine and desloratadine/pseudoephedrine were not cost effective relative to other comparable agents in the newer antihistamine class.

2) The UF scenario that placed desloratadine and desloratadine/pseudoephedrine as non-formulary was the most cost effective scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the NAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to

recommend the following. (See paragraph 6C on page 33 of the P&T Committee minutes.)

1) Fexofenadine, fexofenadine/pseudoephedrine, cetirizine, cetirizine/ pseudoephedrine , and acrivastine/pseudoephedrine should be maintained as formulary on the UF.
2) Desloratadine and desloratadine/pseudoephedrine should be classified as non-formulary under the UF.
3) Loratadine and loratadine/pseudoephedrine should be added to the UF for purposes of the TRICARE OTC Demonstration Program.
4) At such time as cetirizine and cetirizine/pseudoephedrine are made available OTC, both products should be maintained on the UF for purposes of the TRICARE OTC Demonstration Program.
5) Desloratadine and desloratadine/pseudoephedrine should be reclassified as generic on the UF when the generic products are available and cost effective relative to similar agents in the newer antihistamine class.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for desloratadine and desloratadine/pseudoephedrine, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for desloratadine and desloratadine/pseudoephedrine. (See paragraph 6D on page 34 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period in the TMOP and TRRx, and no longer than a 90-day implementation period at MTFs. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 6E on page 34 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BASIC CORE FORMULARY (BCF) RECOMMENDATION – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and

2 absent) to recommend that the current BCF listing for this class be maintained, requiring each MTF to carry at least one single ingredient agent from the NA class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use. (See paragraph 6F on page 34 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

7) DRUG CLASS REVIEW – LEUKOTRIENE MODIFIERS (LMs)

The P&T Committee evaluated the relative clinical effectiveness of the LM agents. The LM class is comprised of two leukotriene receptor antagonists, montelukast (Singulair) and zafirlukast (Accolate); and one 5-lipoxygenase inhibitor, zileuton (Zyflo). A controlled release formulation of zileuton (Zyflo CR) has been approved by the FDA, but is not yet commercially available.

Currently montelukast is the only BCF LM agent. None of the LMs are available in a generic formulation. The LM drug class accounted for $101 million dollars in MHS expenditures in FY 2006, and is ranked #16 in terms of total expenditures during that time period. Over 97% of the utilization is for montelukast; from June 2006 to May 2007, there were over 300,000 montelukast utilizers in the MHS, over 3,000 zafirlukast utilizers and only 300 zileuton utilizers.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (14 for, 0 opposed, 0 abstained, 3 absent) to accept the following clinical effectiveness conclusion:

a) For the treatment of asthma, National Heart, Lung and Blood Institute National Asthma Education Prevention Program guidelines include LMs as an alternative, but not preferred therapy. LMs are more effective than placebo in controlling asthma symptoms, but are less effective than inhaled corticosteroids (ICS), and are less effective when added on to long-acting beta agonist (LABA) vs. use of a LABA with ICS. Addition of a LM to ICS provides modest benefit over use of the ICS as monotherapy.

b) In placebo-controlled trials for asthma, the three LMs montelukast, zafirlukast, and zileuton demonstrate clinical effectiveness in endpoints such as reduction in exacerbations, improvements in forced expiratory volume in 1 second (FEV1), asthma symptoms scores and short acting beta-agonist use. There is insufficient evidence to determine whether one LM is more efficacious at controlling asthma symptoms than another.

c) Limited evidence suggests that LMs may permit a reduced ICS dose, or could be used in patients resistant to or unable to tolerate inhaled steroids. The extent or clinical significance of this “steroid sparing” effect is uncertain.

d) Montelukast is the only LM that is FDA approved for the treatment of allergic rhinitis (AR), and is specifically approved for both SAR and PAR. There are a few small clinical trials that evaluate zafirlukast in the treatment of allergic

rhinitis, but they fail to consistently show efficacy. There is no data to support the use of zileuton in AR.

e) For AR, meta-analyses show that LMs are superior to placebo in clinically relevant AR endpoints such as rhinitis symptom scores and rhinoconjunctivitis quality of life scores; however, the treatment effect is modest. When compared to antihistamines, the LMs show relatively similar efficacy. Nasal corticosteroids (NCS) are clinically superior to montelukast in all clinical endpoints studied. Combinations of an LM with an antihistamine are modestly more effective than either agent alone, but not superior to NCS in improving nasal symptoms of AR.

f) In the pediatric population, montelukast is approved for use in SAR in children age two years and older, and for PAR in age 6 months and older. However, published clinical trial data is limited in the pediatric population, and is primarily based on safety. In two studies in children with PAR, montelukast was less efficacious than cetirizine in most of the endpoints studied.

g) In regard to safety and tolerability, zileuton has been associated with hepato-toxicity, requires liver function test monitoring, and is contraindicated in patients with active liver disease. Zafirlukast has also been associated with hepatotoxicity including liver failure and death; however, this data is from spontaneously reported adverse event reports and must be interpreted cautiously. Zafirlukast and zileuton are associated with more clinically significant drug interactions than montelukast.

h) In regard to other factors, montelukast has the advantage of a greater number of FDA approved indications, pediatric indications, less frequent dosing (once daily versus twice and four-times daily for zafirlukast and zileuton), and availability of alternative dosage formulations.

i) Overall, based on clinical issues alone, montelukast is preferred over zafirlukast, which in turn is preferred over zileuton.

Relative Cost Effectiveness Conclusion – the P&T Committee concluded (14 for, 0 opposed, 1 abstained, and 2 absent) that:

a) Zafirlukast was the least costly agent in the class; montelukast was more costly relative to zafirlukast but provided additional indications, a better adverse event profile, multiple dosage forms, and more evidence in pediatrics than the other agents in the class; zileuton was not cost effective relative to the other products.

b) LMs are not cost effective in the treatment of AR relative to antihistamines and nasal corticosteroids and should not be considered as first-line therapy in the treatment of AR.

c) The Committee concluded that the UF scenario that placed zafirlukast and montelukast on formulary with a step therapy/prior authorization (PA) program required for use in AR was the scenario that resulted in the lowest expected expenditures in the LM class.

A. COMMITTEE ACTION: STEP THERAPY RECOMMENDATION – Although the committee agreed that the LMs are not cost effective for AR, the Committee

voted (6 for, 8 opposed, 1 abstained, and 2 absent) against enacting a step therapy/PA policy for use of LMs in the management of AR. Similar policies have recently been initiated with other drug classes in the MHS and the Committee felt that the most prudent course of action at this time was to delay enacting another step therapy/PA policy. Instead, the PEC will gather additional evidence about the effect of the other step therapy/PA policies recently implemented in the MHS while educating MTF providers to minimize the use of LMs for the management of AR. The PEC will also monitor utilization in the LM class. If the use of LMs for AR continues to proliferate, the Committee will review the class again to determine if further action is required. (See paragraph 7C on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows: "ASD(HA) urges that these patients be followed re: possible CV +/or oncologic benefits or AE's."

B. ***COMMITTEE ACTION: UF RECOMMENDATION*** – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the LMs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that zafirlukast and montelukast be maintained as formulary on the UF and that zileuton be classified as non-formulary under the UF. (See paragraph 7D on page 43 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation for zileuton and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for zileuton. (See paragraph 7E on pages 43-44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and no later than a 90-day implementation period at MTFs. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 7F on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: BCF RECOMMENDATION – The P&T Committee considered the BCF status of the LM agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 1 opposed, 1 abstained, and 2 absent) to recommend that montelukast be retained on the BCF (specific formulations include tablets, chewable tablets, and oral granules). (See paragraph 7G on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

8) DRUG CLASS REVIEW – GROWTH STIMULATING AGENTS (GSAs)

The P&T Committee evaluated the relative clinical effectiveness of the GSAs. This class is divided into two subclasses: growth hormone (GH) agents (somatropin products) and insulin-like growth factor-1 (IGF-1) agents (mecasermin). The GSA drug class accounted for about $23 million in MHS expenditures in FY 2006.

This class of drugs includes only two molecular entities, somatropin and mecasermin. There are multiple competing somatropin products. The majority of these are indicated for the treatment of GH deficiency (GHD), which is the most common use. Mecasermin is an orphan drug approved by the FDA in 2005 to treat severe primary insulin-like growth factor deficiency (IGFD), which affects a very small number of patients (about 6,000 in the United States).

Relative Clinical Effectiveness Conclusion: The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that:

a) Somatropin products appear to be safe and efficacious for the treatment of various growth-related conditions and for a few specialized non-growth related conditions.

b) There are no studies comparing any somatropin product to another for any given indication. Given that all of the products contain the same concentration (3 IU rhGH/mg) of bioidentical recombinant human GH, they are unlikely to differ in efficacy for the treatment of growth-related or other disorders.

c) There are potential differences between somatropin products with respect to delivery devices, formulations, and stability/storage requirements. Differences that may favor particular products include availability of a pen device (preferably along with a vial/syringe product); the ability to use the pen device without having to do dose conversions, and the ability to store products at room temperature before or after initial use.

d) Mecasermin is safe and efficacious for severe IGFD, a much rarer condition than GHD. It is the only product available for the treatment of this condition.

e) Based on clinical issues alone, there are no compelling reasons to classify any of the GSA agents as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: the P&T Committee concluded (15 for, 0 opposed, 0 abstained, and 2 absent) that:

a) Mecasermin (Increlex) and two somatropin products (Zorbtive and Serostim) have a specific niche in therapy and offer sufficient value on a cost/mg basis relative to the other agents within the therapeutic class.

b) Tev-Tropin was the most cost effective somatropin agent based on cost minimization analysis. However, the product offers fewer features than most other growth stimulating agent product lines.

c) Two somatropin product lines, Norditropin and Nutropin, offered more features (pen dosage forms, storage at room temperature, and ease of use) at a middle range of cost.

d) The budget impact analysis results showed that the most cost effective formulary strategy for the somatropin products was the combination of the Tev-Tropin and the Norditropin and Nutropin product lines.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the GSAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend that Tev-Tropin, Nutropin, Nutropin AQ, Norditropin, Nortropin Nordiflex, Serostim, Zorbtive, and Increlex be maintained as formulary on the UF and that the Genotropin, Humatrope, Saizen and Omnitrope brands of somatropin be classified as non-formulary under the UF. (See paragraph 8C on page 57 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) MN criteria for the somatropin products Genotropin, Humatrope, Saizen and Omnitrope. (See paragraph 8D on page 57 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) an effective date of the first Wednesday following a 60-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 8E on pages 57-58 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: PA CRITERIA – Currently, PA criteria apply to both GH (somatropin products) and mecasermin (Increlex). The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) PA criteria for GH (somatropin products) and mecasermin (Increlex). Changes from previous GH (somatropin) criteria are the addition of Noonan's Syndrome and Short Stature Homeobox gene (SHOX) deficiency as covered uses; no changes were recommended to mecasermin criteria. (See paragraph 8F on pages 58-59 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: EXTENDED CORE FORMULARY (ECF) RECOMMENDATION – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 1 abstained, and 3 absent) to recommend that Norditropin and Norditropin / Nordiflex be added to the ECF. (See paragraph 8G on page 59 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

9) QUANTITY LIMITS

A. COMMITTEE ACTION: QL FOR RIZATRIPTAN (MAXALT) – The Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend changing the QL for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) to 12 tablets per 30 days, or 36 tablets per 90 days. (See paragraph 9A on page 59 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

10) BCF STATUS OF ROSIGLITAZONE

The PEC updated the P&T Committee on the two recent alerts issued by the FDA regarding rosiglitazone (Avandia). The P&T Committee discussed the advantages and disadvantages of removing rosiglitazone from the BCF. Ultimately, the P&T Committee determined that there was insufficient clinical evidence to justify removal of rosiglitazone from the BCF at this time. The PEC will update the P&T Committee as more

information becomes available. (See paragraph 10 on pages 59-60 of the P&T Committee minutes.)

***COMMITTEE ACTION*:** The Committee voted (7 for, 6 opposed, 1 abstained, 3 absent) to retain rosiglitazone on the BCF at this time.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

11) BCF / ECF REVIEW

The P&T Committee agreed with a plan to systematically review drug classes represented on the BCF and ECF over the next few meetings with the goals of: 1) removing obsolete medications, 2) defining BCF listings more specifically, 3) reframing or revising BCF listings to be compatible with drug classes as defined or outlined by the P&T Committee, and 4) assessing the need for future review.

The P&T Committee made initial recommendations for clarifying BCF listings in three drug classes or potential drug classes, including atypical antipsychotics (quetiapine and risperidone), osteoporosis agents (alendronate / vitamin D), and cough-cold medications (guaifenesin/pseudoephedrine).

COMMITTEE ACTION: The P&T Committee recommended the following changes to BCF / ECF listings. (See paragraph 11 on page 60 of the P&T Committee minutes and Appendix C).

Drug class or potential drug class	Current BCF / ECF listing	Recommendation	Vote			
			For	Opposed	Abstained	Absent
Atypical antipsychotics	BCF – "Quetiapine"	Clarify BCF listing to: "quetiapine tablets, immediate and extended release"	14	0	1	2
	BCF – "Risperidone oral; does not include orally disintegrating tablets (Risperdal Redi-tabs)"	Clarify BCF listing to: "Risperidone tablets and solution, does not include orally disintegrating tablets"	14	0	1	2
Osteoporosis agents	BCF – "Alendronate 70 mg / vitamin D 2800 IU (Fosamax Plus D)"	Clarify BCF listing to specify new product with higher strength of vitamin D – "Alendronate 70 mg/vitamin D 5600 IU tablets"	14	0	1	2
Cough-cold medications	BCF – "Guaifenesin 600 / PSE 120 mg ER oral"	Remove from BCF	14	0	1	2

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

Appendix A – Implementation Status of UF Recommendations/Decisions
Appendix B – Newly Approved Drugs
Appendix C – BCF Review
Appendix D – Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____// signed // _____

S. Ward Casscells, III, M.D.
17 October 2007

Department of Defense
Pharmacy and Therapeutics Committee Minutes
August 2007

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 14-15 Aug 2007 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
LTC Brett Kelly, MSC, USA	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Capt Jeremy King, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Col Everett McAllister, BSC	Air Force, Pharmacy Officer
LCDR Ronnie Garcia, MC *for* LCDR Michelle Perrelló, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatrics Physician Alternate
CDR David Tanen, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
COL Karl R. Kerchief, MC	Army, Family Practice Physician
LTC Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino, RPh.	Department of Veterans Affairs

B. Voting Members Absent

Lt Col Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
COL Ted Cieslak, MC	Army, Physician at Large

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CDR Kim Lefebvre, MSC	Defense Supply Center Philadelphia
Major Pete Trang, BSC, USAF	Defense Supply Center Philadelphia
Mr. Howard Altschwager	Assistant General Counsel, TMA
LT Thomas Jenkins, MSC, USN	TMA Aurora

D. Non-Voting Members Absent

Martha Taft	Health Plans Operations, TMA

E. Others Present

Col Nancy Misel, BSC, USAF	IMA DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
LTC Chris Conrad, MC, USA	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
Shana Trice, Pharm.D.	DoD Pharmacoeconomic Center
David Bretzke, Pharm.D.	DoD Pharmacoeconomic Center
Angela Allerman, Pharm.D.	DoD Pharmacoeconomic Center
Eugene Moore, Pharm.D.	DoD Pharmacoeconomic Center
Julie Liss, Pharm.D.	DoD Pharmacoeconomic Center
Elizabeth Hearin, Pharm.D.	DoD Pharmacoeconomic Center
David Meade, Pharm.D.	DoD Pharmacoeconomic Center
Harsha Mistry, Pharm.D.	DoD Pharmacoeconomic Center
Todd Semla, Pharm.D.	VAPBM
Bill Coffenberry	TMA Contracting
Brenda Agner	TMA Contracting
Beth Spearman	TMA/POD
CDR Michael J. Contos	USPHS, IHS

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – May 2007 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. Approval of May Minutes – Dr. Samuel Ward Casscells, III., M.D., approved the minutes of the May 2007 DoD P&T Committee meeting on 24 July 2007.

4. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss briefed the members of the P&T Committee regarding the June 2007 BAP meeting. The P&T Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions – The PEC briefed the members of the P&T Committee on the progress of implementation for drug classes reviewed for UF status since February 2005.

C. Status of Newer Sedative Hypnotic Agents (SED-1) Step Therapy Program – The PEC briefed the members of the P&T Committee on a preliminary analysis of the SED-1 Step Therapy Program. The analysis examined the first week of SED-1 transactions (1 – 7 August) following the 1 August 2007 implementation date. During the observation period, 23,790 patients submitted a prescription for a SED-1. A total of 1,592 patients had claims stopped by the Step Therapy Program's automated profile review (APR) process. Of these patients, 771 (48%) subsequently received a SED-1 prescription through 10 August. This represents a window as short as 3 days and is unlikely to be a fair assessment of the Step Therapy Program; the PEC will continue to monitor as more data becomes available. Of patients who subsequently received a SED-1 prescription, 576 (75%) received the preferred product, Ambien IR.

D. Status of Fentanyl Patch Safety Program/Prior Authorization (PA) - The PEC briefed the members of the P&T Committee on a preliminary analysis of the Fentanyl Patch Safety Program. The analysis examined the first week of fentanyl patch transactions (1 – 7 August) following the 1 August 2007 implementation date. During the observation period, 2,732 patients submitted a fentanyl patch prescription. A total of 314 patients had claims stopped by the APR process. Of these patients, 255 (81%) subsequently received a fentanyl patch prescription and 59 (19%) did not, through 10 August (minimum 3-day window). Approximately 11% of patients (314/2732) were affected by the Fentanyl Patch Safety Program.

E. Administrative Actions – Modification of Medical Necessity (MN) Criteria for Duloxetine (Cymbalta) and Pregabalin (Lyrica) – Both of these medications recently gained U.S Food and Drug Administration (FDA) approval for new indications: duloxetine for the treatment of generalized anxiety disorder (February 2007) and pregabalin for the treatment of fibromyalgia (June 2007). MN criteria for these two non-formulary medications are interrelated, since duloxetine also has clinical evidence supporting efficacy in fibromyalgia. The PEC obtained input from members of the P&T Committee regarding the best way to make changes to the MN criteria for these two medications. Changes to MN criteria will be made administratively.

- *Duloxetine for Generalized Anxiety Disorder (GAD)* – Current duloxetine MN criteria allow for the use of the non-formulary serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine in patients treated for depression or other psychiatric illnesses who require treatment with an SNRI (e.g., due to failure of selective serotonin reuptake inhibitor [SSRI] therapy) and who have failed an adequate trial, been unable to tolerate, or have contraindications to the SNRI venlafaxine, which is on the UF. Both venlafaxine and duloxetine are FDA-approved for the treatment of GAD; other medications are FDA-approved either for GAD (e.g., paroxetine, escitalopram) or anxiety in general (e.g., buspirone, lorazepam, alprazolam), or have clinical evidence supporting their use (e.g., sertraline). Based on the results of one head-to-head trial [Hartford et al, 2007] and indirect evidence from placebo-controlled trials with duloxetine and venlafaxine, there is insufficient evidence to conclude that either agent is safer or more efficacious for the treatment of GAD; more clinical evidence is available for venlafaxine. Accordingly, the P&T Committee agreed that the MN criteria were adequate as stated.
- *Pregabalin for Fibromyalgia* – Fibromyalgia is a poorly understood, multifactorial condition that is diagnosed based on a history of widespread pain (bilateral, upper & lower body, spine) and often accompanied by fatigue, difficulty sleeping, and depression. American College of Rheumatology (ACR) criteria, which are based on the presence of excessive tenderness on applying pressure to 11 of 18 specific muscle-tendon sites, appear to be about 85% sensitive and specific for fibromyalgia. Prevalence in the U.S. is about 2% (3.4% women, 0.5% men).

  A 2004 American Pain Society guideline advises a stepwise approach to the treatment of fibromyalgia, including early evaluation and treatment of comorbid conditions (e.g., mood and sleep disturbances), an exercise program, and cognitive behavior therapy. The recommended sequence of drug treatment corresponds to the strength of clinical evidence available to guideline authors. It includes an initial trial of a low-dose tricyclic antidepressant (TCA) or cyclobenzaprine (a muscle relaxant structurally similar to the TCAs), which are considered to be supported by strong clinical evidence, followed by subsequent trials of SSRIs, SNRIs, or tramadol (modest evidence), and possible consideration of combination therapy or use of an anticonvulsant. None of these medications are FDA-approved for the treatment of fibromyalgia; pregabalin is the first medication with this FDA indication.

  Clinical trials evaluating pregabalin for the treatment of fibromyalgia include four randomized controlled trials (RCTs) and three open-label studies (based on information supplied by the manufacturer). One 14-week trial (n = 1077) compared three doses of pregabalin (300, 450, or 600 mg/d) to placebo for 14 weeks, resulting in a significant reduction in the mean pain score of about 1 point on an 11-point scale (0-10) compared to placebo [300 mg/d -0.71; 450 mg/d -0.98; 600 mg/d -1.00]. Withdrawals due to adverse effects were substantially higher with pregabalin than placebo and appeared to be dose-related [300 mg/d 16%; 450 mg/d 22%, 600 mg/d 26%; placebo 12%). Pregabalin was also

compared to placebo in a 6-month randomized withdrawal study (n=566). Significantly more patients on placebo had lost clinical response at endpoint (61%) compared to those on pregabalin (32%). The other two trials consist of a 13-week RCT, which reported about a 0.7 point reduction in endpoint mean pain score with 600 mg/d of pregabalin, compared to placebo ($p<0.05$), and an 8-week trial comparing 150-, 300-, or 450 mg/d of pregabalin to placebo that showed a significant reduction in mean pain score only for the 450 mg/d dose. The latter was not included as part of the FDA approval process; it is the only trial currently published [Crofford et al, 2006].

A small (n=75) placebo-controlled 12-week RCT evaluating gabapentin (a formulary anticonvulsant medication similar to pregabalin) for the treatment of fibromyalgia was recently published [Arnold et al, 2006]. The trial reported significantly greater improvements with gabapentin (1200 – 2400 mg/d) than with placebo at endpoint; results were not inconsistent with those reported during pregabalin trials. However, given the size of the trial and the lack of any comparative evidence, there is probably insufficient evidence to draw any conclusion regarding the relative efficacy or safety of pregabalin or gabapentin for the treatment of fibromyalgia; more clinical evidence is available for pregabalin.

The P&T Committee agreed that pregabalin should be considered medically necessary for patients diagnosed with fibromyalgia based on established criteria (e.g., ACR criteria) who have failed an adequate trial, been unable to tolerate, or for whom treatment with TCAs or cyclobenzaprine is contraindicated or clinically inappropriate (e.g., due to potential cardiac effects).

Duloxetine for Fibromyalgia – Although duloxetine is not FDA-approved for fibromyalgia, its use is supported by two placebo-controlled RCTs [Arnold et al, 2004; Arnold et al, 2005]. Results are not inconsistent with those reported during pregabalin trials, although there is probably insufficient evidence to draw any conclusion regarding relative efficacy or safety of the two agents for the treatment of fibromyalgia. Duloxetine's therapeutic effect in fibromyalgia is most likely due to a distinctly different mechanism than pregabalin and likely includes effects on comorbid conditions, such as depression and anxiety, as well as pain.

Current MN criteria for duloxetine allow for its use in patients who have failed an adequate trial, been unable to tolerate, or for whom treatment with at least one medication from at least two of the following four drug classes is contraindicated or clinically inappropriate: TCAs (e.g., amitriptyline); tricyclic muscle relaxants (cyclobenzaprine); SSRIs (e.g., fluoxetine); or opioids (e.g., tramadol). The P&T Committee agreed that, given the evidence for pregabalin and its recent FDA approval for this indication, duloxetine MN criteria should be changed accordingly. At the same time, the P&T Committee agreed that SSRIs and opioids should be dropped from MN criteria due to inconsistent clinical evidence supporting the use of SSRIs for fibromyalgia and the overly broad definition of opioids. The P&T Committee agreed that duloxetine should be considered medically necessary for patients diagnosed with fibromyalgia based on established criteria (e.g., ACR criteria), who have failed an adequate trial, been

unable to tolerate, or for whom treatment with both TCAs or cyclobenzaprine AND pregabalin is contraindicated or clinically inappropriate.

F. Administration Action – Modification of Mecasermin PA Criteria – The PEC reported an administrative change to mecasermin PA criteria to remove references to mecasermin rinfabate (Iplex) following its withdrawal from the market due to the outcome of litigation. Increlex is now the only mecasermin product on the market. The manufacturer of Iplex will continue to develop it for non-short stature indications (e.g., myotonic muscular dystrophy, Lou Gehrig's disease, HIV-associated adipose redistribution syndrome, and retinopathy of prematurity), but it is likely to be some time before data are available.

G. Statin Budget Impact Analysis (BIA) Review – The P&T Committee reviewed the performance of the Antilipidemic-1 (LIP-1) budget impact model used to estimate the outcome of potential formulary scenarios. The review compared actual Military Health System (MHS) pharmaceutical expenditures to the predicted expenditures that were reported at the August 2006 P&T meeting for the LIP-1 drug class. Data were collected for two quarters following UF implementation in January 2007. The results were compared directly and reported as a percent deviation from the actual values.

Study results showed that the model performed adequately during the first two quarters following the implementation date. The largest departure from actual spending occurred at the military treatment facility (MTF) point of service primarily because of conservative assumptions made about the price of generic simvastatin. The analysis assumed modest reductions in price for simvastatin after generic entry but in actuality the price fell more rapidly then what was predicted. More data will be collected in the future to determine if model performance is sustained. Furthermore, several findings from this review will be incorporated into future budget impact models to improve the validity and reliability of model results.

5. REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on four new drugs which were approved by the FDA (see Appendix B). The P&T Committee determined that these four new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed. The P&T Committee discussed the need for quantity limits (QLs) for budesonide/formoterol (Symbicort) oral inhaler, based on existing QLs for other oral inhalation products and recommendations for use in product labeling.

COMMITTEE ACTION: QUANTITY LIMITS

The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend QLs for budesonide/formoterol of 1 inhaler per 30 days, 3 inhalers per 90 days.

B. Renin Angiotensin Antihypertensive – Aliskiren (Tekturna)

1) Aliskiren Relative Clinical Effectiveness – The DoD P&T Committee evaluated the clinical effectiveness of aliskiren, a new direct renin inhibitor. Aliskiren is classified as a renin angiotensin antihypertensive agent (RAA). The RAA drug

class was defined at the May 2007 DoD P&T Committee meeting, and includes the following categories of drugs:

- *Angiotensin Receptor Blockers (ARBs) - May 2007*
  - **UF/Basic Core Formulary (BCF)**: telmisartan (Micardis), telmisartan/ hydrochlorothiazide (HCTZ) (Micardis HCT)
  - **UF:** candesartan (Atacand), candesartan HCTZ (Atacand HCT), losartan (Cozaar), losartan/HCTZ (Hyzaar)
  - **Non-Formulary**: eprosartan (Teveten), eprosartan/HCTZ (Teveten HCT), irbesartan (Avapro), irbesartan/HCTZ (Avalide), olmesartan (Benicar), olmesartan/HCTZ (Benicar HCT), valsartan (Diovan), valsartan/HCTZ (Diovan HCT)
- *ARB/Calcium Channel Blockers – February 2006*
  - **UF/BCF:** benazepril/amlodipine (Lotrel, generics)
  - **Non-Formulary:** enalapril/felodipine (Lexxel), trandolapril/verapamil sustained release (Tarka)
- *Angiotensin Converting Enzyme (ACE) inhibitors – August 2005*
  - **UF/BCF:** lisinopril (Prinivil, Zestril, generics), lisinopril/HCTZ (Prinzide, Zestoretic, generics), and captopril (Capoten, generics)
  - **UF**: captopril/HCTZ (Capozide, generics), benazepril (Lotensin, generics), benazepril/HCTZ (Lotensin HCT, generics), enalapril (Vasotec, generics), enalapril/HCTZ (Vasoretic, generics), fosinopril (Monopril, generics), fosinopril/HCTZ (Monopril-HCT, generics), trandolapril (Mavik)
  - **Non-Formulary:** ramipril (Altace), quinapril (Accupril, generics), quinapril/HCTZ (Accuretic, generics), perindopril (Aceon), moexipril (Univasc, generics), moexipril/HCTZ (Uniretic, generics)

Pharmacology – Aliskiren is the first direct oral renin inhibitor marketed in the U.S. It decreases plasma renin activity and inhibits the conversion of angiotensinogen to angiotensin I. The correlation between decreased plasma renin activity and improved clinical outcomes is unclear.

Efficacy Measures – Clinical trials evaluating efficacy of aliskiren (typically 8 weeks in duration) have only assessed blood pressure (BP) reductions as the primary endpoint. Clinical trials have included patients with mild to moderate hypertension (mean diastolic BP 95-110 mm Hg); patients with severe hypertension have been excluded from clinical trials, along with patients with severe cardiac disease or renal impairment.

Efficacy Results – A pooled analysis from eight randomized trials reported mean reductions in seated BP with aliskiren 150 mg of 8.7-12/7.8-10.2 mm Hg and with aliskiren 300 mg of 14.1-15.9/10.3-12.3 mm Hg (not placebo adjusted). Aliskiren has been compared to ARBs (irbesartan, losartan and valsartan), diuretics (HCTZ) and the ACE inhibitor ramipril, as monotherapy and as combination therapy.

Overall, BP reductions with aliskiren were dose-related and were similar to that seen with the other drugs used as monotherapy; combination therapy produced additional BP reductions.

Outcomes Trials – Outcomes trials are currently underway, but results are not yet available. Trials are evaluating efficacy and safety of aliskiren in heart failure, post-myocardial infarction, diabetic nephropathy, left ventricular hypertrophy, diabetes, and metabolic syndrome. Initial results are expected in November 2007 for a study evaluating change in urinary albumin to creatinine ratio with aliskiren compared to losartan plus placebo (AVOID study) and a study evaluating reductions in brain natiuretic peptide in patients with hypertension and stable heart failure (ALOFT).

Safety – Available clinical data suggest that aliskiren most closely resembles an ARB in terms of adverse effects. Angioedema and hyperkalemia have been reported. Pooled data from clinical trials reported a discontinuation rate due to adverse effects of 2.2% with aliskiren vs. 3.5% with placebo. Dose-related diarrhea is the most common adverse effect. Clinically, aliskiren does not appear to inhibit or induce cytochrome P450 (CYP450) enzymes. Drug interactions have been reported with furosemide (decreased diuretic blood concentrations), and ketoconazole (increased aliskiren concentrations).

Place in Therapy – The exact place in therapy for aliskiren for treating hypertension is unknown at this time. Although aliskiren is indicated for use as monotherapy, it will likely be used as adjunctive therapy with other antihypertensive drugs (e.g., ACE inhibitors, ARBs, diuretics). A potential role for aliskiren would be in patients requiring double blockade of the renin-angiotensin aldosterone system; clinical trials with an ACE inhibitor plus an ARB in both heart failure and in patients with diabetic renal disease have suggested benefit; aliskiren could potentially be substituted for the ACE inhibitor in these settings.

Clinical Effectiveness Conclusion – The DoD P&T Committee concluded that:

a) Aliskiren is a new antihypertensive agent with a novel mechanism of action as a direct renin inhibitor.

b) Aliskiren's BP lowering effects are similar to those achieved with other antihypertensives, but it does not show improved efficacy compared to other classes of antihypertensive agents.

c) Combination therapy of aliskiren with ACE inhibitors, diuretics and ARBs has shown additive BP lowering effects compared to monotherapy with other antihypertensive agents.

d) Several other safe, once-daily, less costly antihypertensive drugs are available that have proven clinical outcomes (e.g., ACE inhibitors, ARBs, diuretics).

e) The long-term adverse event profile of aliskiren is unknown; diarrhea is the most commonly reported adverse event and the discontinuation rate is similar to placebo.

f) Clinical outcomes of aliskiren are unknown. Trials are underway, with initial results anticipated in November 2007.

The P&T Committee voted (14 for, 1 opposed, 0 abstained, 2 absent) to accept the clinical conclusions stated above. The one opposing vote was due to the opinion that there was insufficient clinical experience with aliskiren.

2) *Aliskiren Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of aliskiren in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly the ARBs. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

A cost minimization analysis (CMA) was employed to evaluate the cost effectiveness of aliskiren. The cost effectiveness of aliskiren was evaluated relative to ARBs, which were recently evaluated at the May 2007 DoD P&T Committee meeting.

The results of the CMA showed that the projected weighted average daily cost of aliskiren was higher than the weighted average daily cost of the ARBs designated as formulary on the UF.

Cost Effectiveness Conclusion – The P&T Committee concluded that:

> Although aliskiren was somewhat more costly relative to the ARBs designated as formulary on the UF, the P&T Committee was reluctant to designate aliskiren non-formulary at this time given its novel mechanism of action and the anticipated availability of clinical outcomes data that would enable the P&T Committee to more definitively asses its value relative to other antihypertensives.

The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to accept the cost effectiveness conclusions stated above.

3) *Aliskiren UF Recommendation*

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of aliskiren, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (10 for, 4 opposed, 1 abstained, 2 absent) to recommend that aliskiren be designated as formulary on the UF.

4) *Aliskiren MN Criteria* – Since aliskiren was not recommended for non-formulary status under the UF, establishment of MN criteria is not applicable.

5) *Aliskiren Implementation Plan* – Since aliskiren was not recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

C. Nasal Corticosteroid – Fluticasone Furoate (Veramyst)

1) *Fluticasone Furoate Relative Clinical Effectiveness* – The P&T Committee reviewed the nasal corticosteroid drug class in November 2005. Nasal corticosteroids on the UF include fluticasone propionate (Flonase, generics),

mometasone furoate (Nasonex) and flunisolide (Nasarel). Fluticasone propionate is classified as the BCF agent. The non-formulary nasal corticosteroid agents are beclomethasone dipropionate (Beconase AQ, Vancenase AQ), budesonide (Rhinocort AQ), and triamcinolone (Nasacort AQ, Nasacort HFA).

Pharmacology – Fluticasone furoate is a new nasal corticosteroid marketed by GlaxoSmithKline, the manufacturer of fluticasone propionate, which has been available in a generic formulation since February 2006. Veramyst is structurally different from Flonase in that fluticasone propionate ester has been replaced with fluticasone furoate ester. Fluticasone furoate is active as the intact molecule and is not a prodrug or alternative salt of fluticasone. The structural change is responsible for higher glucocorticoid receptor binding affinity. However, *in vitro* claims of enhanced receptor binding have not translated into improved clinical effectiveness.

FDA-Approved Indications – Both fluticasone furoate and fluticasone propionate are FDA-approved for treating symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children. Fluticasone furoate and mometasone are approved for use in children down to the age of 2 years, compared to 4 years with Flonase. In contrast to mometasone furoate, Veramyst is not currently approved for treatment of nasal polyps.

Efficacy – Efficacy assessment was based on the total nasal symptom score (TNSS), which was calculated based on the sum of a patient's score for four individual nasal symptoms (rhinorrhea, nasal congestion, sneezing, nasal itching). This was often reported as a reflective total nasal symptom score (rTNSS), which averages previous daytime and nighttime TNSSs over a certain time period.

Head-to-Head Trial-- There is insufficient evidence to determine if there are clinically relevant differences between fluticasone furoate and fluticasone propionate. One head-to-head trial in patients older than 12 years of age with SAR showed that fluticasone furoate was not inferior to fluticasone propionate in terms of changes from baseline in TNSS.

Placebo-Controlled Trials – FDA-approval of fluticasone furoate was based on six placebo-controlled trials.

a) In the trials enrolling adults with SAR (three studies) or PAR (one study), fluticasone furoate 110 mcg/day showed statistically significant improvement in rTNSS when compared to placebo.

b) In one study in children younger than 12 years with PAR, fluticasone furoate 55 mcg showed a statistically significant improvement in nasal symptom scores (rTNSS) compared to placebo; however there was no difference between placebo and Veramyst 110 mcg.

c) In the one pediatric study in patients with SAR, fluticasone furoate 110 mcg but not 55 mcg showed a statistically significant improvement in rTNSS compared to placebo.

Efficacy in Treating Ocular Symptoms – Nasal corticosteroids have not shown efficacy at reducing ocular symptoms of AR, in contrast to benefits seen with oral

antihistamines. With fluticasone furoate, although some improvements were noted in individual ocular symptoms evaluated as secondary endpoints (e.g., eye watering/tearing, eye itching/burning, and eye redness), there was no difference from placebo when reflective total ocular symptom score was evaluated as a primary endpoint.

Safety – The adverse event profile of fluticasone furoate is similar to other nasal corticosteroids. Common adverse events reported with fluticasone furoate included headache, epistaxis, and nasal ulceration. Administration of fluticasone furoate with ritonavir, a potent CYP3A4 inhibitor, is not recommended, due to the potential for increased systemic effects of fluticasone furoate.

Delivery Device – The Committee also evaluated differences in the delivery device, ease of administration, and particle size of fluticasone furoate compared to other nasal corticosteroids, but did not find a unique advantage or disadvantage relative to fluticasone propionate or mometasone furoate.

Clinical Effectiveness Conclusion – The DoD P&T Committee concluded that:

> Fluticasone furoate has no clinically significant differences with respect to safety, efficacy, or tolerability, when compared to other nasal corticosteroids included on the UF.

The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusion stated above.

2) *Fluticasone Furoate Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of fluticasone furoate in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

   A CMA was employed to evaluate the cost effectiveness of fluticasone furoate relative to the UF nasal corticosteroids. The results of the CMA showed that the projected weighted average daily cost of fluticasone furoate was significantly higher than weighted average daily cost of the UF nasal corticosteroids.

   Cost Effectiveness Conclusion – The P&T Committee concluded that:

   > Fluticasone furoate was not cost effective relative to the UF nasal corticosteroids.

   The P&T Committee voted (12 for, 0 opposed, 1 abstained, 4 absent) to accept the cost effectiveness conclusion stated above

3) *Fluticasone Furoate UF Recommendation*

   Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of fluticasone furoate, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 1 abstained, 4 absent) to recommend that fluticasone furoate be classified as non-formulary under the UF.

4) *Fluticasone Furoate MN Criteria* – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended maintaining the medical necessity criteria previously established for the nasal corticosteroid class. The following general MN criteria will be applied for fluticasone furoate:

   1) The use of formulary alternatives is contraindicated.

   2) The patient has experienced significant adverse effects from formulary alternatives.

   3) Formulary alternatives have resulted in therapeutic failure.

   COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

5) *Fluticasone Furoate Implementation Plan* – There have been approximately 650 prescriptions for fluticasone furoate in the MHS, all in the TRICARE Retail Pharmacy Network (TRRx), since market introduction. The Committee discussed the merits of a 60-day implementation period. Additionally, Committee members directed that if operationally feasible, the $22 co-pay should start immediately upon signing of the minutes for new users; the $22 co-pay would go into effect after the 60-day implementation date for current Veramyst users.

   COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. If determined to be operationally feasible, the $22 co-pay would start immediately upon signing of the minutes for new users; the $22 co-pay would go into effect after the 60-day implementation date for current Veramyst users.

6) *Fluticasone Furoate QL* – The P&T Committee evaluated the need for QLs for fluticasone furoate. QLs are in effect for other nasal corticosteroids. Based on both adults and pediatric dosing in manufacturer labeling for fluticasone furoate, the number of doses in an inhaler (120 metered doses), and QLs for other nasal corticosteroids, the P&T Committee recommended QLs for fluticasone furoate.

   COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for fluticasone furoate in the TRRx for 1 inhaler device per 30 days and in the TMOP for 3 inhaler devices per 90 days.

6. DRUG CLASS REVIEW – NEWER ANTIHISTAMINES (NAs)

The P&T Committee evaluated the relative clinical effectiveness of the NA agents. The NA drug class includes the following agents (listed in order of FDA approval): loratadine (Claritin, generics), acrivastine/pseudoephedrine (Semprex-D), fexofenadine (Allegra, generics), cetirizine (Zyrtec), and desloratadine (Clarinex). The class also includes combinations of all of the single agent products with pseudoephedrine. Loratadine (Claritin, generics), cetirizine (Zyrtec), and desloratadine (Clarinex) are FDA-

indicated for the treatment of SAR, PAR, and chronic idiopathic urticaria (CIU). Fexofenadine is indicated for the treatment of SAR and CIU. Acrivastine/ pseudo-ephedrine is only indicated for the treatment of SAR.

All of the NAs are classified as inverse agonists of the H_1-receptor; they act to stabilize the H_1-receptor in its inactive conformation. Histamine is the main inflammatory mediator involved in the development of the majority of the symptoms seen in conditions treated with NAs.

As of June 2007, about three million MHS prescriptions for these agents were filled annually. The NA drug class was ranked #5 in terms of expenditures ($178 million) in FY 2006 . Across the MHS, cetirizine is the most commonly prescribed NA, followed by fexofenadine then loratadine. Usage of desloratadine and pseudoephedrine combination products is low and stable, while usage of acrivastine/pseudoephedrine is rare.

The brand-only agents are desloratadine, acrivastine/pseudoephedrine and cetirizine. Loratadine and fexofenadine are available as generics. Loratadine is only available over-the-counter (OTC). Brand-name cetirizine is expected to become available OTC by the end of 2007 and generic cetirizine OTC products are expected to be marketed in the first quarter of calendar year 2008. Marketing for the newly FDA approved product, levocetirizine (Xyzal), is expected to begin in September/October of 2007. Levocetirizine was not included in the current review; it will be addressed at a future meeting.

A. NAs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the NAs currently marketed in the United States. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

Allergic rhinitis (AR) affects an estimated 20 to 40 million people in the United States. Multiple symptoms are associated with AR, including sneezing, itching, nasal congestion and rhinorrhea. These symptoms arise from different allergens comprised of pollens, molds, dust mites, and animal dander. Although AR is a term collectively used to define these symptoms, there are two different classifications, SAR or intermittent AR, and PAR or persistent AR.

SAR or “hay fever” is the rapid and reproducible onset and offset of symptoms in association with pollen exposure. PAR is more difficult to diagnose, because the symptoms of PAR overlap with symptoms of chronic sinusitis, upper respiratory infections and vasomotor rhinitis. Patients with PAR are affected with symptoms at least 9 months of a year. It is estimated that about 20% of the patients with AR suffer

from SAR, 40% from PAR, and 40% with both SAR and PAR (PAR with seasonal exacerbations).

CIU is defined as the occurrence of daily, or almost daily, wheals and itching for at least 6 weeks, with no obvious cause. CIU has not been the subject of detailed epidemiological studies. Published figures for frequency are confounded by uncertainty of the diagnosis, since the term "chronic idiopathic urticaria" is often taken to encompass physical urticarias. It has been estimated that about 0.1% of the population suffers from CIU, and 50% of these patients have symptoms for more than a year. Up to 20% of patients with symptoms greater than one year go on to have symptoms for 20 years or more. CIU is a major affliction causing serious disability.

1) *Efficacy*

The relative clinical effectiveness evaluation was based upon an evidence-based review of the clinical literature found in PubMed, Cochrane Library, National Guidelines Clearinghouse and reference lists of systematic review articles published through June 2007. In particular, this evaluation relied heavily upon the following sources: the Allergic Rhinitis and Its Impact on Asthma (ARIA) 2001 Guidelines and the draft 2007 update; the Agency for Healthcare Research and Quality 2002 Evidence and Technology Report/World Health Organization: Rhinitis; the European Dermatology Forum 2004 Consensus Statement: Urticaria; and the Oregon Drug Effectiveness Review Project (DERP) 2004 and 2006 Drug Class Review.

a) Seasonal Allergic Rhinitis

Adults

The Committee concluded that for the treatment of SAR in adults that there was insufficient evidence to suggest clinically significant differences in efficacy between fexofenadine, loratadine and cetirizine or desloratadine and fexofenadine. There is insufficient evidence to compare acrivastine/ pseudoephedrine to the other agents in the treatment of SAR.

Five head-to-head comparative trials assessed the efficacy of various NAs in the treatment of SAR in adults. The trials varied in country, season, and baseline characteristics of patients. These trials demonstrated no statistically significant difference between agents in total symptom score (TSS) change from baseline between cetirizine versus loratadine, cetirizine versus fexofenadine, or loratadine versus fexofenadine. The trials were too heterogeneous for meta-analysis. A recent head-to-head trial [Berger 2006] compared the efficacy of desloratadine and fexofenadine to placebo in patients with SAR. Results showed that both agents provided comparable efficacy, and were more effective than placebo. In the trial, subjects were randomized to desloratadine 5 mg, fexofenadine 180 mg once daily, or placebo. Mean daytime instantaneous TSS was significantly reduced from baseline by 28% with desloratadine, $p = 0.006$ and by 27% with fexofenadine, $p = 0.024$ versus placebo. The between agent mean TSS reduction was not statistically different ($p = 0.491$).

Children

There is insufficient evidence to suggest any clinical significant differences in efficacy in the treatment of SAR in children ≤ 12 years. There were no head-to-head comparative trials identified for children with SAR. Placebo and active controlled trials demonstrated that cetirizine, fexofenadine, and loratadine were more effective than placebo.

b) Perennial Allergic Rhinitis

Adults

The committee concluded that for the treatment of PAR in adults there is insufficient evidence to suggest clinically significant differences between the agents. Desloratadine has shown efficacy in the treatment of PAR in adults in a placebo-controlled trial, while loratadine has shown efficacy compared to placebo in an active-controlled trial that also included the older antihistamine clemastine. There were no head-to-head trials of sufficient quality identified for adults with PAR.

Children

There is insufficient evidence to suggest any clinically significant differences in efficacy in the treatment of PAR in children ≤ 12 years. There was one head-to-head comparative trial for loratadine versus cetirizine. The parent assessment results of this 4-week trial in 80 children, ages 2 to 6, showed cetirizine to be more effective than loratadine ($p < 0.001$) in relieving nasal symptoms associated with PAR. However, the global evaluation score by investigator showed no statistically significant difference. Placebo- and active-controlled trials for cetirizine and a placebo-controlled trial for loratadine showed the agents to be more effective than placebo in the treatment of PAR.

c) Chronic Idiopathic Urticaria

Adults

For CIU, the P&T Committee concluded that limited evidence suggests loratadine may be more effective than cetirizine and that cetirizine may be more effective than fexofenadine in adults.

Two fair quality head-to-head trials in adults with CIU were identified. One trial reported that loratadine 10 mg QD was more effective ($p<0.01$) in reducing TSS than cetirizine 10 mg QD or placebo [loratadine -81%, cetirizine -69%, placebo -55%]. There was no statistically significant difference in response rate between the two active agents [loratadine 63% vs. Cetirizine 45%, placebo 13%]. The other comparative trial reported that cetirizine 10 mg QD was more effective (p-value not reported) than fexofenadine 180 mg QD in symptom-free patients [cetirizine 51.9% vs. Fexofenadine 4.4%].

Children

Only cetirizine has evidence of efficacy for the treatment of CIU in children, based on both an active- and placebo-controlled trial.

2) *Safety / Tolerability*

As a class, the NAs are safe and well tolerated. There are few drug-drug interactions and clinical trial withdrawal rates are low (2 to 3%). The drugs can be used extensively in special populations.

Adverse Effects – While adverse effects with NAs occurred at a rate between 21 to 51% in clinical trials included in the 2006 DERP review, they tended to be minor, similar to placebo, and associated with a low discontinuation rate (2 to 3%). Minor adverse effects included stomach pain, lightheadedness, headache, and nausea.

Sedation – The NAs generally cause less drowsiness and sedation than older antihistamines. Cetirizine has been shown to cause more sedation than fexofenadine and loratadine. Loratadine and desloratadine, while causing minimal sedation at recommended dosages, have shown to cause significant sedation at higher doses. Fexofenadine has not shown sedation even in doses as high as 360 mg.

Cardiac arrhythmias – Cardiac toxicity has been a concern with NAs in the past, but does not appear to be a major issue with currently marketed products. Astemizole (Hismanal) and terfenadine (Seldane), two of the first newer antihistamines, were removed from the market because of their potential to cause prolonged QTc and torsade de pointes. However, newer second generation antihistamines have undergone extensive testing regarding their propensity to cause cardiac arrhythmias. Juniper et al (2005) reviewed these studies and concluded that cetirizine, fexofenadine and loratadine appear to have little potential to cause arrhythmias.

Pseudoephedrine-Containing Products – Combination products with pseudoephedrine can cause central nervous system stimulation, dizziness, weakness and insomnia. Pseudoephedrine has also been noted to cause palpitations as well as anxiety. Combination products containing pseudoephedrine are contraindicated in patients with narrow angle glaucoma, urinary retention, and with monoamine oxidase inhibitors (MAOIs). They should be used with *caution* in patients with hypertension, diabetes mellitus, ischemic heart disease, increased in ocular pressure, hyperthyroidism, renal impairment, and prostatic hypertrophy, and with *extreme* caution in patients with severe hypertension and/or severe coronary artery disease.

Use in Special Populations

- *Renal Failure* – All the NAs except acrivastine/pseudoephedrine have alternative dosing recommendations for patients with moderate to severe renal failure. Acrivastine/pseudoephedrine is not recommended in patients with a creatinine clearance less than or equal to 48 mL per minute.
- *Hepatic Failure* – Cetirizine, desloratadine, and loratadine have alternative dosing recommendations for patients with hepatic failure. Because

fexofenadine is metabolized to a very small extent, dosing changes in patients with hepatic failure is not necessary. The manufacturers of acrivastine/ pseudoephedrine have not made recommendations for alternative dosing of patients with hepatic failure.

- *Geriatrics* – There is insufficient data for manufacturers to make recommendations in populations greater than 70 years of age.
- *Pediatrics* – All the drugs, except acrivastine/pseudoephedrine and pseudoephedrine combination products, have indications for pediatric patients. Cetirizine, fexofenadine, and desloratadine have dosing recommendations for patients down to age 6 months. Loratadine has indications for patients to age 2 years and older.
- *Pregnancy and Lactation* – Acrivastine/pseudoephedrine, cetirizine and loratadine are FDA pregnancy category B. Although evidence from a randomized, controlled trial is not available, a cohort study of Israeli women showed no increase in major abnormalities of children born to women exposed to loratadine (RR 0.77; 95% CI 0.27 to 2.19) when compared to a no treatment control group. Secondary measures, including rate of still births, preterm deliveries and median birth weight, were similar between cohort groups. Desloratadine, fexofenadine and the combination products containing pseudoephedrine are FDA pregnancy category C.

  The manufacturer states that loratadine is compatible with breast-feeding. The manufacturers of other agents state that infant risk cannot be ruled out.

Drug Interactions

Drug interactions with ketoconazole and/or erythromycin have been reported with loratadine, desloratadine, and fexofenadine. However, despite the increased blood levels, there were no changes in QT interval, clinical condition, lab tests, or reported adverse events; dosage changes are not considered to be necessary. Antacids appear to reduce the area under the curve of fexofenadine by ~43%. Acrivastine/ pseudoephedrine and pseudoephedrine combination products can interact with antihypertensive drugs and reduce their antihypertensive effect. They should not be given within 14 days of a MAOI.

3) *Other Factors*

   The NAs do not appear to differ significantly with regard to the availability of additional formulations, with the exception of acrivastine/pseudoephedrine. All the single agent products have multiple alternate dosage formulations (oral dissolving tablets, rapid dissolving tablets, solutions or suspensions) and combination products containing pseudoephedrine.

4) *Clinical Effectiveness Conclusion* – The P&T Committee concluded that:

   a) Based on randomized placebo-controlled trials, cetirizine, desloratadine and loratadine are more efficacious than placebo for the symptomatic relief of SAR, PAR and CIU. Fexofenadine is more efficacious than placebo for the

symptomatic relief of SAR, and CIU. Acrivastine/pseudoephedrine is more efficacious than placebo for the symptomatic relief of SAR.

b) Based on six comparative trials in adults with SAR, there is insufficient evidence to suggest that there are clinically significant differences between cetirizine, fexofenadine, and loratadine, or desloratadine and fexofenadine. There is insufficient evidence to compare any of the agents in children less than 12 years old with this condition.

c) For the treatment of PAR in adults, there is insufficient evidence to suggest clinically significant differences between the agents. In children 2 to 6 years old, limited evidence based on one fair/poor quality comparative trial suggests that cetirizine may be more efficacious than loratadine with PAR.

d) For the treatment of CIU in adults, limited evidence based on two poor quality comparative trial suggests suggest that loratadine may be more efficacious than cetirizine for total symptom score reductions (but not response time), and cetirizine may be more efficacious than fexofenadine. In children, only cetirizine has evidence of efficacy for the treatment of CIU in children, based on both an active- and placebo-controlled trial.

e) The NAs appear to have similar adverse effect profiles and to result in similar low rates of discontinuation due to adverse events in clinical trials. There do not appear to be any major disadvantages for any one agent with respect to drug-drug interactions.

f) No NA appears preferable in hepatic impaired, renal impaired and pediatric patients. Loratadine, cetirizine and acrivastine/pseudoephedrine are FDA pregnancy category B, while desloratadine, fexofenadine and the combination products containing pseudoephedrine are FDA pregnancy category C.

g) All the parent products have multiple dosage forms and a pseudoephedrine-containing combination product.

h) It is likely that at one NA is sufficient for adequate clinical coverage, based on provider responses regarding prescribing practices and likely patient response.

i) Loratadine has been identified as a candidate drug for the DoD OTC Demonstration Program.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. NAs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the NAs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the NAs differed in regards to efficacy, safety, tolerability, or

clinical outcomes data. As a result, CMAs were performed to compare the relative cost effectiveness of the single agent NAs and the pseudoephedrine combinations. The CMAs compared the weighted average cost per day of treatment for each drug product across all three points of service.

Results from the NA CMAs showed that desloratadine and desloratadine/pseudoephedrine were not cost effective relative to the other agents in the newer antihistamine class. All other medications in the class were determined to be cost effective relative to their comparators.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost shares). The goal of the BIA was to aid the Committee in determining which group of NAs best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The P&T Committee concluded that:

1) Desloratadine and desloratadine/pseudoephedrine were not cost effective relative to other comparable agents in the newer antihistamine class.
2) The UF scenario that designated desloratadine and desloratadine/pseudoephedrine as non-formulary under the UF was the most cost effective scenario.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the cost effectiveness conclusion stated above.

C. NAs – UF Recommendations

COMMITTEE ACTION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the NAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that:

1) Fexofenadine, fexofenadine/pseudoephedrine, cetirizine, cetirizine/pseudoephedrine, and acrivastine/pseudoephedrine should be maintained as formulary on the UF.
2) Desloratadine and desloratadine/pseudoephedrine should be classified as non-formulary under the UF.
3) Loratadine and loratadine/pseudoephedrine should be added to the UF for purposes of the TRICARE OTC Demonstration Program.
4) At such time as cetirizine and cetirizine/pseudoephedrine are made available over-the-counter, both products should be maintained on the UF for purposes of the TRICARE OTC Demonstration Program.
5) Desloratadine and desloratadine/pseudoephedrine should be reclassified as generic on the UF when the generic products are available and cost effective relative to similar agents in the newer antihistamine class.

D. NAs – MN Criteria

Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for desloratadine and desloratadine/pseudo-ephedrine:

1) The use of formulary alternatives is contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.
3) Formulary alternatives have resulted in therapeutic failure.

The P&T Committee noted that acrivastine/pseudoephedrine, like other NA combination products with pseudoephedrine, is not indicated in children younger than 12 years of age.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. NAs – UF Implementation Period

The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA

MTFs will not be allowed to have desloratadine and desloratadine/pseudoephedrine on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary NA agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. NAs – BCF Review and Recommendations – The P&T Committee considered the BCF status of the NA agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that the current BCF listing for this class be maintained, requiring each MTF to carry at least one single-ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use. The P&T Committee noted that loratadine is the most cost effective NA in the MTFs, at approximately 1/12 the cost of the next most competitively priced agent.

7. DRUG CLASS REVIEW – LEUKOTRIENE MODIFIERS (LMs)

The P&T Committee evaluated the relative clinical effectiveness of the LMs. The LM class is comprised of two leukotriene receptor antagonists, montelukast (Singulair) and zafirlukast (Accolate); and one 5-lipoxygenase inhibitor, zileuton (Zyflo). A controlled release formulation of zileuton (Zyflo CR) has been approved by the FDA, but is not yet commercially available and was not included in the review.

Currently montelukast is the only BCF LM agent. None are available in a generic formulation. The LM drug class accounted for $101 million dollars in MHS expenditures in FY 2006, and is ranked #16 in terms of total expenditures during that time period. Over 97% of the utilization is for montelukast; from June 2006 to May 2007, there were over 300,000 montelukast utilizers in the MHS, over 3,000 zafirlukast utilizers and only 300 zileuton utilizers.

A. LMs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the LMs marketed in the U.S. By considering information regarding their safety, effectiveness and clinical outcomes. The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 CFR 199.21(e)(1).

1) *FDA-approved indications*

a) Asthma

Montelukast, zafirlukast and zileuton are all indicated for the treatment of asthma in adults and children. Montelukast is approved in children as young as one year of age, zafirlukast is indicated in children down to age of six years, and zileuton is approved for use in children aged 12 years and older. The LMs are most often used as adjunctive therapy to first-line asthma therapies including inhaled corticosteroids (ICSs) and long-acting beta agonists (LABAs).

b) SAR and PAR

Montelukast is the only LM with indications other than asthma; it is FDA-approved for treating allergic rhinitis in adults and children. For SAR, montelukast is approved down to the age of two years, and for PAR down to the age of six months.

c) Exercise-Induced Bronchoconstriction (EIB)

In April 2007, montelukast received approval for use in EIB in patients older than 15 years of age.

2) Efficacy

a) Asthma

i) National guidelines – The National Heart, Lung and Blood Institute's (NHLBI) National Asthma Education Prevention Program (NAEPP)

guidelines state that LMs are not first-line therapy. For all age groups, ICSs are considered first-line. In adolescents older than 12 years and adults, LABAs are preferred over LMs for adjunctive therapy; in this age group zileuton is an alternative, but not preferred therapy due to limited efficacy data and requirements for liver function test (LFT) monitoring. For younger children, LMs are an alternative based on the convenience of delivery device (oral administration vs. Nebulizer or oral inhaler) and safety data, rather than efficacy data.

ii) Meta-Analyses and Systematic Reviews – Three meta-analyses evaluated efficacy of the LMs compared with other asthma controller therapies.

- Sin et al (JAMA 2004) found that LMs were less effective than ICSs in reducing asthma exacerbations and improving forced expiratory volume in 1 second (FEV1) (RR 1.72; 95% CI 1.28-2.31).
- ICSs were also preferred in a Cochrane review (Ducharme, DiSilva) where patients taking LMs versus those taking ICSs were approximately 60%-70% more likely to have an asthma exacerbation (RR 1.65; 95% CI 1.36-2.0). Other endpoints such as FEV1 improvements, withdrawal rates from therapy due to poor symptom control, and asthma symptoms scores were consistently more favorable with ICSs.
- A second Cochrane review (Ducharme, Kakauma) that compared the combination of LMs to ICS versus ICS alone demonstrated minimal differences in combination therapy versus monotherapy (e.g., decreased need for albuterol by only one puff per week and no change in steroid dose vs. using the ICS alone). The combination of LABA plus ICS was superior in preventing asthma exacerbations requiring oral steroids than the combination of LM plus ICS.

iii) Clinical Trials – There are no head–to-head clinical trials evaluating the LMs for asthma. Results of placebo controlled trials or trials using ICS as an active comparator show that all three LMs produced statistically significant changes in FEV1, peak expiratory flow, and asthma symptoms score, compared to placebo. Indirect comparisons of placebo-controlled trials with similar study design using montelukast and zafirlukast suggest similar effects on asthma control, based on increases in FEV1 and as-needed beta agonist use. Fewer studies are available with zileuton.

iv) Steroid-Sparing Effects –Whether the LMs allow a reduction in ICS dose is controversial. The product labeling for montelukast states that a lower dose of ICS than previously used was able to control asthma symptoms when the LM was added on to ICS in one study in 226 patients. The Ducharme/Kakauma Cochrane analysis found no effect on steroid dose when a LM was added on to ICS. There is insufficient evidence to determine the steroid sparing effects of zafirlukast and zileuton. NHLBI/ NAEPP guidelines caution that the steroid sparing effects of the LMs are inconclusive, and that patients cannot be entirely weaned from the ICS.

b) Exercise Induced Bronchoconstriction

i) National Guidelines – NHLBI/NAEPP guidelines for EIB consider albuterol as the drug of choice, as albuterol prevents EIB in more than 80% of patients and is backed by good quality (Level A) evidence. Similar efficacy rates are seen with the LABAs (also considered Level A evidence); however, caution is required as tolerance develops with chronic use. In contrast, montelukast attenuates EIB in 50% of patients and is supported by Level B evidence. The guidelines stress that EIB is frequently a marker of inadequate asthma management, and that prevention and improved asthma control are recommended.

ii) Clinical Trials – Montelukast received FDA approval for EIB in patients older than 15 years in April 07 based on a placebo controlled trial showing a statistically significant benefit 2 hours after dosing. Montelukast has an onset of action of 1-2 hours, and a duration of action lasting up to 24 hours. There are no head-to-head trials comparing montelukast with albuterol. Two comparative trials with montelukast and salmeterol (Serevent) showed similar efficacy at preventing EIB within one hour prior to exercise. One study has evaluated efficacy of zileuton for EIB, but it is not approved by the FDA for this use.

c) Allergic Rhinitis

i) Efficacy Measures - Meta-analyses and clinical trials evaluating treatment for AR most frequently used two efficacy measures; variations of the rhinitis symptom score where the severity of nasal symptoms of congestion, itching, rhinorrhea are assessed, and the rhinoconjunctivitis-specific quality of life (RQLQ).

ii) National Guidelines – A preview of the updated Allergic Rhinitis in Asthma (ARIA) guidelines from the World Health Organization lists NAs or nasal corticosteroids (NCS) as first-line therapy for mild AR; the combination of a NA and NCS for moderate AR; and the combination of NA and NCS plus a LM for severe AR.

iii) Meta-Analyses and Systematic Reviews - Two meta-analyses have evaluated efficacy of the LMs vs. NCS and NAs for SAR; one by Wilson et al (2004) and the other by Rodrigo et al (2006).

- *LM vs. Placebo* – The Wilson meta-analysis included eight RCTs (one with zafirlukast; 7 with montelukast; over 3,900 patients) comparing a LM either alone or in combination with NAs or NCS vs. placebo or other treatments. The LMs significantly improved the nasal symptom score 5% more than placebo (95% CI 3-7%). This was of questionable clinical significance, as the authors used a 10% change as designating a minimally important result. There is no one recognized minimally important change in nasal score.

  The four studies where RQLQ was evaluated found that the LM significantly improved RQLQ by 0.3 units compared with placebo

(95% CI 0.24 to 0.36). A minimally important change in RQLQ is accepted to be a change of at least 0.57 units.

- *LM vs. NAs* – The treatment efficacy of LMs vs. NAs was compared in both the Wilson (4 RCTs) and Rodrigo (5 RCTs) meta-analyses. The trials included all compared montelukast with loratadine. In the Wilson analysis, loratadine improved nasal symptom score 2% more than montelukast, but the results were not statistically significant (95% CI 0% to 4%). Treatment with loratadine significantly improved RQLQ by 0.11 units more than montelukast (95% CI 0.04 to 0.18 units). The Rodrigo meta-analysis found no statistically significant difference between montelukast and loratadine in nasal symptom score or RQLQ; additionally, when individual eye symptoms were scored, there was no significant difference between montelukast and loratadine.
- *LM vs. NCS* – In the Wilson meta-analysis, montelukast was compared with fluticasone (3 RCTs), mometasone (1 RCT), budesonide (1 RCT), and zafirlukast was compared with beclomethasone (1 RCT). NCS improved nasal symptom score 12% more than the LM (95% CI 5% to 18%); RQLQ was not assessed.
- *LM plus NA vs. NCS* – The Rodrigo meta-analysis evaluated the combination of LM with a NA vs. NCS. Overall there were only minimal differences noted, although there was a trend toward superiority of the NCS.

iv) PAR – There are no meta-analyses evaluating LM efficacy for PAR. Montelukast is the only LM approved for PAR, which was supported by one placebo-controlled trial in over 1,900 patients that showed statistically significant improvements in daytime and nighttime symptom scores, RQLQ scores, and provider and patient global assessment.

In the pediatric population, montelukast is approved for use in SAR in children age two years and older, and for PAR in age 6 months and older. However, published clinical trial data is limited in the pediatric population, and is primarily based on safety. In two studies in children with PAR, montelukast was less efficacious than cetirizine in most of the endpoints studied.

v) Pediatric Issues

- *FDA Labeling* – Although montelukast is approved for patients as young as 6 months with PAR, and as young as 2 years with SAR, the product labeling states that efficacy data is extrapolated from studies with adolescents older than 15 years with AR.
- *Clinical Trials* – Two small placebo-controlled studies evaluated montelukast with cetirizine in Taiwanese children ranging in age from 2-6 years and 6-12 years with PAR. Cetirizine was statistically

significantly superior to montelukast in improving total nasal symptoms and the individual symptom of nasal congestion.

- *National Guidelines* – The ARIA guidelines for children recommend following the same principles as adults. They acknowledge that NCS are the most effective treatment of pediatric AR, but recognize that long-term safety remains controversial for growth suppression and hypothalamic-pituitary axis suppression.
- *Other Treatments* – Other treatments for AR are approved for use in children as young as 6 months (cetirizine, fexofenadine, and desloratadine), two years (loratadine and mometasone), and 4 years (fluticasone propionate).

d) Off-Label Uses

The Committee reviewed several off-label uses for the LMs; most of these lack sufficient data to prove safe and efficacious use at this time. Treatment of nasal polyps and treatment of reactive airways disease after acute respiratory syncytial virus illness in children appear to have sufficient published evidence to prove safe and clinically effective.

3) *Safety and Tolerability*

a) Serious Adverse Effects

i) Churg-Strauss Syndrome – Case reports of montelukast and zafirlukast causing systemic eosinophilic vasculitis in patients with asthma and AR are available. However, it is uncertain whether this is a direct effect of the LM or due to concomitant withdrawal of corticosteroids. There is insufficient evidence to determine whether one LM is more likely than another to cause this syndrome.

ii) Hepatotoxicity

- *Montelukast* – The product labeling states there are rare reports of hepatic injury without increases in LFTs. The incidence of in aspartate aminotransferase (AST) elevations is 1.7% with montelukast vs. 1.2% with placebo.
- *Zafirlukast* – Product labeling describes rare reports of hepatic failure, with resolution of symptoms and LFT elevations upon drug discontinuation; there is no requirement in labeling for LFT monitoring. According to the manufacturer, there have been eight published cases linking zafirlukast with hepatic failure, two of which required transplant. Information received in response to a Freedom of Information Act request to the FDA revealed 66 cases of hepatitis or liver failure and 23 deaths between 1997 and 2002. These cases were spontaneous reports, and a direct causality with zafirlukast has not been assessed.
- *Zileuton* – Use is contraindicated in patients with active hepatic disease of LFT elevations greater than 3 the upper limit of normal

(ULN). In clinical trials of over 5,000 patients, the incidence of AST elevations more than 3 times the ULN was 4.6% with zileuton. LFT monitoring is required at baseline, monthly for the initial three months of treatment, and every 2-3 months thereafter.

b) Minor Adverse Effects – Overall the LMs have a low incidence of minor adverse effects, with headache and gastrointestinal complaints reported most commonly. Pooled data from the product labeling suggests that there is no relevant difference between the LMs in minor adverse effects.

c) Drug-Drug Interactions – Montelukast has not been associated with clinically significant drug interactions. Zafirlukast and zileuton both can increase the prothrombin time when administered with warfarin (Coumadin). Zileuton can decrease theophylline metabolism, leading to increased theophylline concentrations; theophylline dosage reductions of 50% are required with concomitant use.

d) Special Populations – Montelukast is rated pregnancy category B, while both zafirlukast and zileuton are rated pregnancy category C. Dosage adjustments in renal impairment are not necessary with the LMs. Zileuton is contra-indicated for use in patients with active liver disease.

4) *Other Factors*

Montelukast is available in several dosage formulations (tablets, chewable tablet, and granules), and is dosed once daily. Zafirlukast requires BID dosing, while zileuton requires QID dosing.

5) *Therapeutic Interchangeability*

There is a low degree of therapeutic interchangeability between the three LMs. Montelukast has advantages in terms of multiple indications, multiple formulations, a more favorable safety profile, and FDA approval in the pediatric population.

6) *Clinical Coverage*

To meet the needs of MHS patients, one LM is required; however, it must have a favorable safety profile. For EIB, availability of montelukast, the only LM approved for this indication, is less urgent, due to efficacy and acceptance of albuterol and LABA.

7) *Overall Clinical Effectiveness Conclusion* – The P&T Committee concluded that:

a) For the treatment of asthma, NHLBI/NAEPP guidelines include LMs as alternative, but not preferred therapy. LMs are more effective than placebo in controlling asthma symptoms, but are less effective than ICS, and are less effective when added on to LABA vs. use of a LABA with ICS. Addition of a LM to ICS provides modest benefit over use of the ICS as monotherapy.

b) In placebo-controlled trials for asthma, the three LMs montelukast, zafirlukast, and zileuton demonstrate clinical effectiveness in endpoints such as reduction in exacerbations, improvements in FEV1, asthma symptoms

scores and short acting beta-agonist use. There is insufficient evidence to determine whether one LM is more efficacious at controlling asthma symptoms than another.

c) Limited evidence suggests that LMs may permit a reduced inhaled steroid dose, or could be used in patients resistant or unable to tolerate ICS. The extent or clinical significance of this "steroid sparing" effect is uncertain.

d) Montelukast is the only LM that is FDA approved for the treatment of AR, and is specifically approved for both SAR and PAR. There are a few small clinical trials that evaluate zafirlukast in the treatment of AR, but they fail to consistently show efficacy. There is no data to support the use of zileuton in AR.

e) For AR, meta-analyses show that LMs are superior to placebo in clinically relevant AR endpoints such as rhinitis symptoms scores and rhinoconjunctivitis quality of life scores; however, the treatment effect is modest. When compared to antihistamines, the LMs show relatively similar efficacy. NCSs are clinically superior to montelukast in all clinical endpoints studied. Combinations of an LM with an antihistamine is modestly more effective than either agent alone, but not superior to NCS in improving nasal symptoms of AR.

j) In the pediatric population, montelukast is approved for use in SAR in children age two years and older, and for PAR in age 6 months and older. However, published clinical trial data is limited in the pediatric population, and is primarily based on safety. In two studies in children with PAR, montelukast was less efficacious than cetirizine in most of the endpoints studied.

k) In regard to safety and tolerability, zileuton has been associated with hepatotoxicity, requires LFT monitoring, and is contraindicated in patients with active liver disease. Zafirlukast has also been associated with hepatotoxicity including liver failure and death; however, this data is from spontaneously reported adverse events reports and must be interpreted cautiously. Zafirlukast and zileuton are associated with more clinically significant drug interactions than montelukast.

l) In regard to other factors, montelukast has the advantage of a greater number of FDA approved indications, pediatric indications, less frequent dosing (once daily versus twice and four-times daily for zafirlukast and zileuton), and availability of alternative dosage formulations.

m) Overall, based on clinical issues alone, montelukast is preferred over zafirlukast, which in turn is preferred over zileuton.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 0 abstained, 3 absent) to accept the clinical effectiveness conclusions stated above.

B. LMs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the LM agents in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation determined that there was enough evidence to show that the LM medications differed in regards to efficacy and safety in the treatment of asthma, AR, and EIB. Moreover, the clinical review concluded that the LMs have a role in the management of asthma and are gaining acceptance in the treatment of EIB. However, the use of LMs in AR remains controversial. As a result, the pharmacoeconomic analysis first compared the LMs in a CMA to gauge the cost effectiveness of the agents within the LM class. Once complete, the analysis then considered the cost effectiveness of LMs as compared to NAs and NCS in the treatment of AR. Each analysis compared the weighted average cost per day of treatment across all three points of service.

Results from the LM CMA showed that zafirlukast was the least costly agent in the class. In comparison, montelukast was more costly per day of treatment but also provided additional indications, a better adverse event profile, multiple dosage forms, and more evidence in pediatrics than the other agents in the class. The least cost effective product was zileuton.

In the treatment of AR, the cost effectiveness analysis showed that NA agents and NCS agents were the most cost effective options for the treatment of AR. The LMs were less effective than the NCS and provided comparable efficacy to the NAs. However, the LMs were significantly more costly per day of treatment than either the NAs or the NCS agents. Hence, pervasive use of LMs as first-line therapy in AR should be discouraged to optimize treatment of AR in the MHS.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of a UF scenario that required a step therapy/PA program for use of LMs in allergic rhinitis (with no PA for other indications) was compared to a scenario with no PA required for use of LMs in any indication. The analysis was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost shares). The goal of the BIA was to estimate the impact of enacting a step therapy/PA policy for AR in the LM class and to aid the Committee in determining which group of LMs best met the clinical needs of the majority of the DOD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The P&T Committee concluded that:

1) Zafirlukast was the least costly agent in the class; montelukast was more costly relative to zafirlukast but provided additional indications, a better adverse event profile, multiple dosage forms, and more evidence in pediatrics than the other agents in the class; zileuton was not cost effective relative to the other products.
2) LMs are not cost effective in the treatment of AR relative to antihistamines and NCS agents and should not be considered as first-line therapy in the treatment of AR.

3) The Committee concluded that the UF scenario that placed zafirlukast and montelukast on formulary with a step therapy/PA required for use in AR was the scenario that resulted in the lowest expected expenditures in the LM class.

COMMITTEE ACTION: The DOD P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to accept the LM relative cost effectiveness analysis as presented by the PEC.

C. LMs – Step Therapy Consideration

For SAR and PAR (although montelukast is the only LM with this indication) the LMs are considered third-line agents after antihistamines and NCS. The Committee reviewed several programs utilized by civilian health plans to address use of the LMs for AR. Several plans allow unrestricted use of the LMs for asthma, but require PA for AR, primarily based on previous use of an antihistamine and/or NCS.

The Committee considered a step therapy/PA program where LMs would be allowed for MHS patients with asthma, but PA would be required for LM use in AR patients older than 5 years of age. Patients older than the age of 5 would require prior use of a NA and NCS, before LM use would be allowed.

COMMITTEE ACTION*:* Although the committee agreed that the LMs are not cost effective for AR, the Committee voted (6 for, 8 opposed, 1 abstained, and 2 absent) against enacting a step therapy/PA policy for use of LMs in the management of AR. Similar policies have recently been initiated with other drug classes in the MHS and the Committee felt that the most prudent course of action at this time was to delay enacting another step therapy/PA policy. Instead, the PEC will gather additional evidence about the effect of the other step therapy/PA policies recently implemented in the MHS while educating MTF providers to minimize the use of LMs for the management of AR. The PEC will also monitor utilization in the LM class. If the use of LMs for AR continues to proliferate, the Committee will review the class again to determine if further action is required.

D. LMs – UF Recommendations

COMMITTEE ACTION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the LMs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that zafirlukast and montelukast be maintained as formulary on the UF and that zileuton be classified as non-formulary under the UF.

E. LMs – MN Criteria

Based on the clinical evaluation for zileuton, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for zileuton:

1) Use of formulary alternatives is contraindicated.

2) The patient has experienced significant adverse effects from formulary alternatives.

3) Formulary agents have resulted in therapeutic failure.

4) Patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.

With respect to criterion #4, the P&T Committee's primary concern was for asthma patients stabilized on zileuton, although this is likely to apply to very few patients considering the low usage of zileuton.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

F. LMs – UF Implementation Period

Approximately 145 beneficiaries (0.07% of those using agents in the LM class) will be affected by the UF decision. The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have zileuton on their local formularies. MTFs will be able to fill non-formulary requests for zileuton only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary LM agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

G. LMs – BCF Review and Recommendation

The P&T Committee considered the BCF status of the LM agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 1 opposed, 1 abstained, and 2 absent) to recommend that montelukast be retained on the BCF (specific formulations include tablets, chewable tablets, and oral granules).

8. DRUG CLASS REVIEW – GROWTH STIMULATING AGENTS (GSAs)

The P&T Committee evaluated the relative clinical effectiveness of the GSAs. This class is divided into two subclasses: growth hormone (GH) agents (somatropin products) and insulin-like growth factor-1 (IGF-1) agents (mecasermin). The GSA drug class accounted for about $23 million in MHS expenditures in FY 2006.

A. GSAs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the GSA agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but

was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

Table 1: Growth Stimulating Agents Available in the U.S.

Subclass	Generic Name	Brand Name	FDA Indication
Growth Hormone	Somatropin	Genotropin (Pfizer) Genotropin Miniquick	GHD, PWS, TS, SGA
		Humatrope (Eli Lilly)	GHD, TS, ISS, SHOX
		Nutropin (Genentech) Nutropin AQ	GHD, TS, CRI, ISS
		Norditropin (Novo Nordisk) Norditropin Nordiflex	GHD, Noonan's Syndrome
		Omnitrope (Sandoz)	GHD
		Saizen (Serono)	GHD
		Serostim (Serono)	AIDS/HIV wasting
		Tev-Tropin (Teva/Gate)	GHD (pediatric patients only)
		Zorbtive (Serono)	SBS
Insulin-like growth factor (IGF-1)	Mecasermin	Increlex (Tercica)*	IGFD

*A second mecasermin product, mecasermin rinfabate (Iplex; Insmed) has been withdrawn from the market due to patent litigation settlement; the manufacturer continues to develop the product for the treatment of non-growth related conditions.

GHD = Growth Hormone Deficiency; PWS = Prader-Willi Syndrome; TS = Turner Syndrome; SGA = Small for Gestational Age; ISS = Idiopathic Short Stature; SHOX = Short Stature Homeobox gene deficiency; CRI = Chronic Renal Insufficiency; SBS = Short Bowel Syndrome; IGFD = Insulin-like Growth Factor Deficiency

1) Background

a) Growth stimulant agents

i) Products

This class of drugs includes only two molecular entities, somatropin and mecasermin. There are multiple competing somatropin products. The majority of these are indicated for the treatment of GH deficiency (GHD), which is the most common use, although manufacturers are constantly researching additional FDA indications. Mecasermin is an orphan drug approved by the FDA in 2005 to treat severe primary insulin-like growth factor deficiency (IGFD), which affects a very small number of patients (about 6,000 in the United States).

ii) FDA Approval process

At present, the FDA has no mechanism for approving "generic" versions of biologic drugs (large-molecule or complex proteins that are synthetic or recombinant versions of natural biological substances), which are

regulated under Section 351 of the Public Health Service Act. The lack of a mechanism for approval of generic biologic products produces a unique situation in this class, with multiple competitive branded products available.

iii) Off-Label Uses

GH has the potential for substantial off-label use. It has been proposed as an anti-aging medication based on its effect on growth and metabolism. However, a systematic review found little evidence that GH is clinically beneficial in healthy elderly patients and substantial evidence suggesting high adverse event rates. The data did not support improvements in bone mineral density, lipid levels, or fasting glucose and insulin levels.

2) Efficacy

a) Efficacy Measures

The following measures are used as efficacy trial endpoints for both somatropin and mecasermin in growth-related condition:

- *Height expressed in centimeter (cm) or inches (in):* Absolute or change from baseline
- *Standard Deviation Score (SDS):* Actual height minus mean height for age divided by the standard deviation of height for age. The normal population mean is zero; a normal SD score will lie between -2 SD and +2 SD.
- *Final height:* Stipulates that the individual has stopped growing based on 1) the growth rate has slowed to less than 1-2 cm/year or 2) epiphyseal closure has occurred as confirmed by radiography
- *Near final height:* Based on height velocity less than a certain value, chronological age greater than 15-17 years, or skeletal age greater than 14-16 years
- *Height velocity:* Growth per period of time
- *Mid-parental height:* For boys, add 2.5 in or 6.5 cm to the mean of the parents' heights. For girls, subtract 2.5 in or 6.5 cm from the mean of the parents' heights. This sex-adjusted mid-parental height represents the statistically most probable adult height for the child, based on parental contribution.
- Predicted Adult Height (assuming no intervention): Predicted based on current height, age, and a set of tables known as the Bayley-Pinneau tables, which use radiographic bone age to determine growth potential.

b) Somatropin Efficacy

i) Introduction

GH (somatropin) treatment is indicated for treatment of a variety of conditions that largely affect linear growth. FDA indications overlap to

some degree (see Table 1). All products except Zorbtive and Serostim are indicated to treat GHD, but only three are indicated for treatment of short stature associated with Turner Syndrome, and only one is indicated for treatment of Prader-Willi Syndrome. However, treatment endpoints are similar across all growth-related conditions, and treatment goals are achieved by physiologic replacement or supplementation of growth hormone.

Of prescriptions filled by the Air Force High Dollar Program in July 2007, 62% were for pediatric GHD, another 16% were for adult GHD, 8% were for panhypopituitarism, 6% were for Turner Syndrome, and the rest were split out across various miscellaneous indications. While these data are limited, usage of the growth hormones products by age across the MHS confirms that the great majority of use is for pediatric indications (usage peaks in the 5-14 year age group), with some use in adults (45 years and older).

ii) Somatropin Clinical Efficacy

All marketed somatropin products contain recombinant human GH that is bioequivalent and equally biopotent, and are therefore unlikely to differ in efficacy for the treatment of growth related disorders. There are no studies that compare two or more somatropin products for any indication.

- *Treatment of Childhood Growth Disorders* – Published evidence supports clinical efficacy of somatropin in achieving growth-related clinical endpoints in these conditions, including GHD, Turner Syndrome, Prader-Willi Syndrome, growth restriction related to chronic kidney disease, and small for gestational age. Clinical endpoints evaluated in published clinical trials comparing GH to untreated controls have included: total gains in height, increases in growth velocity, and final or near final adult height vs. mid-parental height or normal population means.
- *Treatment of Adult GHD* – Published evidence supports the clinical efficacy of somatropin treatment in achieving various clinical endpoints, including improvements in body composition (reduction of fat mass, increases in lean body mass); modest reductions in cardiovascular risk factors such as blood pressure, total and LDL cholesterol, and triglycerides; and reduction of C-reactive protein. Modest improvements in bone mineral density (4-10% via DEXA) have also been shown. The data do not support clinically and statistically meaningful improvements in adults without GHD.
- *HIV/AIDS related wasting / cachexia and sShort Bowel Syndrome (SBS) in adults* – GH has been demonstrated to be efficacious in these conditions. The use of somatropin in AIDS wasting results in increased lean body mass and improved muscular strength and endurance, compared to untreated controls. No mortality benefit has been demonstrated. Treatment of SBS with somatropin is based on

evidence that somatropin accelerates the process of bowel adaptation. This process involves morphologic changes of the remaining bowel allowing it to have greater absorption of nutrients and fluids and lessen the need for parenteral nutrition. Data are limited, but suggest that up to four weeks of GH treatment has been beneficial in reducing the need for parenteral nutrition in SBS patients.

- *Noonan Syndrome and Short Stature Homeobox gene (SHOX) deficiency* – The FDA recently approved somatropin for use in two additional pediatric growth disorders: Noonan Syndrome and SHOX deficiency. Both of these conditions are genetic disorders associated with severely restricted growth. Published clinical trials have demonstrated significant improvements in growth-related endpoints in both conditions, compared to untreated control patients.
- *Idiopathic Short Stature (ISS)* – ISS, or non-GHD short stature, refers to individuals who are at least 2.25 standard deviations shorter than the mean height for sex and age (the shortest 1.2% of the population). These individuals have no identified physiologic abnormality affecting growth and appear to be healthy otherwise. Growth velocity and final height gains are modest even with somatropin treatment; individuals usually remain shorter than average regardless of treatment. There are no data showing that the gains in height following GH treatment are associated with improvements in quality of life or psychosocial functioning. Treatment of ISS is not considered medically necessary and is therefore not a covered benefit under TRICARE.

iii) Mecasermin Clinical Efficacy

FDA approval of mecasermin was based on the results of five clinical trials, which are unpublished but summarized in product labeling. These trials enrolled a total of 71 children (mean age 7 years) with symptoms of primary IGFD (slow growth rates, low IGF-1 serum concentrations, and normal GH secretion) and extreme short stature (height almost 7 SD below normal). For years 1 through 6, pooled results showed a significant increase in height velocity in mecasermin-treated patients, compared to baseline. Although statistical interpretation was complicated by the uncontrolled, longitudinal nature of the data and the varying lengths of exposure to mecasermin treatment (range <1 to 11.5 years), children appeared to gain, on average, an additional one inch per year for each year on therapy, compared to pretreatment growth patterns.

Bone age, relative to chronological age, was assessed in 49 subjects, since a disproportional acceleration of bone age (specifically epiphyseal closure) could lessen the eventual height reached even if the drug was otherwise effective at accelerating growth. Radiographically-assessed bone age advanced only marginally above chronologic age (4.9 $\pm$ 3.4 years mean $\pm$ SD change in chronological age vs. A 5.3 + 33.4 years change in bone

age). Subjects felt to be close to adult height all exceeded the mean height of untreated subjects, suggesting a positive net effect.

iv) GSA Efficacy Conclusion

Somatropin appears to be efficacious for the treatment of a number of growth-related disorders, including GHD, Prader Willi Syndrome, Turner Syndrome, chronic renal insufficiency, children who are small for gestational age, SHOX deficiency, and Noonan Syndrome, as well as non-growth related disorders, including adult GHD, AIDS/HIV wasting, and SBS. There are no studies that compare any somatropin product to another for any given indication. Given that all of the products contain the same concentration (3 IU rhGH/mg) of bioidentical recombinant human growth hormone, they are unlikely to differ in efficacy for the treatment of growth-related or other disorders.

Mecasermin increased height in children with severe IGFD, especially in the first year of administration, but not enough to bring these children close to the normal range. It is unlikely to be as effective as GH treatment for children who can respond to GH.

3) *Safety and Tolerability*

a) Somatropin

Mortality in children with GHD is due almost entirely to other pituitary hormone deficiencies. These children have an increased relative risk of death in adulthood from cardiovascular causes resulting from altered body composition and dyslipidemia. Adverse effects of somatropin appear to be dose-related. Initial somatropin studies used higher doses associated with many adverse effects; lower dosages are currently used.

i) Serious Adverse Effects

- *Pseudotumor cerebri or benign intracranial hypertension* – This is more common in children than adults; the FDA has received at least 23 reports in children, 1 in an adult. In all cases, symptoms of intracranial hypertension (headaches) resolved after discontinuation of GH therapy. Only a few patients experienced recurrent headaches and papilledema upon resuming therapy.
- *Slipped capital femoral epiphysis* – This condition is attributed to GH therapy, but may be linked to the result of diathesis induced by GHD and intensified by rapid growth. Children on GH therapy complaining of hip or knee pain should be carefully examined for slipped capital femoral epiphysis.
- *Patients with acute catabolism* – Use of somatropin products is contraindicated in this patient population, including preoperative and post-operative patients, critically ill patients, and burn patients. In a phase III prospective, randomized, placebo-controlled trial in Europe conducted in critically ill patients in an intensive-care unit facility,

patients were given 5.3 mg or 8 mg per day (weight-dependant) of GH therapy for 21 days. A significantly higher mortality (41.7% vs. 18.2%) was seen in the GH-treated group compared to placebo.

- *Retinopathy* is a rare complication of GH treatment. Three case reports (1 adult; 2 children) reported development of retinopathy following GH treatment, although one trial involving 85 children showed no retinopathy after 6.4 ± 2.9 years. A baseline funduscopic evaluation is recommended before starting GH treatment.
- *Malignancies* – Concern has surfaced about the association of GH treatment with tumor recurrence or development of malignancies. This has not been reported in adult GHD patients. An increase in leukemia was reported in Japanese pediatric GHD patients, although this was not confirmed by subsequent studies. Studies in the United States did not confirm an increase in frequency and have shown some differences in incidence related to other risk factors, for example, patients who previously received radiation therapy. This question remains unanswered.

ii) More Common Adverse Effects reported with somatropin include injection site reactions, hypothyroidism, transient gynecomastia, headaches, agitation, fatigue, seizures, and nausea/vomiting. Fluid retention and edema of the extremities, as well as arthralgia, myalgia, carpal tunnel syndrome, and blood pressure increases, are reported primarily in adults. GH may also be associated with insulin resistance and glucose intolerance. Some adverse effects appear to be dose-related.

Reported rates of adverse effects do vary from product to product, although this is potentially due to a number of factors, including differences in dosing regimens for specific indications, patient populations studied, or methods of collecting adverse effects. All products contain the same molecular entity (somatropin).

- *Fluid retention, edema, arthralgia, myalgia, and carpal tunnel syndrome* – Adult starting doses for GH were initially higher than those currently recommended. These higher doses were associated with fluid retention in conjunction with edema of the extremities, resulting in arthralgias, myalgias, and carpal tunnel syndrome. These adverse effects are more frequent in adults but do occur occasionally in GH-treated pediatric patients. In a study of 115 adult patients with GHD given GH therapy for 6 months, 37.4% developed edema, 19.1% developed arthralgia, 15.7% myalgia, 7.8% paresthesias, and 1.7% carpal tunnel syndrome. Most adverse effects occurred at the beginning of treatment and resolved within 1 to 2 months with continued treatment. Fluid retention can also cause increases in blood pressure.
- *Effects on blood glucose* – High doses of GH have been associated with hypoglycemia followed by hyperglycemia, since GH induces

transient resistance to the actions of insulin. In patients with limited insulin reserve, glucose intolerance may result. Insulin resistance and type 2 diabetes were reported in a few patients in early large clinical trials. A placebo-controlled GH trial reported that a higher number of patients receiving GH had worsening glucose tolerance compared to those receiving placebo, with impaired glucose tolerance seen in 13% and diabetes in 4% of GH patients.

iii) Contraindications – Somatropin is contraindicated in patients with active neoplasms or intracranial lesions and treatment should be stopped if evidence of tumor growth develops. Treatment should not be initiated in patients with proliferative or preproliferative diabetic retinopathy; Prader Willi Syndrome patients who are severely obese or have severe respiratory impairment; acute critically ill patients; and patients with growth-related disorders whose epiphyses have closed. Somatropin products containing the preservative benzyl alcohol are not suitable for use in newborns.

iv) Drug-Drug Interactions – Limited published data suggest that somatropin treatment increases CYP450-mediated antipyrine clearance in man. Somatropin may therefore alter the clearance of compounds known to be metabolized by CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, or cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CYP450 liver enzymes. Formal drug interaction studies have not been conducted.

v) Tolerability – There is insufficient evidence to conclude that any one somatropin product is more tolerable or leads to better compliance than any other somatropin product. Any such differences are likely to be based on factors such as formulation / preservative differences and packaging.

Table 2: Somatropin Products – Other Consideration

Drugs	Preservative-free	Delivery Device			Storage		1-800 number
		Vial	Pen Device	Dose calculation to use pen	Ready to use	Room Temperature Storage	
Genotropin	yes		yes	Not required	Miniquick syringe only (single-dose)	Before initial use: Miniquick syringe	yes
Humatrope		yes	yes	Required			yes
Norditropin			yes	Not required	yes	After initial use: (21 days for Nordiflex 5 & 10 mg pens)	yes
Nutropin & Nutropin AQ		yes	yes	Required	yes		yes
Omnitrope	yes	yes		-			yes
Saizen		yes	yes, pen & needle-free pen	Required		Before initial use	yes
Serostim	yes	yes	yes, needle-free pen	Required		Before initial use	yes
Tev-Tropin		yes	*	-			yes
Zorbtive		yes		-			yes

*Approval of pen device anticipated

vi) Other Considerations – Since marketed somatropin products appear to be similar in efficacy and safety, the primary differences between products is based on educational materials; drug formulations / preservatives; delivery devices (pen or vial/syringe); and storage requirements (refrigeration vs. room temperature). Table 2 outlines differences between somatropin products with regard to many of these issues.

- *Educational material* **–** All manufacturers provide some type of educational material for their products, ranging from a hotline number for information and assistance to the patient or caregiver (provided by all manufacturers) to complete packages including a hotline number, website, nurse educator for initial instruction, and a safety registry website for physicians. The literature assessing the value of these educational programs is sparse. In MTFs, certain components of the educational programs are handled by MTF staff and manufacturer offerings such as nurse educators may be of little additional value.
- *Formulations* **–** The primary reason for the selection of preservatives is to prevent leaching of the drug into its glass or plastic container. The availability of a preservative-free product may be an advantage, although the need for such a product for use in infants should be rare. In addition, ready-to-use formulations that do not require reconstitution may increase accuracy of dosing.
- *Delivery Devices* **–** Availability of a product in a pen device allows for accuracy in dosing and may enhance compliance. Pens are available for these product lines: Genotropin, Humatrope, Norditropin, and Nutropin. Providers in general reported that patients prefer pens to vials; indeed, 67% of MHS utilization from June 2006 to July 2007 was for pens, followed by vials (26%) and disposable syringes (7%).

  Some pen devices conceal the needle from view, an advantage in children who fear needles. The Serono products, Saizen and Serostim, are the only products with a needle-free pen device. An additional consideration is the requirement for dose calculations on the part of the caregiver/patient; some pens require users to convert the milligram dose prescribed to the units dosed on the pen. Products requiring conversions are the Nutropin product line, Saizen, and Serostim.
- *Drug Wastage* **–** Packaging for the two somatropin products that lack a GHD indication (Serostim and Zorbtive) is designed for dosage regimens used in AIDS/HIV wasting and SBS, not for use in GHD. Drug wastage would be inevitable if these products were used for GHD. In addition, educational materials available for these products do not address GHD.

b) Mecasermin

i) Serious Adverse Effects

- *Hypoglycemia* – Mecasermin can cause hypoglycemia due to its insulin-like effects. Hypoglycemia was reported in 30 of 71 patients in clinical trials (42%) at least once during their course of therapy. Most cases of hypoglycemia were mild or moderate in severity. Five patients had severe hypoglycemia that required assistance and treatment on one or more occasion, while four experienced hypoglycemic seizures/loss of consciousness on one or more occasion. Of the 30 patients reporting hypoglycemia, 14 (47%) had a history of hypoglycemia before treatment. The incidence of hypoglycemia was highest in the first month of therapy, and episodes were more frequent in younger children. Symptomatic hypoglycemia was usually avoided when a meal or snack was consumed either shortly (i.e., 20 minutes) before or after the administration of mecasermin.
- *Lymphoid tissue hypertrophy* – Hypertrophy of lymphoid tissues (e.g. Tonsillar) can result in snoring, sleep apnea, and chronic middle-ear effusions. Tonsillar hypertrophy was noted in 11 (15%) subjects in the first 1 to 2 years of therapy with lesser tonsillar growth in succeeding years. Tonsillectomy or tonsillectomy/adenoidectomy was performed in 7 subjects; 3 of these had obstructive sleep apnea, which resolved after the surgery in all three cases.
- *Intracranial hypertension* – Intercranial hypertension with papilledema, visual changes, headache, nausea and/or vomiting have been reported with mecasermin (as with therapeutic GH administration). Intracranial hypertension occurred in three subjects, and in two subjects, resolved without interruption of mecasermin treatment. Mecasermin therapy was discontinued in the third subject and resumed later at a lower dose without recurrence.
- *Scoliosis* due to slipped capital femoral epiphysis can occur with rapid growth.

ii) Common Adverse Effects reported in the pooled mecasermin trials were hypoglycemia (42% of patients), lipohypertrophy, and tonsillar hypertrophy (15%). Other adverse effects occurring in at least 5% of patients include bruising, otitis media, headache, dizziness, convulsions, vomiting, hypoacusis, fluid in the middle ear, ear pain, abnormal tympanometry, arthralgia, pain in extremity, and thymus hypertrophy. Adverse effects were generally mild to moderate and no patients withdrew from the pooled trials as a result.

Also reported during clinical trials were: mild elevations in serum AST, alanine aminotransferase (ALT), and lactate dehydrogenase not leading to treatment discontinuation; increases in cholesterol and triglycerides to above the upper limit of normal; increases in renal and/or splenic length

reaching or surpassing the 95th percentile in some patients but not associated with impairments in renal function (as defined by serum creatinine and calculated creatinine clearance); echocardiographic evidence of cardiomegaly/valvulopathy without associated clinical symptoms ; and development of anti-IGF-1 antibodies with no apparent clinical consequence (e.g., allergic reactions or attenuation of growth).

iii) Contraindications – Mecasermin is contraindicated in patients whose epiphyses are already closed and those with active or suspected neoplasia. Mecasermin is not suitable for use in neonates due to its benzyl alcohol preservative.

iv) Monitoring – Preprandial glucose monitoring should be considered at treatment initiation, until a well tolerated dose is established, or if frequent or severe symptoms of hypoglycemia occur. Funduscopic exams are recommended at the start of therapy and periodically thereafter. Patients should also be monitored for *t*hickening of soft tissues of the face and symptoms suggesting the occurrence of scoliosis due to a *s*lipped capital femoral epiphysis.

v) Special Populations – Safety and effectiveness has not been established in children less than 2 years of age or in adults.

c) Safety/Tolerability Conclusion

i) Growth Hormone (Somatropin)

Serious adverse events of GH include benign intracranial hypertension, slipped capital femoral epiphyses, and retinopathy. Whether or not GH treatment has tumorigenic effects remains debatable, due to possible associations with underlying disease states. The most common adverse events are edema, arthralgias, injections site reactions, diabetogenic effects, and hypothyroidism. Consistent lab monitoring is necessary to decrease the potential for adverse effects from possible excessive dosing or exacerbation of other disease states; required monitoring does not differ among marketed products. GH is not recommended in critically ill patients.

Although all products contain the same molecular entity, reported rates of adverse events vary from product to product, possibly due to different dosing schemes for specific indications or differences between study populations. There is limited evidence concerning differences between products attributable to excipients. Preservatives are primarily used as a way to prevent the drug leaching into the plastic or glass container. Products containing the preservative benzyl alcohol are not suitable for use in newborns; preservative-free products are available.

Since marketed somatropin products appear to be similar in efficacy and safety, the primary differences between products is based on educational materials; drug formulations / preservatives; delivery devices (pen or

vial/syringe); and storage requirements (refrigeration vs. room temperature).

The biggest difference is in available delivery devices (e.g., a pen device, vial/syringe, needle-less system). A pen device is advantageous for ease of use and may increase accuracy in dosing. A pen device that does not require the caregiver or patient to convert from milligrams to "units" or "clicks" is more convenient and less likely to cause errors than one that requires conversion. Only one manufacturer, Serono, offers a needle-free device (for Saizen and Serostim).

Most of the products require refrigeration before and after initial use; products with room temperature storage may be advantageous in terms of limiting waste of the product and facilitating use while traveling. All products have a hotline number for patients and caregivers; other materials vary.

ii) Mecasermin

Mecasermin can cause disruptions in blood glucose and may require blood glucose monitoring. Lymphoid tissue hypertrophy, intracranial hypertension: and scoliosis due to slipped capital femoral epiphysis related to rapid growth can also occur.

4) *Overall Clinical Effectiveness Conclusion* – The P&T Committee concluded that:

a) Somatropin products appear to be safe and efficacious for the treatment of various growth-related conditions and for a few specialized non-growth related conditions.

b) There are no studies comparing any somatropin product to another for any given indication. Given that all of the products contain the same concentration (3 IU rhGH/mg) of bioidentical recombinant human growth hormone, they are unlikely to differ in efficacy for the treatment of growth-related or other disorders.

c) There are potential differences between somatropin products with respect to delivery devices, formulations, and stability/storage requirements. Differences that may favor particular products include availability of a pen device (preferably along with a vial/syringe product); the ability to use the pen device without having to do dose conversions, and the ability to store products at room temperature before or after initial use.

d) Mecasermin is safe and efficacious for severe IGF-1 deficiency, a much rarer condition than GHD. It is the only product available for the treatment of this condition.

e) Based on clinical issues alone, there are no compelling reasons to classify any of the GSA agents as non-formulary under the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions above.

B. GSAs – Relative Cost Effectiveness

In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

The GSAs are divided into the IGF-1 and somatropin subclasses. The sole IGF-1 agent is mecasermin. It is indicated for the treatment of IGF-1 deficiency and therefore occupies a unique place in therapy within the GSAs. Among the somatropin products, two (Serostim and Zorbtive) are primarily used in disorders most commonly seen in adult patients (HIV wasting and short bowel syndrome). These two somatropin products are therefore available in dosage forms/ concentrations that would make delivery of a pediatric dose difficult. For these reasons, mecasermin, Serostim, and Zorbtive were excluded from the CMA and BIA. However, they were compared to the other GSAs on a cost per milligram basis.

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the remaining somatropin products within the GSA class differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of GHD. As a result, CMA was performed to compare the relative cost effectiveness of these somatropin products.

Results from the somatropin CMA revealed: 1) Tev-Tropin was the most cost effective somatropin product. However, Tev-Tropin does not offer some of the features (pen dosage forms, storage at room temperature, and ease of use) that some of the more costly products offer; 2) two product lines, Norditropin and Nutropin, are the most cost effective agents that offer physician- and patient-preferred features.

The BIA evaluated the potential impact of various scenarios with one or more somatropin products designated as formulary on the UF. The BIA included a single agent in front of a step-edit (automated PA) as well as two or more (up to all) somatropin products on the UF.

Cost Effectiveness Conclusion – The P&T Committee concluded that:

1) Mecasermin and two somatropin products (Zorbtive and Serostim) have a specific niche in therapy and are offer sufficient value on a cost/mg basis relative to the other agents within the therapeutic class.
2) Tev-Tropin was the most cost effective somatropin agent based on cost-minimization analysis. However, the product offers fewer features than most other growth stimulating agent product lines.
3) Two somatropin product lines, Norditropin and Nutropin, offered more features (pen dosage forms, storage at room temperature, and ease of use) at a middle range of cost.
4) The BIA results showed that the most cost effective formulary strategy for the somatropin products was the combination of the Tev-tropin and the Norditropin and Nutropin product lines.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstention, and 2 absent) to accept the GSA relative cost effectiveness analysis as presented by the PEC.

C. GSAs – UF Recommendations

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the GSA agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend that Tev-Tropin, Nutropin, Nutropin AQ, Norditropin, Nortropin Nordiflex, Serostim, Zorbtive, and mecasermin be maintained as formulary on the UF and that the Genotropin, Humatrope, Saizen and Omnitrope brands of somatropin be classified as non-formulary under the UF.

D. GSAs – MN Criteria

Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for the somatropin products Genotropin, Humatrope, Saizen and Omnitrope:

1) Use of formulary alternatives is contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.

The P&T Committee noted that since the somatropin products all contain the same active ingredient, the most likely scenario under which criterion #2 would apply would be issues specific to specific formulations / preservatives (e.g., injection site reactions).

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to approve the MN criteria outlined above.

E. GSAs – UF Implementation Period

The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have the somatropin products Genotropin, Humatrope, Saizen and Omnitrope on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary Somatropin agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) an effective date of the first Wednesday following a 60-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 60-

day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. GSAs – PA Criteria

Currently, PA criteria apply to both GH (somatropin products) and mecasermin. The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) that the following PA criteria should apply to GH and mecasermin. Changes from previous GH (somatropin) criteria are the addition of Noonan's Syndrome and SHOX deficiency as covered uses; no changes were recommended to mecasermin criteria.

1) *Growth Hormone (Somatropin)* – Coverage would be approved for the treatment of any of the following:
   a) GHD in children and adults as a result of pituitary disease, hypothalamic disease, surgery or radiation therapy
   b) Chronic renal insufficiency before renal transplantation with associated short stature
   c) Other known renal indications: autorecessive polycystic kidney disease, cystinosis and hypophosphatemic rickets in the pediatric population
   d) Short stature in patients with Turner Syndrome or Prader-Willi Syndrome
   e) Infants born small for gestational age that have not reached age appropriate height by 24 months of age
   f) Human immunodeficiency virus-associated wasting in adults
   g) Noonan Syndrome
   h) SHOX deficiency
2) *Mecasermin* – Coverage would be approved for the treatment of:
   a) Patients with severe primary IGFD defined by the following:
      i) Height standard deviation score $\leq$ -3
      ii) Basal IGF-1 standard deviation score $\leq$ -3
      iii) Normal or elevated GH levels

      OR
   b) Patients with GH gene deletion who have developed neutralizing antibodies to GH

   In addition, patients must meet the following criteria:

   - Are receiving ongoing care under the guidance of a health care provider skilled in the diagnosis and management of patients with growth disorders (e.g., pediatric endocrinologist)
   - Thyroid and nutritional deficiencies have been corrected before initiating mecasermin treatment
   - Have been educated on monitoring and management of hypoglycemia

Coverage is NOT provided for:

- Patients with closed epiphyses (bone growth plates)
- Patients with active or suspected neoplasia (therapy should be discontinued if evidence of neoplasia develops)
- Patients with other causes of growth failure (secondary forms of IGF-1 deficiency, such as GHD, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroid

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend the PA criteria outlined above.

G. GSAs – Extended Core Formulary (ECF) Review and Recommendations

The P&T Committee considered the ECF status of the GSA agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 1 abstained, and 3 absent) to recommend that Norditropin / Norditropin Nordiflex be added to the ECF.

9. QUANTITY LIMITS

A. Rizatriptan (Maxalt) – The current QL for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) is 18 tablets per 30 days, or 36 tablets per 90 days. This QL was increased from 12 to 18 tablets per 30 days in May 2006 to accommodate a change in packaging (from 6 tablets per package to 9 tablets per package). Packaging for rizatriptan recently changed again, from 9 tablets per package to 12 tablets per package. QLs for triptans are based on the lack of safety evidence for treating more than 3-4 headaches per month with triptans, dosing recommendations, and package size.

***COMMITTEE ACTION*:** The Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend changing the QL for rizatriptan tablets and orally disintegrating tablets to 12 tablets per 30 days, or 36 tablets per 90 days.

10. BCF STATUS OF ROSIGLITAZONE

Rosiglitazone (Avandia) – The PEC updated the P&T Committee on the two recent alerts issued by the FDA regarding rosiglitazone.

1) *FDA Alert #1: 8/14/2007:* Important revisions to the full prescribing information (labeling) highlighting increased risks of congestive heart failure associated with rosiglitazone. The updated information includes a new BOXED WARNING, and additional updated WARNINGS, PRECAUTIONS and CONTRAINDICATIONS to emphasize that rosiglitazone may cause or exacerbate heart failure, particularly in certain patient populations. *Source*: www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazone200707HCP.htm

2) FDA Alert #2: 5/21/2007**:** Ongoing FDA review of clinical data to assess a potential increased risk of ischemic cardiovascular events in patients taking rosiglitazone. FDA is aware of a potential safety issue related to rosiglitazone maleate. Safety data from a pooled analysis of controlled clinical trials have shown a significant increase in the risk of heart attack and heart-related deaths in patients taking rosiglitazone.

However, other published and unpublished data from long-term clinical trials of rosiglitazone provide contradictory evidence about the risk of ischemic cardiovascular events in patients taking rosiglitazone. FDA's review of all available data is ongoing. FDA has not confirmed the clinical significance of the reported increased risk of ischemic cardiovascular events in the context of other studies. Myocardial ischemic events are currently described in the WARNINGS section of the rosiglitazone label. FDA does not know whether the other approved medication in the same pharmacologic class or other oral drugs for treating type 2 diabetes have less, the same, or greater risks. Switching diabetic patients to other therapies also confers its own risks. For those reasons, FDA is providing this emerging information to prescribers so that they and their patients can make individualized treatment decisions. *Source:* www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazone200707HCP.htm

The P&T Committee discussed the advantages and disadvantages of removing rosiglitazone from the BCF. Ultimately, the P&T Committee determined that there was insufficient clinical evidence to justify removal of rosiglitazone from the BCF at this time. The PEC will update the P&T Committee as more information becomes available.

***COMMITTEE ACTION*:** The Committee voted (7 for, 6 opposed, 1 abstained, 3 absent) to not remove rosiglitazone from the BCF at this time.

11. BCF / ECF REVIEW

The P&T Committee agreed with the PEC's plan to systematically review drug classes represented on the BCF over the next few meetings with the goals of: 1) removing obsolete medications, 2) defining BCF listings more specifically, 3) reframing or revising BCF listings to be compatible with drug classes as defined or outlined by the P&T Committee, and 4) assessing the need for future review. The P&T Committee agreed that BCF/ECF listings will in the future be framed with greater specificity as drug classes are reviewed or reviewed.

The P&T Committee made initial recommendations for clarifying BCF listings in three drug classes or potential drug classes, including atypical antipsychotics (quetiapine and risperidone), osteoporosis agents (alendronate/vitamin D), and cough-cold medications (guaifenesin/pseudoephedrine). Details are outlined in Appendix C.

COMMITTEE ACTION: The P&T Committee recommended the following changes to BCF / ECF listings (see Appendix C for rationale):

Table 3: Recommended BCF / ECF Changes

Drug class or potential drug class	Current BCF / ECF listing	Recommendation	Vote			
			For	Opposed	Abstained	Absent
Atypical antipsychotics	BCF – "Quetiapine"	Clarify BCF listing to: "quetiapine tablets, immediate and extended release"	14	0	1	2
	BCF – "Risperidone oral; does not include orally disintegrating tablets (Risperdal Redi-tabs)"	Clarify BCF listing to: "Risperidone tablets and solution, does not include orally disintegrating tablets"	14	0	1	2
Osteoporosis agents	BCF – "Alendronate 70 mg / vitamin D 2800 IU (Fosamax Plus D)"	Clarify BCF listing to specify new product with higher strength of vitamin D – "Alendronate 70 mg/vitamin D 5600 IU tablets"	14	0	1	2
Cough-cold medications	BCF – "Guaifenesin 600 / PSE 120 mg ER oral"	Remove from BCF	14	0	1	2

12. CLASS OVERVIEWS

Class overviews for the osteoporosis agents were presented to the P&T Committee. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed during the February 2008 meeting; no action is necessary.

13. ADJOURNMENT

The second day of the meeting adjourned at 1700 hours on 15 August 2007. The next meeting will be 14-15 November 2007.

_____// signed // _____

Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

Appendix A – Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 07	Newer Antihistamines	▪ desloratadine (Clarinex) ▪ desloratadine/pseudoephedrine (Clarinex D)	BCF	▪ MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	Pending approval	Pending approval
Aug 07	Leukotriene Modifiers	▪ Zileuton (Zyflo)	BCF	▪ montelukast (Singulair)	Pending approval	Pending approval
Aug 07	Growth Stimulating Agents	▪ somatropin (Genotropin, Genotropin Miniquick) ▪ somatropin (Humatrope) ▪ somatropin (Omnitrope) ▪ somatropin (Saizen)	ECF	▪ somatropin (Norditropin)	Pending approval	Pending approval
Nov 05 (updated for new drug Aug 07)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone propionate (Flonase)	19 Jan 06	19 Apr 06 (90 days)
		Recommended Aug 07 ▪ fluticasone furoate (Veramyst)			Pending approval	Pending approval
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)
May 07	Antilipidemic Agents II	▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	▪ gemfibrozil ▪ fenofibrate IDD-P (Triglide)	24 July 07	21 Nov 07 (120 days)
May 07 re-review (Feb 05 original)	ARBs	▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	24 July 07	21 Nov 07 (120 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications)	**Effective Date for Non-Formulary Medications** (Implementation period)
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	24 July 07	24 Oct 07 (90 days)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	NA
Nov 06	ADHD Agents	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07 (90 days)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
May 06 (updated for new drugs Nov 06)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg rospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	18 Mar 07 (60 days)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05 (updated Aug 07)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated for new drugs Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
		Recommended Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			17 Jan 07	18 Mar 07 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications)	**Effective Date for Non-Formulary Medications** (Implementation period)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	**-**
Feb 05	ARBs – see May 07 for re-review	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs – see May 07 for re-review	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary

ER = extended release; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle

ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs = thiazolidinediones

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Newly Approved Drugs. August 2007 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Budesonide / formoterol inhaler (Symbicort, Astra Zeneca) corticosteroid with long-acting beta agonist	Jul 06 (launched Jul 07) ▪ Long term maintenance treatment of asthma in patients 12 years of age and older.	No UF recommendation at this meeting. Consideration of UF status deferred until inhalational asthma drugs are reviewed; UF review anticipated within the next 12 months. Quantity limits recommended: ▪ TMOP o #3 inhalers per 90 days ▪ Retail Network o #1 inhaler per 30 days
Rotigotine topical patch (Neupro; Schwarz Biosciences) non-ergoline D3/D2/D1 dopamine agonist	May 07 (launched Jul 07) ▪ Treatment of signs and symptoms of early stage idiopathic Parkinson's disease	No UF recommendation at this meeting. Consideration of UF status deferred until Parkinson's drugs are reviewed; UF review not anticipated in the next 12 months.
Estradiol 0.1% gel (Divigel; Upsher-Smith) estrogen for hormone replacement	Jun 07 (launched Aug 07) ▪ Treatment of moderate to severe hot flashes associated with menopause.	No UF recommendation at this meeting. Consideration of UF status deferred until hormone replacement therapies are reviewed; UF review not anticipated in the next 12 months.
Estradiol 0.06% gel (Elestrin; Bradley Pharmaceuticals) estrogen for hormone replacement	Dec 06 (launched Jun 07) Treatment of moderate to severe vasomotor symptoms associated with menopause.	No UF recommendation at this meeting. Consideration of UF status deferred until hormone replacement therapies are reviewed; UF review not anticipated in the next 12 months.

Appendix C – Basic / Extended Core Formulary (BCF/ECF) Review

Drug Class or Potential Drug Class	BCF / ECF listing	Recommendation/ Rationale
Atypical antipsychotics	BCF – "Quetiapine"	• ER formulation (Seroquel XR) approved May 07; manufacturer willing to supply at no higher cost than IR quetiapine; no generics anticipated for some time (~2011). • Available in IR tabs (6 strengths), ER tabs (4 strengths). • Recommendation: • Clarify BCF listing to "Quetiapine tablets, immediate and extended release."
	BCF – "Risperidone oral; does not include orally disintegrating tablets (Risperdal Redi-tabs)"	• Oral dosage forms available: solution, tablets (6 strengths), rapidly disintegrating tablets (5 strengths) • Several manufacturers have tentative ANDAs listed for risperidone solution and tablets; patent expires Dec 2007, pediatric exclusivity ends Jun 2008. Unclear when orally disintegrating tablets will become generically available. • Recommendation: • Clarify BCF listing to "Risperidone tablets and solution, does not include orally disintegrating tablets."
Osteoporosis agents	BCF – "Alendronate 70 mg / vitamin D 2800 IU (Fosamax Plus D)"	• Alendronate 70 mg / vitamin D 5600 IU approved Apr 07; manufacturer willing to extend current pricing agreement for Fosamax Plus D; class to be reviewed soon. • 5600 IU combination recommended for "most" osteoporotic patients. • Recommendation • Clarify BCF listing to specify product with higher strength of vitamin D – "Alendronate 70 mg/vitamin D 5600 IU tablets."
Cough-cold medications	BCF – "Guaifenesin 600 / PSE 120 mg ER oral" (Entex LA generic)	• Guaifenesin containing timed release prescription products targeted for regulatory action by FDA in May 2007. • Companies expected to stop manufacturing unapproved products containing timed-release guaifenesin within 90 days and must cease shipping them in interstate commerce within 180 days. • Only guaifenesin products expected to remain on market are Adams' Labs over-the-counter products (e.g., Mucinex D). • Recommendation: • Remove listing from BCF.

Appendix D – Table of Abbreviations

ACE	angiotensin converting enzyme
ACR	American College of Rheumatology
ALT	alanine aminotransferase
APR	automated profile review
ARB	angiotensin receptor blocker
AR	allergic rhinitis
ARIA	Allergic Rhinitis and Its Impact on Asthma
AST	aspartate aminotransferase
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BP	blood pressure
CEA	cost effectiveness analysis
CFR	Code of Federal Regulations
CI	confidence interval
CIU	chronic idiopathic urticaria
CMA	cost minimization analysis
CRI	chronic renal insufficiency
CYP	cytochrome (P450)
DERP	Drug Effectiveness Review Project (state of Oregon)
DoD	Department of Defense
EIB	exercise-induced bronchoconstriction
ER	extended release
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FY	fiscal year
GAD	generalized anxiety disorder
GH	growth hormone
GHD	growth hormone deficiency
GI	gastrointestinal
GSA	Growth Stimulating Agent (drug class)
HCTZ	hydrochlorothiazide
IGFD	insulin-like growth factor deficiency
ICS	inhaled corticosteroids
ISS	idiopathic short stature
LABA	long-acting beta agonists
LDL	low density lipoprotein
LFT	liver function test
LM	Leukotriene Modifier (drug class)
MAOI	monoamine oxidase inhibitor
MHS	Military Health System
MN	medical necessity
MTF	military treatment facility
NA	Newer Antihistamine (drug class)
NCS	nasal corticosteroids
NHLBI NAEPP	National Heart, Lung and Blood Institute National Asthma Education Prevention Program
OTC	over-the-counter
PA	prior authorization
PAR	perennial allergic rhinitis
P&T	Pharmacy and Therapeutics
PEC	Pharmacoeconomic Center

Appendix D – Table of Abbreviations (continued)

QD	once daily
QID	four times daily
RAAs	renin-angiotensin antihypertensive (drug class)
RCT	randomized controlled trial
RQLQ	rhinoconjunctivitis-specific quality of life
RR	relative risk
rTNSS	reflective Total Nasal Symptom Score
SAR	seasonal allergic rhinitis
SBS	Short bowel syndrome
SED-1	Sedative Hypnotic-1 (drug class)
SGA	small for gestational age
SHOX	Short Stature Homeobox gene
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TID	three times daily
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TNSS	Total Nasal Symptom Score
TRRx	TRICARE Retail Pharmacy Network
TS	Turner Syndrome
UF	Uniform Formulary
ULN	upper limit of normal

DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

May 2007

1. **CONVENING**
2. **ATTENDING**
3. **REVIEW MINUTES OF LAST MEETING**
4. **ITEMS FOR INFORMATION**
5. **REVIEW OF RECENTLY APPROVED AGENTS**

A. Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF) – The Pharmacy and Therapeutics (P&T) Committee was briefed on three new drugs which were approved by the Food and Drug Administration (FDA) (see Appendix B). The P&T Committee determined that these three new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed. The P&T Committee discussed the need for quantity limit (QL) or prior authorization (PA) requirements for the drugs (see paragraph 5A on pages 19-20 of the P&T Committee minutes).

COMMITTEE ACTION: QL RECOMMENDATIONS

- Arformoterol (Brovana) –The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend QLs for arformoterol of 60 unit dose vials per 30 days, 180 unit dose vials per 90 days.
- Lapatinib (Tykerb) – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for lapatinib as follows: 150 tablets per 30 days at retail network pharmacies, with a days supply limit of 30 days (no multiple fills for multiple co-pays); and 225 tablets per 45 days at mail order, with a days supply limit of 45 days.
- Vorinostat (Zolinza) – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for vorinostat as follows: 120 tablets per 30 days at retail network pharmacies, with a days supply limit of 30 days (no multiple fills for multiple co-pays); and 180 tablets per 45 days at mail order, with a days supply limit of 45 days.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. Over-the-Counter Terbinafine 1% Cream (Lamisil AT) – The John Warner National Defense Authorization Act for FY 2007 directs the Secretary of Defense to conduct a demonstration project to assess the impact of authorizing TRICARE coverage for over-the-counter (OTC) agents recommended for inclusion on the UF. The DoD P&T Committee must find that the OTC drug is cost effective and therapeutically equivalent to a prescription drug. The P&T Committee, after consultation with the TRICARE Management Activity (TMA) Pharmacy Program Office, selected the topical antifungal terbinafine 1% cream OTC (Lamisil AT) as the second OTC product for the demonstration.

The P&T Committee reviewed the topical antifungal drug class in May 2005. Topical antifungals on the UF include clotrimazole (Lotrimin, generics), nystatin (Mycostatin, generics), miconazole (Monistat Derm, generics), ketoconazole (Nizoral, generics), butenafine (Mentax), and naftifine (Naftin). Clotrimazole (Lotrimin, generics) and nystatin (Mycostatin, generics) are classified as Basic Core Formulary (BCF) agents. Topical antifungal agents classified as non-formulary under the UF are econazole (Spectazole, generics), sertaconazole (Ertaczo), sulconazole (Exelderm), ciclopirox (Loprox, generics; excludes ciclopirox topical solution (Penlac) for onychomycosis), oxiconazole (Oxistat) and 0.25% miconazole/15% zinc oxide (Vusion).

Relative Clinical Effectiveness – The P&T Committee concluded (14 for, 0 opposed, 1 abstained, 2 absent) that terbinafine 1% cream OTC has no clinically significant differences with respect to safety, efficacy, or tolerability, when compared to other allylamines included on the UF (butenafine and naftifine). The P&T Committee also concluded that it was unlikely that clinically significant differences exist between OTC terbinafine and the other prescription allylamines for the treatment of common dermatologic infections.

Relative Cost Effectiveness – Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) that terbinafine 1% cream OTC is more cost effective than other allylamines in the topical antifungal class (butenafine and naftifine) across all three points of service.

COMMITTEE ACTION: UF RECOMMENDATION –Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that terbinafine 1% cream OTC be classified as formulary on the UF (see paragraph 5B on pages 20-22 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

6. DRUG CLASS REVIEW – ANTILIPIDEMIC II AGENTS (LIP-2s)

The P&T Committee evaluated the relative clinical effectiveness of the Antilipidemic II (LIP-2) agents. This class is divided into three subclasses: fibric acid derivatives, omega-3 fatty acids, and bile acid sequestrants (BAS). The fibric acid derivatives available commercially include gemfibrozil (Lopid, generics) and several formulations of fenofibrate (Tricor, Lofibra, Antara, and Triglide). Omega-3 fatty acid ("fish oil") products include the prescription product Omacor, along with a number of nutritional supplement products available OTC. Of these, only Omacor is eligible for inclusion on the UF. The BAS class consists of cholestyramine/sucrose (Questran, generics), cholestyramine/aspartame (Questran Light, generics), colestipol (Colestid, generics), and the newest agent, colesevelam (Welchol).

The LIP-2 drug class accounted for $63 million in Military Health System (MHS) expenditures in FY 2006, ranking in the top 20 in terms of total expenditures.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the following clinical effectiveness conclusion:

1) Fibric acid derivatives

   a) Both gemfibrozil and fenofibrate reduce triglycerides (TG) by 20-50% and raise high density lipoprotein (HDL) by 10-20%. There is insufficient evidence to conclude that gemfibrozil and fenofibrate differ in their ability to reduce TG and raise HDL.

   b) Two placebo-controlled trials with gemfibrozil have shown a benefit in reducing the risk of cardiovascular events in a primary prevention setting and the risk of nonfatal myocardial infarction (MI) and coronary heart disease (CHD) death in a secondary prevention setting. Mixed results were demonstrated with fenofibrate in a large outcomes trial in a primary/secondary prevention setting; fenofibrate did not result in a statistically significant benefit in reducing the composite of CHD death or nonfatal MI, but was associated with significant reductions in nonfatal MI (p=0.01) and coronary revascularization (p=0.035).

   c) Although gastrointestinal (GI) adverse effects occurred in fewer than 5% of patients taking fibric acid derivatives, they appeared to occur more frequently in patients taking gemfibrozil than those taking fenofibrate, based on pooled data from product labeling. Gemfibrozil must be taken twice daily prior to meals.

   d) Monotherapy with either fibric acid derivatives or statins has been associated with an increased risk of myalgia, myositis, and rhabdomyolysis. This risk appears to be increased with gemfibrozil/statin combination therapy, based on spontaneous adverse event reporting data from the FDA. These data showed a higher reporting rate of rhabdomyolysis with a statin plus gemfibrozil (8.6) compared to a statin plus fenofibrate (0.58), based on the number of spontaneous case reports per 1 million U.S. prescriptions from 1998 to 2002. This study excluded cerivastatin, which has now been withdrawn from the market. Limitations include varying definitions of myotoxicity, lack of verification of data, and the use of spontaneous reporting rates, which are subject to reporting bias and do not establish a causal relationship. It is unclear whether combination therapy with fenofibrate and a

statin increases the risk of myotoxicity more than either agent given alone. One trial comparing statin monotherapy vs. combination therapy with fenofibrate plus a statin reported similar rates of myalgia.

e) Pharmacokinetic differences in glucuronidation pathways between gemfibrozil and fenofibrate are postulated to account for potential differences in the risk of developing myotoxicity when used in combination with a statin. However, there are no head-to-head trials supporting a lower risk of myotoxicity with gemfibrozil than with fenofibrate, either alone or in combination with a statin, and professional organizations have not favored one fibric acid derivative over the other. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the National Heart Lung and Blood Institute conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

f) Fenofibrate formulations include nanocrystallized fenofibrate (Tricor), micronized fenofibrate (Antara), insoluble drug delivery microparticle (IDD-P) fenofibrate (Triglide) and generic formulations of non-micronized and micronized fenofibrate (Lofibra). These newer formulations, regardless of dosage strength or particle size, are bioequivalent to 200 mg of the original fenofibrate formulation. Changes in particle size are designed to address bioavailability issues, allowing the most recent products (Tricor, Antara and Triglide) to offer once daily dosing and be taken without regard to meals. There is insufficient evidence to conclude that newer formulations offer improved efficacy, safety, or tolerability compared to each other or to older formulations.

2) Omega-3 Fatty Acids (Omacor)

a) Omacor is the only prescription omega-3 fatty acid product approved by the FDA. FDA oversight of the manufacturing process for Omacor offers increased assurance of its omega-3 fatty acid content and purity, in contrast to some fish oil supplements.

b) Overall, Omacor decreases TG by 20-45%. However, Omacor has also been associated with increases in low density lipoprotein (LDL), which may offset beneficial reductions in TG.

c) The TG-lowering effects of Omacor are slightly lower than those achieved with fibric acid derivatives or niacin. Omacor is associated with similar increases in HDL compared to fibric acid derivatives and niacin. Niacin and gemfibrozil both have clinical trial evidence supporting long-term benefits on cardiovascular outcomes.

d) The omega-3 fatty acid formulation found in Omacor does not have outcomes studies that demonstrate beneficial cardiovascular effects (e.g., reductions in cardiovascular death, MI or stroke).

3) Bile Acid Sequestrants

a) The BAS agents reduce LDL by 15 to 30%. This subclass has largely been replaced by the statins, which reduce LDL by 18% to 55%. There is insufficient evidence to conclude that BAS differ in their ability to lower LDL.

Cholestyramine is the only BAS to show beneficial effects on cardiovascular outcomes.

b) Colesevelam has no major efficacy advantages compared to cholestyramine or colestipol, despite manufacturer claims of enhanced bile acid binding capacity. It has a more favorable pregnancy category rating than the older products (B vs. C) and may cause less constipation, which may be clinically relevant in patients with a previous history of GI obstruction.

c) Issues with palatability of powder formulations and/or large daily tablet burdens are a concern with the class as a whole and may affect compliance.

d) The BAS agents have a high degree of therapeutic interchangeability.

Overall Clinical Effectiveness Conclusion – Based on clinical issues alone, there are no compelling reasons to classify any of the LIP-2 agents as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: Based on the results of the pharmacoeconomic analyses and other clinical and cost considerations, the DoD P&T Committee voted (15 for, 0 opposed, 0 abstained, and 2 absent) that:

1) Gemfibrozil was the most cost-effective fibric acid derivative evaluated. Of the various fenofibrate formulations, IDD-P fenofibrate demonstrated the best cost effectiveness profile.

2) Colesevelam was recognized as not cost effective in the treatment of hyperlipidemia compared to other BAS.

3) In the management of hypertriglyceridemia, Omacor was identified as not cost-effective compared to gemfibrozil, fenofibrate, and niacin.

4) The UF scenario that maintained fenofibrate, IDD-P fenofibrate, cholestyramine/ aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil on the UF was the most cost effective UF scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the LIP-2s, and other relevant factors, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) that: 1) fenofibrate, IDD-P fenofibrate, cholestyramine/aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil be maintained as formulary on the UF; 2) micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and Omacor be classified as non-formulary under the UF; and 3) the normal brand formulary cost-share of $9.00 for IDD-P fenofibrate (Triglide) be lowered to the generic formulary cost-share of $3.00 (see paragraphs 6A, 6B, and 6C on pages 22-37 of the P&T Committee minutes).

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that “when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate.” The objective is to maximize use of IDD-P fenofibrate in the retail network and mail

order, given its significantly lower cost relative to other fenofibrate products. Lowering the cost-share for brand name IDD-P fenofibrate will provide a greater incentive for beneficiaries to use the most cost effective fenofibrate formulation in the purchased care arena.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) general MN criteria for micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and Omacor (see paragraph 6D on page 37 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 6E on pages 37-38 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows: for 120 days

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that gemfibrozil and IDD-P fenofibrate (Triglide) be designated as the BCF selections in this class (see paragraph 6F on page 38 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

7. DRUG CLASS REVIEW – 5-ALPHA REDUCTASE INHIBITORS (5-ARIs)

The P&T Committee evaluated the relative clinical effectiveness of the 5-alpha reductase inhibitor agents (5-ARIs). The 5-ARI drug class includes finasteride (Proscar, generics) and dutasteride (Avodart). Both have been approved by the FDA for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate.

The 5-ARI drug class accounted for $31.2 million in MHS expenditures for FY 2006 and is ranked #50 in terms of total expenditures. More than 281,000 prescriptions for 5-ARIs

were filled in the MHS during a one-year period (January 2006 to December 2006). Of these, 59% were for finasteride and 41% were for dutasteride.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the following clinical effectiveness conclusion:

1) There is insufficient evidence to conclude that there are significant differences in efficacy between finasteride and dutasteride. Indirect comparisons from long-term efficacy trials suggest similar decreases in total prostate volume, increases in urinary flow rate, improvement in symptoms, and similar reductions in the risk of acute urinary retention and BPH-related surgery.
2) The only fully published head-to-head trial suggests that dutasteride therapy reduces serum dihydrotestosterone levels by 95%, compared to 71% with finasteride. The clinical significance of this finding has yet to be determined. This 24-week trial contributes no useful comparative data concerning long-term efficacy. A large but as yet unpublished head-to-head trial (the Enlarged Prostate International Comparator Study) reported no differences in efficacy outcomes with finasteride vs. dutasteride after one year of treatment.
3) There is insufficient evidence to compare the two agents when used in combination with alpha blockers. More data are available with finasteride than with dutasteride, including a long-term trial with finasteride and doxazosin (the Medical Therapy of Prostatic Symptoms trial); there are no published long-term combination trials with dutasteride.
4) The overall effect of 5-ARIs on prostate cancer prevention is unclear.
5) There appear to be few differences in the incidence of adverse effects with finasteride or dutasteride, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated. The most common adverse effects are related to sexual dysfunction; they diminish with chronic dosing.
6) Reported withdrawal rates due to adverse effects are low in clinical trials of finasteride and dutasteride, similar during the first year of therapy, and decrease further with both agents during continued treatment.
7) There are no major differences between finasteride and dutasteride with regard to use in special populations or drug interactions.
8) Neither agent appears to interfere with prostate cancer detection.
9) Finasteride and dutasteride appear to have a high degree of therapeutic interchangeability; either could be expected to meet the needs of the majority of DoD BPH patients.

Relative Cost Effectiveness Conclusion: Based on the results of the cost minimization analysis (CMA) and other clinical and cost considerations, the DoD P&T Committee voted (15 for, 0 opposed, 0 abstained, and 2 absent) that:

1) Finasteride was the most cost effective agent, with a lower cost per day of treatment than dutasteride across all condition sets evaluated.

2) A cost-effectiveness analysis that evaluated the cost per BPH surgery averted showed that finasteride was the preferred choice with a lower expected cost per surgery averted than dutasteride.

3) The UF scenario that placed finasteride as the sole 5-ARI on the UF was the most cost effective scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the 5-ARIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that: 1) finasteride be classified as formulary on the UF, and 2) that dutasteride be classified as non-formulary under the UF (see paragraphs 7A, 7B, and 7C on pages 38-44 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for dutasteride and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for dutasteride (see paragraph 7D on page 44 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 7E on pages 44-45 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend designating finasteride as the BCF selection in this class (see paragraph 7F on page 45 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

8. DRUG CLASS REVIEW – PROTON PUMP INHIBITORS (PPIs)

The P&T Committee evaluated the relative clinical effectiveness of the PPIs. The PPI drug class includes the following agents: esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec and generics), omeprazole/sodium bicarbonate (Zegerid), omeprazole magnesium (Prilosec OTC), pantoprazole (Protonix), and rabeprazole (Aciphex). Omeprazole magnesium (Prilosec OTC) was added to the UF for purposes of the OTC Demonstration Project as a result of the February 2007 P&T Committee meeting.

PPIs have become the standard of care for treatment of acid-related gastrointestinal disorders. As of March 07, about 350,000 MHS prescriptions for PPIs are filled per month. This drug class has now taken over the #1 spot in terms of MHS expenditures: more than $485 million over the 12 months from April 2006 to March 2007, compared to about $350 million in FY 2005. Military treatment facility (MTF) pharmacies dispense 47% of all PPI tablets, compared to 36% dispensed by retail network pharmacies and 17% dispensed by the TRICARE Mail Order Pharmacy (TMOP). Across the MHS, rabeprazole is the most commonly prescribed PPI, due mainly to its favorable formulary status and high utilization at MTFs. The next four most-prescribed PPIs – lansoprazole, esomeprazole, pantoprazole, and omeprazole – have similar utilization patterns. Of the PPIs, only prescription omeprazole is generically available.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the following clinical effectiveness conclusion:

1) Based on head-to-head and other controlled trials, PPIs have similar efficacy in a wide range of acid related disorders and are highly therapeutically interchangeable.

2) Although some trials appear to demonstrate superior efficacy for healing of erosive esophagitis (EE) with esomeprazole, actual differences are small and inconsistent among trials. Evidence for clinical efficacy is similar enough to consider all agents equally effective in healing of EE.

3) There is sufficient evidence to support the use of PPIs for maintenance of initial healing and symptomatic relief of EE for as long as five years. However, the evidence is insufficient to conclude that one PPI is superior to the others for maintenance of EE healing.

4) There appear to be no comparative differences among PPIs for healing, maintenance of healing, or symptom improvement in peptic ulcer disease and/or non-steroidal anti-inflammatory drug (NSAID) induced ulcers.

5) Based on available clinical trials, PPIs appear to be similarly efficacious in the short-term treatment of endoscopy-negative reflux disease (ENRD); there are insufficient data to draw conclusions regarding efficacy for long-term or on-demand treatment.

6) *H. pylori* eradication rates appear similar among PPIs when differing doses of antibiotics and treatment duration are taken into account.

7) There are insufficient data to suggest superiority of one PPI over the others for treatment of pediatric patients; omeprazole, lansoprazole, and esomeprazole have FDA indications for use in pediatric patients.

8) The class as a whole is well-tolerated, with an adverse effect profile similar to placebo; most drug interactions are minor in nature. In general, PPIs appear very similar with respect to safety and tolerability.

9) Minor differences include the lack of a requirement to adjust the dose of pantoprazole (Protonix) in patients with severe hepatic disease (unlike other PPIs); a less favorable pregnancy category rating for omeprazole than the more recently introduced PPIs (C vs. B); and the availability of liquid dosage forms for esomeprazole, lansoprazole, and omeprazole/sodium bicarbonate.

Relative Cost Effectiveness Conclusion: Based on the results of the CMAs and other clinical and cost considerations, the P&T Committee voted (14 for, 0 opposed, 0 abstained, 3 absent) that:

1) The CMA of each potential UF scenario showed that, as expected, the more restrictive the UF scenario, the lower the cost per day of treatment.

2) Among UF scenarios with two agents on the UF, omeprazole and esomeprazole were the most cost effective option.

3) Among UF scenarios with three to four agents on the UF, omeprazole, esomeprazole, pantoprazole, and rabeprazole were the most cost effective agents.

4) The UF scenario that maintained omeprazole and esomeprazole as the only two agents on the UF in conjunction with a PA requiring a trial of either agent for new patients was the most cost effective scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that: 1) omeprazole and esomeprazole be maintained as formulary on the UF with a PA requiring a trial of either agent for new patients; 2) that rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate be classified as non-formulary under the UF with a PA requiring a trial of either omeprazole or esomeprazole for new patients; and 3) that the normal brand formulary cost-share of $9.00 for esomeprazole be lowered to the generic formulary cost-share of $3.00.

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T may also designate that the drug be cost-shared at the generic rate." Lowering the cost-share for brand name esomeprazole will provide a greater incentive for beneficiaries to use esomeprazole rather than the less cost effective branded products – rabeprazole, lansoprazole, pantoprazole, or omeprazole/sodium bicarbonate – in the

purchased care arena (see paragraphs 8A, 8B, and 8C on pages 46-53 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: PA CRITERIA

The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) that the following PA criteria should apply to PPIs other than omeprazole or esomeprazole. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:
    a) The patient has received a prescription for any PPI agent at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.
2) PA criteria if automated criteria are not met:
    a) The patient has tried omeprazole or esomeprazole and had an inadequate response or was unable to tolerate treatment due to adverse effects.
    b) Treatment with omeprazole or esomeprazole is contraindicated.

(See paragraph 8D on pages 53-54 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate (see paragraph 8E on page 54 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 8F on page 54 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend designating generic omeprazole (Prilosec 40 mg specifically omitted) and esomeprazole as the BCF selections in this class (see paragraph 8G on page 55 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

9. DRUG CLASS REVIEW – ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

The P&T Committee evaluated the relative clinical effectiveness of the seven angiotensin receptor blockers (ARBs) marketed in the U.S. The ARB drug class is comprised of losartan (Cozaar), irbesartan (Avapro), valsartan (Diovan), candesartan (Atacand), telmisartan (Micardis), eprosartan (Teveten), olmesartan (Benicar) and their respective combinations with hydrochlorothiazide (HCTZ).

Utilization of the ARBs has been steadily increasing in the MHS. The ARB drug class accounted for $137 million in MHS expenditures in FY 2006, and is ranked #10 in terms of total expenditures during that time period.

The P&T Committee focused on efficacy differences with respect to labeled indications, particularly in those areas where a benefit in clinical outcomes (e.g., death, hospitalization for heart failure, decreased need for dialysis or renal transplantation) was demonstrated. The primary areas evaluated were efficacy for hypertension, chronic heart failure, and type 2 diabetic nephropathy.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the following clinical effectiveness conclusion:

1) There is no evidence that any one ARB is more efficacious than the others for lowering blood pressure.
2) Although losartan is labeled to reduce the risk of stroke in patients with left ventricular hypertrophy (LVH), Joint National Commission (JNC) guidelines support use of other antihypertensive drugs (e.g., angiotensin converting enzyme (ACE) inhibitors, diuretics) in this setting. Differences in blood pressure reduction largely account for differences in cardiovascular outcomes seen in trials comparing ARBs to other antihypertensives.
3) There is no evidence to support clinically significant differences in efficacy between candesartan and valsartan in reducing heart failure (HF) hospitalizations in patients with chronic HF.
4) There is no evidence to support clinically significant differences in efficacy between irbesartan and losartan in improving clinical outcomes (e.g., reducing the risk of doubling of serum creatinine, death, or development of end stage renal disease) in patients with type 2 diabetic nephropathy.
5) Valsartan is the only ARB labeled to reduce death and development of heart failure in post-MI patients with left ventricular systolic dysfunction (LVSD).

However, ACE inhibitors have a larger body of evidence supporting a mortality benefit in post-MI patients with LVSD than valsartan. The aldosterone antagonists spironolactone (Aldactone, generics) and eplerenone (Inspra) are also labeled for use or have shown efficacy in the post-MI setting.

6) There is no evidence that the ARBs differ significantly with regard to safety and tolerability profiles.

7) Based on clinical issues alone, there are no compelling reasons to classify any of the ARBs as nonformulary under the UF.

Relative Cost Effectiveness Conclusion: Based on the results of the CMAs and other clinical and cost considerations, the Committee voted (15 for, 0 opposed, 0 abstained, and 2 absent) that:

1) A UF scenario with three or fewer agents on the UF was more cost effective than scenarios that included additional agents on the UF.

2) Telmisartan was the most cost effective agent for the management of hypertension; candesartan was more cost effective for management of chronic HF than valsartan; losartan and irbesartan had similar cost effectiveness profiles for treatment of type 2 diabetic nephropathy.

3) The UF scenario that included candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ was the most cost effective UF scenario evaluated.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ARBs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ be maintained as formulary on the UF and that eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ be classified as non-formulary under the UF (see paragraphs 9A, 9B, and 9C on pages 55-61 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) general MN criteria for eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ (see paragraph 9D on pages 61-62 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 9E on pages 62 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the results of the clinical and economic evaluations, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that telmisartan and telmisartan/HCTZ remain on the BCF (see paragraph 9F on page 62 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows

10. QUANTITY LIMITS

The P&T Committee agreed that current QLs for two nasal inhalers should be increased, based on daily maximum doses recommended in product labeling and increases in QL override requests based on higher dosing consistent with labeling (see paragraph 10 on pages 63-64 of the P&T Committee minutes).

COMMITTEE ACTION: QL RECOMMENDATIONS

- Mometasone nasal spray (Nasonex) – The Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that the QL for mometasone nasal spray (Nasonex) be increased to 34 gm (2 inhalers) per 30 days (retail network pharmacies), 102 gm (6 inhalers) per 90 days (mail order), based on daily maximum dosing recommended in product labeling.
- Ipratropium nasal spray (Atrovent) – The Committee voted (13 for, 0 opposed, 2 abstained, and 2 absent) to recommend that 1) the QL for ipratropium nasal spray (Atrovent) be changed from a collective limit to a QL by strength; 2) the QL for the 0.03% strength be increased to 2 inhalers (60 mL) per 30 days (retail network pharmacies), 6 inhalers (180 mL) per 90 days (mail order); and 3) the QL for the 0.06% strength be increased to 3 inhalers (45 mL) per 30 days (retail network pharmacies), 9 inhalers (135 mL) per 90 days (mail order), based on daily maximum dosing recommended in product labeling.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

11. RE-EVALUATION OF NON-FORMULARY AGENTS

Amlodipine (Norvasc) was designated non-formulary at the August 2005 P&T Committee meeting. In early 2007, the FDA approved Mylan Pharmaceutical's first-time generic for Norvasc (amlodipine, Pfizer). The price of amlodipine remains high enough that the Committee felt that even the generic was not cost effective relative to other drugs in the calcium channel blocker class. However, as part of its re-evaluation of the non-formulary UF status of amlodipine, the P&T Committee recognized that there will be situations in the future in which it would be helpful if a procedure were in place that allowed reclassification of such a drug from non-formulary to generic in a more expeditious manner than can be accomplished through the normal quarterly P&T Committee cycle. Such a procedure would be advantageous for both the MHS and its beneficiaries. The P&T Committee proposed the following process to more expeditiously reclassify non-formulary agents:

1) For each drug class in which such a reclassification is a possibility, the P&T Committee will recommend criteria under which non-formulary agents will be reclassified as generic agents on the UF. These criteria will be reviewed and adopted as a recommendation of the committee. The recommendation will be subject to comment by the Beneficiary Advisory Panel (BAP), and final decision by the Director, TMA (see recommended criteria below).
2) When the pre-established criteria for reclassification are met, the Chairperson of the P&T Committee will call for an electronic vote by the members of the P&T Committee on the matter.
3) Upon a majority vote affirming that the non-formulary drug should be reclassified as generic, that agent will be changed from non-formulary status to formulary status as a generic.
4) Committee members will be briefed on any reclassification of a non-formulary agent at the next meeting of the P&T Committee. This information will be recorded as an information-only item in the meeting minutes. The item will be included in information provided for the BAP's next meeting; however, since the BAP will have already made any comments on the subject, it is not expected the item will normally generate further BAP comment.

The DoD P&T Committee recommended the following criteria for the re-evaluation of non-formulary agents for UF status. These criteria would apply only to drug classes in which UF status was NOT awarded based on condition sets that specified the number of similar agents on the UF (i.e., agents in the same class or subclass). All three criteria must be met for the reclassification of a non-formulary agent.

1) The P&T Committee had concluded previously that the non-formulary agent had similar relative clinical effectiveness (i.e., similar efficacy, safety, and tolerability) compared to similar agents on the UF, and the drug had not been excluded from the UF based on clinical issues alone.
2) The non-formulary agent becomes generically available and:
    a) The generic product is "A-rated" as therapeutically equivalent to the brand name product according to the FDA's classification system

b) The generic market supply is stable and sufficient to meet DoD MHS supply demands.

3) The non-formulary agent is cost effective relative to similar agents on the UF. A non-formulary agent becomes cost-effective when:

a) The non-formulary agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the UF class to which they were compared.

b) The non-formulary agent's total weighted average cost based on an alternate measure used during the previous review is less than or equal to that for the UF class to which they were compared. For example, antibiotics may be compared on the cost per course of therapy used to treat a particular condition.

(See paragraph 11 on pages 64-65 of the P&T Committee minutes).

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 against, 3 absent) that the process and criteria described above should be adopted.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

Appendix A – TABLE 1. Implementation Status of UF Recommendations/Decisions
Appendix B – TABLE 2. Newly Approved Drugs
Appendix C – TABLE 3. Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____signed_____

S. Ward Casscells
24 July 2007

Department of Defense
Pharmacy and Therapeutics Committee Minutes
May 2007

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on May 15-16, 2007 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
LTC Brett Kelly, MSC, USA	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Lt Col Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
Capt Jeremy King, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
LCDR Ronnie Garcia, MC *for* LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician
CDR David Tanen, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL David Estroff, MC *for* COL Ted Cieslak, MC	Army, Physician at Large
LTC Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino, RPh.	Department of Veterans Affairs

B. Voting Members Absent

Col Everett McAllister, BSC	Air Force, Pharmacy Officer
LCDR Scott Akins, MC	Navy, Pediatrics Physician

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CPT Alvin Blackmon, MSC, USA	Defense Supply Center Philadelphia
Mr. Lynn T. Burleson	Assistant General Counsel, TMA

D. Non-Voting Members Absent

LT Thomas Jenkins, MSC, USN	TMA Aurora
Martha Taft	Health Plans Operations, TMA

E. Others Present

Col Nancy Misel, BSC, USAF	IMA DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
LCDR Joe Lawrence, MSC, USN	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
Shana Trice, Pharm.D.	DoD Pharmacoeconomic Center
David Bretzke, Pharm.D.	DoD Pharmacoeconomic Center
Angela Allerman, Pharm.D.	DoD Pharmacoeconomic Center
Eugene Moore, Pharm.D.	DoD Pharmacoeconomic Center
Julie Liss, Pharm.D.	DoD Pharmacoeconomic Center
Elizabeth Hearin, Pharm.D.	DoD Pharmacoeconomic Center
David Meade, Pharm.D.	DoD Pharmacoeconomic Center
Harsha Mistry, Pharm.D.	DoD Pharmacoeconomic Center
Lisa Longo, Pharm.D.	VAPBM
Lisa McNair	TMA
LCDR Rob Hayes	DHHS, Indian Health Service

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – February 2007 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. Approval of February Minutes – MG Elder Granger, USA, MC, Deputy Director, TMA, approved the minutes of the February 2007 DoD P&T Committee meeting on May 2, 2007.

4. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss briefed the members of the P&T Committee regarding the March 2007 BAP meeting. The P&T Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions – The PEC briefed the members of the P&T Committee on the progress of implementation for drug classes reviewed for UF status since February 2005.

C. Administrative Action – Modification of Modafinil (Provigil) Prior Authorization (PA) Criteria – A PA for modafinil (Provigil) was recommended by the P&T Committee at the November 2006 meeting and subsequently approved by the Director, TMA, with an effective date of April 18, 2007. The PEC briefed the members of the P&T Committee on an administrative action to omit the PA criterion addressing use for cocaine dependence from PA criteria posted on the TRICARE Pharmacy website and incorporated into PA forms. The criterion provided for coverage of modafinil for cocaine dependence, based on two randomized trials supporting the use of modafinil for the treatment of cocaine dependency. (One trial reported decreased euphoria with cocaine use, the other an increased abstinence rate; modafinil is thought to counteract the glutamate-depleting effect of cocaine, possibly reducing craving.) The criterion was administratively omitted because coverage of substance abuse treatment in settings other than authorized institutional providers falls under another TRICARE approval process and is affected by other TRICARE regulations, not because of clinical considerations. The P&T Committee concurred with the change.

5. REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on three new drugs which were approved by the Food and Drug Administration (FDA) (see Appendix B). The P&T Committee determined that these three new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed. The P&T Committee discussed the need for quantity limit (QL) or PA requirements for the drugs.

The P&T Committee agreed that the three new drugs required QLs, based on existing QLs for similar agents (oral cancer agents and products for oral inhalation) and recommendations for use in product labeling.

COMMITTEE ACTION: QLs

- Arformoterol (Brovana) – The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend QLs for arformoterol (Brovana) of 60 unit dose vials per 30 days, 180 unit dose vials per 90 days.

- Lapatinib (Tykerb) – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for lapatinib (Tykerb) as follows: 150 tablets per 30 days at retail network pharmacies, with a days supply limit of 30 days (no multiple fills for multiple co-pays); and 225 tablets per 45 days at mail order, with a days supply limit of 45 days.
- Vorinostat (Zolinza) – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for vorinostat (Zolinza) as follows: 120 tablets per 30 days at retail network pharmacies, with a days supply limit of 30 days (no multiple fills for multiple co-pays); and 180 tablets per 45 days at mail order, with a days supply limit of 45 days.

B. Over-the-Counter (OTC) terbinafine 1% Cream (Lamisil AT)

Section 705 of the John Warner National Defense Authorization Act for Fiscal Year 2007 directs the Secretary of Defense to conduct a demonstration project under section 1092 of title 10, U.S. Code, to allow particular OTC drugs to be included on the UF under section 1074g of such title. The purpose is to assess the impact of authorizing TRICARE coverage for OTC agents recommended for inclusion on the UF. For an OTC drug to be included as part of the OTC Demonstration Project, the P&T Committee must find that the OTC drug is cost effective and therapeutically equivalent to a prescription drug. Beneficiaries will be required to have a prescription for the OTC product. OTC drugs provided under the demonstration project shall be made available through military treatment facilities (MTFs) and the TRICARE Mail Order Pharmacy (TMOP).

The P&T Committee, after consultation with the TMA Pharmacy Program office, selected the topical antifungal terbinafine 1% cream OTC (Lamisil AT) as the second OTC product for the project. Since this is the first opportunity for terbinafine 1% cream OTC to be considered for UF inclusion, it was reviewed as a new drug in a class previously reviewed.

The P&T Committee reviewed the topical antifungal drug class in May 2005. Topical antifungals on the UF include clotrimazole (Lotrimin, generics), nystatin (Mycostatin, generics), miconazole (Monistat Derm, generics), ketoconazole (Nizoral, generics), butenafine (Mentax), and naftifine (Naftin). Clotrimazole and nystatin are classified as Basic Core Formulary (BCF) agents. Topical antifungal agents classified as non-formulary under the UF are econazole (Spectazole, generics), sertaconazole (Ertaczo), sulconazole (Exelderm), ciclopirox (Loprox, generics; excludes ciclopirox topical solution (Penlac) for onychomycosis), oxiconazole (Oxistat) and 0.25% miconazole/15% zinc oxide (Vusion).

1) *Relative Clinical Effectiveness* – Terbinafine is a synthetic allylamine derivative that interferes with synthesis of the fungal cell wall. Terbinafine was originally available as a prescription product in 1992, but as of 1999 is solely available OTC. FDA-approved indications for terbinafine include tinea pedis, tinea cruris, and tinea corporis. Terbinafine is also effective for treating tinea versicolor, although it is not labeled for this indication. Dosing and administration vary with the indication; for tinea pedis, terbinafine is applied twice daily for seven days, or once daily for four weeks. For tinea versicolor, tinea corporis, or tinea cruris, the

recommended dosing is once daily for 14 days. Terbinafine 1% OTC is available in several different formulations, including cream, spray, and gel; only the cream is under consideration for UF inclusion.

Allylamines on the UF include butenafine (Mentax) and naftifine (Naftin). The allylamines, including terbinafine, appear to be slightly more efficacious than azoles for treatment of tinea pedis. A Cochrane analysis evaluated efficacy of the allylamines (terbinafine, naftifine) and azoles (clotrimazole, econazole, miconazole, and sulconazole) for treating tinea pedis. Pooled analyses of trials comparing azoles with allylamines yielded cure rates of 73% with the azoles vs. 80% with the allylamines. There were no detectable differences in efficacy between individual allylamines or individual azoles.

In general, topical antifungals are recognized as safe and well-tolerated, allowing for the switch from prescription to OTC status for terbinafine. Common adverse events reported with terbinafine include burning, stinging, peeling or other local reactions, which are commonly attributed to the vehicle or the condition itself; terbinafine does not appear to be any more likely to cause these adverse reactions than the other allylamine products on the UF.

Conclusion: The P&T Committee concluded that terbinafine 1% cream OTC has no clinically significant differences with respect to safety, efficacy, or tolerability, when compared to other allylamines included on the UF. The P&T Committee also concluded that it was unlikely that clinically significant differences exist between OTC terbinafine and the prescription allylamines for the treatment of common dermatologic infections.

2) *Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of terbinafine 1% cream OTC in relation to efficacy, safety, tolerability, and clinical outcomes of the other allylamines in the topical antifungal class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

   Based on the information reported from the relative clinical effectiveness evaluation, there was evidence to suggest that terbinafine 1% cream OTC has similar efficacy, safety, tolerability, and clinical outcomes compared to the other allylamines in the topical antifungal class.

   The cost review for terbinafine 1% cream OTC compared the Federal Supply Schedule cost per 30 grams to the other allylamines, naftifine and butenafine.

   Conclusion: The results of the cost review showed that terbinafine 1% cream OTC is more cost effective than other allylamines in the topical antifungal class (butenafine and naftifine) across all three points of service.

3) *Clinical and Cost Effectiveness Conclusions* – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to accept the clinical and cost effectiveness conclusions stated above.

   COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional

judgment, voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend that terbinafine 1% cream OTC be classified as formulary on the UF for the OTC Demonstration Project.

4) *Medical Necessity (MN) Criteria* – Since terbinafine 1% cream OTC was not recommended for non-formulary status under the UF, establishment of MN criteria is not applicable.

5) *UF Implementation Period* – Since terbinafine 1% cream OTC was not recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

6. DRUG CLASS REVIEW – ANTILIPIDEMIC AGENTS II (LIP-2s)

The P&T Committee evaluated the relative clinical effectiveness of the Antilipidemic Agents II (LIP-2) agents. This class is divided into three subclasses: fibric acid derivatives, omega-3 fatty acids, and bile acid sequestrants. Omega-3 fatty acid ("fish oil") products include the prescription product Omacor, along with a number of nutritional supplement products available OTC. Of these, only Omacor is eligible for inclusion on the UF.

The LIP-2 drug class accounted for $63 million in Military Health System (MHS) expenditures in FY 2006, ranking in the top 20 in terms of total expenditures. By comparison, the LIP-1 drug class reviewed in August 2006 (statins, ezetimibe, niacin, and combinations) accounted for $500 million in MHS expenditures and was ranked #1.

A. LIP-2s – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the LIP-2 agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

Table 1: Antilipidemic II Agents Available in the U.S.

Subclass	Generic Name	Brand Name
Fibric Acid Derivatives	Gemfibrozil	Lopid, generics
	Fenofibrate	
	Nanocrystallized	Tricor
	Non-micronized/micronized	Lofibra (generic to innovator Tricor)
	Micronized	Antara
	IDD-P (micronized)	Triglide
Omega-3 fatty acids	Omega-3 fatty acid	Omacor
Bile Acid Sequestrants	Cholestyramine/aspartame	Questran Light, Prevalite, generics
	Cholestyramine/sucrose	Questran, generics
	Colestipol	Colestid, generics
	Colesevelam	Welchol

IDD-P = Insoluble Drug Delivery - microParticle

1) Formulations

a) Fibric Acid Derivatives

i) Products

The fibric acid derivatives available commercially include gemfibrozil (Lopid, generics) and several formulations of fenofibrate. Fenofibrate is a prodrug that is metabolized to its active ingredient, fenofibric acid. The innovator fenofibrate product launched in 1998 under the trade name Tricor by Abbott Laboratories was very insoluble in water, thus was poorly absorbed and required administration with food. Drug particle size has been reduced in newer fenofibrate formulations to enhance absorption compared to the original fenofibrate product. As products are re-formulated, previous versions are typically removed from the market.

The most recent fenofibrate formulations are micronized fenofibrate (Antara), insoluble drug delivery microparticle (IDD-P) fenofibrate (Triglide), and nanocrystallized fenofibrate (Tricor). Antara, Triglide, and Tricor can be taken without regard to meals.

The innovator fenofibrate formulation has been discontinued by Abbott, along with a later version. The current Tricor product (nanocrystallized) is the third version on the market. Lofibra is a branded generic to the two earlier Tricor formulations, and is available in both a micronized and non-micronized version.

ii) FDA approval process

The newer fenofibrate formulations received FDA approval via a 505b(2) application. Under this process, newer products are approved by demonstrating bioequivalence to the original new drug application of the innovator fenofibrate 200 mg product. The newer formulations are marketed in varying dosage strengths lower than 200 mg. However, bioequivalence is similar between innovator fenofibrate 200 mg, IDD-P micronized fenofibrate (Triglide) 160 mg, nanocrystallized fenofibrate 145 mg, and micronized fenofibrate (Antara) 130 mg.

b) Omega-3 Fatty Acids

i) Products

Fish oil Supplements – The omega-3 fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Several formulations of omega-3 fatty acids (fish oils) are available as dietary supplements. Dietary products do not undergo the rigorous approval process required for prescription products.

Prescription omega-3 fatty acids (Omacor) – Omacor is a marine-derived omega-3 polyunsaturated fatty acid product that was approved by the FDA in 2004. It is the first and only prescription fish oil product available. Each 1-gram Omacor capsule contains 90% omega-3 acid esters,

consisting of 465 mg (46%) EPA, 375 mg (38%) DHA), 6% other omega-3 acid esters, and 10% omega-6 fatty acids.

ii) FDA indication

Fish Oil Supplements – The FDA allows a qualified health claim for dietary supplements and conventional foods containing EPA and DHA omega-3 fatty acids to reduce the risk of coronary heart disease (CHD).

Omacor – Omacor is currently approved only as an adjunct to diet in patients with very high triglyceride (TG) levels (>500 mg/dL).

iii) Off-label uses

Prevention of CHD – In Europe, fish oil supplements are approved by regulatory authorities for secondary prevention of CHD. The U.S. FDA has not approved use of the Omacor product for CHD prevention, as it considers the data incomplete. In February 2007, the manufacturer added wording to the labeling stating that Omacor has not been shown to prevent myocardial infarction (MI) or strokes. However, Omacor is likely to be used off-label for CHD prevention.

c) Bile Acid Sequestrants

i) Products – The bile acid sequestrants (BAS) have been marketed since the 1960s and are still utilized for lowering low density lipoprotein (LDL). The class consists of cholestyramine/sucrose (Questran, generics), cholestyramine/aspartame (Questran Light, generics), colestipol (Colestid, generics), and the newest agent, colesevelam (Welchol).

ii) Indications – The BAS are all indicated for use as either monotherapy or in combination with statins to reduce LDL.

iii) Pharmacokinetics – The BAS are not absorbed and are not hydrolyzed by digestive enzymes. The older agents preferably bind to dihydroxy bile acids over trihydroxy bile acids. Colesevelam binds to both dihydroxy and trihydroxy bile acids equally, thus removing both types of bile acids from the circulation. *In vitro* lab data suggests that colesevelam is 4 to 6 times more potent than the older BAS in regard to lower total cholesterol and LDL levels, possible due to enhanced binding of trihydroxy bile acids. However, this difference in *in vitro* binding has not translated into enhanced efficacy of colesevelam in clinical trials assessing lipid parameters.

2) Efficacy

a) Efficacy Measures

The primary efficacy measures used to assess efficacy of the LIP-2 agents are reduction in LDL, TG, and total cholesterol levels (TC), and increases in high-density lipoprotein (HDL). The fibric acid derivatives and omega-3 fatty acids primarily reduce elevated TG levels and raise HDL. The BAS primarily reduce LDL.

When available, clinical outcomes data (reduction of CHD risk, including MI, mortality (all-cause or CHD), need for revascularization, and stroke) were also evaluated to assess differences between agents.

b) Fibric Acid Derivatives

i) Lipoprotein efficacy

Package inserts – The majority of clinical trials evaluating lipid effects have compared gemfibrozil or fenofibrate (Tricor, Antara, Triglide, Lofibra) with placebo. Both fenofibrate and gemfibrozil reduce TG levels by 20 to 50% and increase HDL by 10 to 20%. Varying effects on LDL concentrations are seen, ranging from reductions to increases of 5 to 20%.

Head-to-head trial – One small comparative trial with the fibric acid derivatives is available. Micronized fenofibrate 200 mg (an earlier Tricor formulation) was compared to gemfibrozil in 21 patients with type IIa and IIb hyperlipidemia. After six weeks, similar reductions in triglycerides were seen between the two agents (54% with fenofibrate vs. 46.5% with gemfibrozil; not statistically significant). However, micronized fenofibrate resulted in greater reductions in LDL and TC than gemfibrozil. The differences in LDL effects were likely attributed to the fact that a gemfibrozil dose of 900 mg QD was used, rather than the FDA-approved 600 mg BID dosage.

ii) Clinical outcomes

Three placebo-controlled trials are available that assessed clinical outcomes for gemfibrozil (HHS, VA-HIT) and fenofibrate (FIELD). There are no published head-to-head trials available that assess clinical outcomes (e.g. all-cause mortality, CHD mortality, MI, etc).

- *Helsinki Heart Study 1987 (HHS)* – HHS was a double-blind, placebo-controlled study conducted in 4,000 Finnish men (average age 47 years) who did not have CHD (primary prevention trial). After five years, gemfibrozil 600 mg BID resulted in a significant reduction (34%) in nonfatal MI and CHD death, compared to placebo. There was no difference between gemfibrozil and placebo in all-cause mortality.
- *Veteran Affairs High density lipoprotein cholesterol Intervention Trial 2001 (VA-HIT)* – VA-HIT was a secondary prevention trial conducted in over 2,000 male VA patients who had a history of CHD (average age 64 years). After five years, compared to placebo, treatment with gemfibrozil 600 mg BID resulted in a significant reduction (22%) in the risk of nonfatal MI or CHD death. There was no difference in death due to any cause. Thirty percent of the study participants were diabetic, and when this subpopulation was analyzed, significant reductions in the composite of nonfatal MI, stroke and CHD death were seen.

- *Fenofibrate Intervention and Event Lowering in Diabetes 2005 (FIELD)* – The FIELD trial was a randomized double-blinded placebo-controlled trial which included 9,975 type 2 diabetic participants, 2,131 of whom had cardiovascular disease. Patients were treated with fenofibrate 200 mg QD or placebo for 5 years. Patients were not receiving statins at the start of the study, but could start antilipidemic therapy, including statins, during the trial.

  After five years, there was no statistically significant difference between fenofibrate and placebo in the primary composite endpoint of nonfatal MI and CHD death (5.9% vs. 5.2%, respectively, hazard ratio 0.89, 95% CI 0.75-1.05). However, statistically significant reductions in nonfatal MI (4% vs. 3%) and total cardiovascular events (14% vs. 13%) were seen with fenofibrate. Reductions in total cardiovascular events were primarily due to a significant reduction in the need for coronary revascularization (7% vs. 6%). The concomitant use of statins in 17% of the placebo group vs. only 8% of the fenofibrate group may have accounted for the modest effect of fenofibrate in reducing cardiovascular events.

  An unexpected finding was a 19% (p=0.22) increase in CHD death with fenofibrate compared to placebo, reflecting an increase in sudden deaths in the fenofibrate group.

iii) Efficacy conclusion

Clinically the fibric acid derivatives are useful in reducing elevated TG concentrations and raising HDL. There are no major clinical differences between gemfibrozil and fenofibrate in terms of changes in lipid parameters as shown in the HHS, VA-HIT and FIELD clinical trials; both drugs reduce TG by 20-50%, and increase HDL by 10-20%. Varying effects on LDL have been reported. One small head-to-head trial reported that fenofibrate resulted in greater reductions in TG and LDL than gemfibrozil; however, the gemfibrozil dose was lower than that recommended in the product labeling.

Two placebo-controlled trials with gemfibrozil have shown a benefit in reducing the risk of cardiovascular events in a primary prevention setting and the risk of nonfatal MI and CHD death in a secondary prevention setting. Mixed results were demonstrated with fenofibrate in a large outcomes trial in a primary/secondary prevention setting; fenofibrate did not result in a statistically significant benefit in reducing the composite of CHD death or nonfatal MI, but was associated with significant reductions in nonfatal MI and coronary revascularization.

b) Omega-3 fatty acids

i) Lipoprotein efficacy

Fish oil supplements: placebo-controlled trials – One meta-analysis of 36 crossover and 32 parallel studies of dietary and supplemental omega-3 fatty acids reported that a 3- to 4-gram daily dose resulted in a reduction of TG by

25-34%, and an increase in LDL by 4-11%, regardless of source or formulation.

Omacor: placebo-controlled trials – Ten prospective, randomized clinical trials have examined the effects of the marketed Omacor formulation on TG and LDL concentrations in patients with elevated TG levels. Overall, Omacor 4 grams daily resulted in a 20-45% reduction in TG levels when compared to placebo. The TG-lowering response appears to correlate with baseline TG levels (e.g. patients with higher baseline TG levels will generally have a greater TG-lowering response).

Increases in LDL ranging from 17 to 31% were reported in four of the ten studies. Increases in LDL also appeared to correlate with baseline TG levels. Concomitant use of a statin may blunt any increase in LDL associated with Omacor.

ii) Omacor vs. fish oil supplements – There are no head-to-head trials comparing the lipid effects of Omacor vs. nutritional omega-3 fatty acid supplements.

iii) Omacor vs. other lipid-lowering therapies – The TG-lowering effects of Omacor are slightly lower than those achieved with fibric acid derivatives or niacin. Omacor is associated with similar increases in HDL compared to fibric acid derivatives and niacin.

iv) Clinical outcomes

- *Fish oil supplements: systematic reviews/meta-analyses* – The effects of dietary or supplemental omega-3 fatty acids on cardiovascular disease outcomes have been evaluated in several meta-analyses and systematic reviews, with conflicting results reported. Some reports suggest a beneficial effect when omega-3 fatty acids are used for either primary or secondary cardiovascular disease prevention. In contrast, a 2004 Cochrane review of randomized controlled trials and cohort studies found no strong evidence that dietary or supplemental omega-3 fatty acids reduced total mortality, cardiovascular events, or cancer.
- *Fish oil supplements: placebo-controlled trial (GISSI-Prevenzione)* – In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto miocardico (GISSI)-Prevenzione Trial, an omega-3 fatty acid with a different ratio of EPA and DHA than Omacor was evaluated. Fish oil supplementation was associated with a 15% reduction in the risk of the composite endpoint of death, nonfatal MI, and stroke in 11,324 survivors of a recent MI. There was a 20% reduction in all-cause mortality, which was driven by a 45% reduction in sudden death. There was no difference in nonfatal MI between the groups. Limitations to the study include the open label study design, a dropout rate nearing 30% by study completion, use of a fish oil supplement different than Omacor, and high dietary intake of fish (which in itself has cardiovascular benefits).

- *Omacor: placebo-controlled trial* – One placebo-controlled, double-blinded trial evaluated the effect of Omacor on cardiovascular outcomes. In this study, 300 patients with acute MI were randomly assigned to receive Omacor 4 grams daily or corn oil placebo for a median time period of 1.5 years. There was no statistically significant difference in the rate of cardiac events (cardiac death, resuscitation, recurrent MI, and unstable angina) between groups (28% with Omacor vs. 24% with placebo, hazard ratio 1.19, 95% CI 0.76-1.86). The lack of difference was attributed to the small size and short duration of the trial, as well as the inclusion of Norwegian patients whose diets already contained a high content of fish.
- *Omacor vs. fish oil supplements* – There are no head-to-head trials of Omacor versus fish oil supplements.
- *Omacor vs. other lipid-lowering therapies* – Niacin and gemfibrozil both have clinical trial evidence supporting long-term benefits on cardiovascular outcomes.

v) Efficacy conclusion: Randomized clinical trials showed a reduction in TG levels of 20-45% with Omacor 4 grams once daily. However, Omacor has also been associated with increases in LDL, which may offset beneficial reductions in TG. Concomitant use of a statin may blunt increases in LDL.

The GISSI-Prevenzione trial is the largest trial showing a benefit of omega-3 fatty acids on cardiovascular outcomes, but it assessed a different omega-3 fatty acid product and not Omacor. Its validity may also be limited by its open-label design, high dropout rate, and high dietary fish intake. A small, short-duration placebo-controlled trial specifically assessing the cardio-vascular outcomes of Omacor did not demonstrate a reduction in cardiac events.

The TG-lowering effect of Omacor is slightly less than that achieved with either fibric acid derivatives or niacin. In the National Cholesterol Education Panel (NCEP) guidelines, fibric acid derivatives or niacin are listed as first-line treatments for patients with TG >500 mg/dL; both have clinical outcomes data supporting a benefit in reducing the risk of cardiovascular events.

c) Bile Acid Sequestrants

i) Lipoprotein efficacy – There are only a few clinical trials available for the BAS, and most were conducted in the 1970s and early 1980s. No trials have compared the older agents, cholestyramine and colestipol, with colesevelam.

- *Cholestyramine* – The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was a large placebo-controlled trial that compared cholestyramine 24 g QD to placebo in preventing coronary artery disease (CAD) in 3,806 men with primary hypercholesterolemia. Treatment with cholestyramine resulted in greater reductions in TC and

LDL than placebo (TC -17% with cholestyramine vs. -1% with placebo; LDL -26% with cholestyramine vs. -5% with placebo ($p<0.001$).

The National Heart, Lung, and Blood Institute (NHLBI) compared cholestyramine with placebo in 143 patients. Cholestyramine reduced LDL by 26% vs. 5% with placebo ($p<0.001$). There was no significant difference between cholestyramine and placebo in TG or HDL levels.

- *Colesevelam* – One double-blind study compared various doses of colesevelam to placebo for 24 weeks in 494 patients with primary hypercholesterolemia. LDL levels decreased by 18% at the highest dose; all colesevelam doses reduced LDL significantly versus placebo ($p<0.001$). There were small, non-clinically significant increases in HDL and TG.
- *Colestipol* – One large placebo-controlled trial with colestipol published in 1978 reported a 12% reduction in TC; LDL values were not reported.
- *Cholestyramine or colestipol vs. placebo* – In 1972, a study of 45 adults with hyperlipidemia examined the cholesterol lowering activity and safety of colestipol monotherapy or cholestyramine monotherapy versus placebo. After one year of therapy, colestipol and cholestyramine had a similar effect on TC (40% reduction).

ii) Combination therapy with a statin – The BAS are uncommonly used as monotherapy; they are more likely to be used as adjunctive therapy with a statin. Colestipol plus simvastatin (Zocor, generics) has produced LDL reductions of 45-50%. Colesevelam plus simvastatin has resulted in a 48% reduction in LDL.

iii) Clinical outcomes – The only BAS trial that evaluated clinical outcomes was the LRC-CPPT with cholestyramine. This trial reported a 19% reduction in the combined rate of CHD death plus nonfatal MI with cholestyramine vs. placebo (7% vs. 95, respectively; $p<0.05$).

iv) Efficacy conclusion – Treatment with a BAS reduces LDL by15-30%. Use of BAS as monotherapy has declined in popularity, since statins offer greater LDL reduction. Based on indirect comparison of placebo-controlled trials, cholestyramine, colestipol, and colesevelam have comparable efficacy in lowering LDL. There are no direct comparative trials. There is clinical evidence supporting the use of cholestyramine for reducing the risk of cardiovascular events; no such benefit has been documented with colestipol or colesevelam.

3) 3) Safety / Tolerability

a) Fibric Acid Derivatives

i) Myopathy with statin combination therapy

- *Background* – An increased risk of myositis and potentially fatal rhabdomyolysis has been reported with fibric acid derivatives, either as monotherapy or in combination with a statin (particularly cerivastatin); it

appears to be dose-related. This risk was first identified via spontaneous reports to the FDA Adverse Event Reporting System (AERS).

- *Gemfibrozil vs. fenofibrate* – Mechanistically, differences in glucuronidation pathways between gemfibrozil and fenofibrate are postulated to account for potential differences in the risk of developing myotoxicity. Gemfibrozil undergoes glucuronidation metabolism through the uridine diphosphate glucuronosyl transferase (UGT) 1A1 and 1A3 pathways, which results in competition with the statins. Fenofibrate is eliminated via UGT 1A9 and 2B7 pathways, which do not appear to interfere with statin glucuronidation.
- *FDA retrospective review* – A retrospective data analysis of the FDA AERS database found that half of the cases of statin-induced rhabdomyolysis identified were associated with concomitant medications affecting statin metabolism, and of these more than one third were associated with fibric acid derivatives, gemfibrozil in particular. Many of these reports involved cerivastatin, which has now been withdrawn from the market.

  Another study evaluating the FDA AERS database analyzed the reporting rate (not incidence rate) of myotoxicity between fenofibrate plus a statin vs. gemfibrozil plus a statin. Based on 606 adverse event reports compiled from 1998 to 2002, the reporting rate (rhabdomyolysis cases per million U.S. prescriptions) was 0.58 for fenofibrate and 8.6 with gemfibrozil. This study excluded cerivastatin, which has now been withdrawn from the market. Limitations include varying definitions of myotoxicity, lack of verification of data, and the use of spontaneous reporting rates, which are subject to reporting bias and do not establish a causal relationship.
- *Fenofibrate/statin combination trial* – In 2005, one randomized, double-blinded 18-week trial (n=600) evaluated safety of monotherapy with low-dose simvastatin (20 mg) versus combination therapy with a standard dose of fenofibrate plus simvastatin 20 mg. The incidence of myalgia in the combination group was 2.2% vs. 2.4% with simvastatin. There were no reports of rhabdomyolysis.
- *Clinical practice guidelines* – Professional organizations have not favored one fibric acid derivative over the other with respect to safety of use in combination with statins. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the NHLBI conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

ii) Minor adverse effects

- *Lab abnormalities* – Both gemfibrozil and fenofibrate have been associated with abnormal liver function tests when administered as monotherapy. Increases in serum creatinine ranging from 8 to 18% have

been reported with fenofibrate in patients with normal or impaired renal function. Product labeling advises monitoring of serum creatinine during therapy with either fenofibrate or gemfibrozil.

- *Gemfibrozil vs. fenofibrate: minor adverse effects* – Gastrointestinal (GI) complaints (e.g., nausea, vomiting, and diarrhea) are most common for both fenofibrate and gemfibrozil. Although they occur in fewer than 5% of patients taking fibric acid derivatives, they appear to occur more often with gemfibrozil than with fenofibrate, based on pooled data from product labeling. The head-to-head efficacy trial mentioned earlier (conducted in 21 patients) did not report adverse events.
- *Fenofibrate formulations: minor adverse effects* – There are no head-to-head trials assessing differences in adverse effects among the newer fenofibrate formulations. Differences in fenofibrate formulations are primarily related to decreases in particle size designed to address bioavailability issues, allowing the most recent products (Tricor, Antara, and Triglide) to offer once daily dosing and be taken without regard to meals. These differences do not appear to equate to differences in GI adverse effects, although comparative data are not available.

iii) Special populations – None of the fibric acid derivatives are FDA-approved for use in pediatric patients. All are rated Pregnancy Category C. Dosage adjustments for both gemfibrozil and fenofibrate are required in patients with mild renal impairment.

iv) Drug interactions –There appear to be no major clinical differences between the products with respect to drug interactions with products other than statins, which were discussed previously.

v) Safety conclusion – There are no head-to-head trials supporting a lower risk of myotoxicity with gemfibrozil than with fenofibrate, either alone or in combination with a statin, and professional organizations have not favored one fibric acid derivative over the other. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the NHLBI conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

GI complaints (e.g., nausea, vomiting, and diarrhea) are most common for both fenofibrate and gemfibrozil. Although they occur in fewer than 5% of patients taking fibric acid derivatives, they appear to occur more often with gemfibrozil than with fenofibrate, based on pooled data from product labeling. There are no comparative data. There are no clinically significant differences between gemfibrozil and fenofibrate with regard to use in special populations or drug interaction potential.

b) Omacor

i) Minor adverse events – Omacor appears to be safe and well tolerated, with GI disturbances reported most commonly. Patients frequently complain of fishy-smelling breath and taste perversion, which may limit compliance.

ii) Special populations – Safety of Omacor has not been evaluated in pediatric patients or pregnant patients. No dosage adjustments are required in renal or hepatic impairment.

iii) Drug-drug interactions – Patients receiving Omacor and anticoagulants require periodic monitoring, due to the potential risk of increased bleeding. Clinically significant drug interactions due to inhibition of CYP450 metabolism are not expected with Omacor.

c) Bile Acid Sequestrants

i) Systemic adverse events – The BAS are not absorbed, thus are associated with a low incidence of systemic effects. Non-GI effects (such as angina and tachycardia, or rash) are rare.

ii) GI adverse events – Constipation is the most common minor adverse effect with all the BAS, occurring with an incidence of greater than 10%. In the LRC-CPPT trial, the incidence of constipation with cholestyramine was 39% vs. 10% with placebo; however, GI distress from cholestyramine appeared to decrease with time. Constipation appears to occur less frequently with colesevelam than with other BAS, based on pooled data in product labeling. Rare reports of GI obstruction, including two deaths, have been reported in pediatric patients receiving cholestyramine.

Chronic use of BAS can cause bleeding due to hypoprothrombinemia secondary to malabsorption of vitamin K.

iii) Drug-drug interactions – Drug interactions with BAS are primarily due to effects on absorption of concomitant oral medications.

iii) Special populations

Pediatrics – Cholestyramine is the only BAS that is FDA-indicated to treat hypercholesterolemia in the pediatric population.

Pregnancy – Cholestyramine and colestipol have a Pregnancy Category C rating; colesevelam has a Category B rating. Because statins are rated Pregnancy Category X, NCEP guidelines state that BAS are recommended for women with elevated cholesterol who are considering pregnancy.

4) Other Factors

a) Fibric Acid Derivatives – Gemfibrozil is given twice daily before meals, while the newer formulations of fenofibrate ((Tricor, Triglide, Antara) may be given once daily without regard to meals.

b) Omega-3 Fatty Acids – Since Omacor has undergone the new drug approval process, the ratio and amount of DHA and EPA contained in each capsule and the amount of other ingredients is known. The FDA has more authority to oversee manufacturing of Omacor than fish oil supplements. Fish oil supplement manufacturers are not required to list ingredients other than omega-3 fatty acids (e.g., omega-6 fatty acids, cholesterol) in their label. The

Omacor formulation requires four capsules daily; higher capsule burdens are necessary with some fish oil supplements.

c) Bile Acid Sequestrants – Cholestyramine is only available in a powder form, which some patients find unpalatable. Cholestyramine and colestipol are available as powders or granules for oral suspension, with colestipol also available in tablet form. Both colestipol and colesevelam require large daily tablet burdens (up to sixteen tablets per day for colestipol and seven for colesevelam).

5) Place in Therapy

a) Fibric Acid Derivatives – Fibric acid derivatives have been used clinically since the 1970s and are effective at lowering TG levels and raising HDL. They are widely used as adjunctive treatment with statins, which primarily reduce LDL.

b) Prescription Omega-3 Fatty Acids (Omacor) – Omacor provides an alternative for patients with elevated TG who are not candidates for niacin or fibric acid derivatives. The American Heart Association (AHA) recommends niacin as first-line for elevated TG. The AHA recommends consumption of a variety of fish as primary prevention, with omega-3 fatty acids potentially considered for secondary prevention. NCEP guidelines recommend either fibric acid derivatives or niacin as first line for elevated TG, along with a high dietary intake of fatty fish or omega-3-containing vegetable oils.

c) Bile Acid Sequestrants – NCEP guidelines recommend BAS for LDL-lowering in patients with moderately elevated LDL; women who are considering pregnancy and have elevated LDL; and patients who need only modest reductions in their LDL to reach their target goal.

6) *Overall Clinical Effectiveness Conclusion* – The P&T Committee concluded that:

a) Fibric Acid Derivatives

i) Both gemfibrozil and fenofibrate reduce TG by 20-50% and raise high density lipoprotein (HDL) by 10-20%. There is insufficient evidence to conclude that gemfibrozil and fenofibrate differ in their ability to reduce TG and raise HDL.

ii) Two placebo-controlled trials with gemfibrozil have shown a benefit in reduction of cardiovascular events in a primary prevention setting and a reduction in nonfatal MI and CHD death in a secondary prevention setting. Mixed results were demonstrated with fenofibrate in a large outcomes trial in a primary/secondary prevention setting; fenofibrate did not result in a statistically significant benefit in reducing the composite of CHD death or nonfatal MI, but was associated with significant reductions in nonfatal MI (p=0.01) and coronary revascularization (p=0.035).

iii) Although GI adverse effects occurred in fewer than 5% of patients taking fibric acid derivatives, they appeared to occur more frequently in patients taking gemfibrozil than those taking fenofibrate, based on pooled data

from product labeling. Gemfibrozil must be taken twice daily prior to meals.

iv) Monotherapy with either fibric acid derivatives or statins has been associated with an increased risk of myalgia, myositis, and rhabdomyolysis. This risk appears to be increased with gemfibrozil/statin combination therapy, based on spontaneous adverse event reporting data from the FDA. These data showed a higher reporting rate of rhabdomyolysis with a statin plus gemfibrozil (8.6) compared to a statin plus fenofibrate (0.58), based on the number of spontaneous case reports per 1 million U.S. prescriptions from 1998 to 2002. This study excluded cerivastatin, which has now been withdrawn from the market. Limitations include varying definitions of myotoxicity, lack of verification of data, and the use of spontaneous reporting rates, which are subject to reporting bias and do not establish a causal relationship. It is unclear whether combination therapy with fenofibrate and a statin increases the risk of myotoxicity more than either agent given alone. One trial comparing statin monotherapy vs. combination therapy with fenofibrate plus a statin reported similar rates of myalgia.

v) Pharmacokinetic differences in glucuronidation pathways between gemfibrozil and fenofibrate are postulated to account for potential differences in the risk of developing myotoxicity when used in combination with a statin. However, there are no head-to-head trials supporting a lower risk of myotoxicity with gemfibrozil than with fenofibrate, either alone or in combination with a statin, and professional organizations have not favored one fibric acid derivative over the other. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the NHLBI conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

vi) Fenofibrate formulations include nanocrystallized fenofibrate (Tricor), micronized fenofibrate (Antara), insoluble drug delivery microparticle (IDD-P) fenofibrate (Triglide) and generic formulations of non-micronized and micronized fenofibrate (Lofibra). These newer formulations, regardless of dosage strength or particle size, are bioequivalent to 200 mg of the original fenofibrate formulation. Changes in particle size are designed to address bioavailability issues, allowing the most recent products (Tricor, Antara and Triglide) to offer once daily dosing and be taken without regard to meals. There is insufficient evidence to conclude that newer formulations offer improved efficacy, safety, or tolerability compared to each other or to older formulations.

b) Omega-3 Fatty Acids

i) Omacor is the only prescription omega-3 fatty acid product approved by the FDA. FDA oversight of the manufacturing process for Omacor offers

increased assurance of its omega-3 fatty acid content and purity, in contrast to some fish oil supplements.

ii) Overall, Omacor decreases TG by 20-45%. However, Omacor has also been associated with increases in LDL, which may offset beneficial reductions in TG.

iii) The TG-lowering effects of Omacor are slightly lower than those achieved with fibric acid derivatives or niacin. Omacor is associated with similar increases in HDL compared to fibric acid derivatives and niacin. Niacin and gemfibrozil both have clinical trial evidence supporting long-term benefits on cardiovascular outcomes.

iv) The omega-3 fatty acid formulation found in Omacor does not have outcomes studies that demonstrate beneficial cardiovascular effects (e.g., reductions in cardiovascular death, MI or stroke).

c) Bile Acid Sequestrants

i) The BAS agents reduce LDL by 15-30%. This subclass has largely been replaced by the statins, which decrease LDL by 18% to 55%. There is insufficient evidence to conclude that BAS differ in their ability to lower LDL. Cholestyramine is the only BAS to show beneficial effects on cardiovascular outcomes.

ii) Colesevelam has no major efficacy advantages compared to cholestyramine or colestipol, despite manufacturer claims of enhanced bile acid binding capacity. It has a more favorable pregnancy category rating than the older products (B vs. C) and may cause less constipation, which may be clinically relevant in patients with a previous history of GI obstruction.

iii) Issues with palatability of powder formulations and/or large daily tablet burdens are a concern with the class as a whole and may affect compliance.

iv) The BAS agents have a high degree of therapeutic interchangeability.

Overall Clinical Effectiveness Conclusion – Based on clinical issues alone, there are no compelling reasons to classify any of the LIP-2 agents as non-formulary under the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions above.

B. B. LIP-2s – Relative Cost Effectiveness

In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the agents within the fibric acid derivative and BAS subclasses differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of hypertriglyceridemia and hyperlipidemia, respectively. As a result, cost minimization analyses (CMAs) were performed to compare the relative cost effectiveness of the agents within the fibric acid derivative and BAS subclasses. Since Omacor is the only prescription omega-3 fatty acid product, a cost effectiveness analysis (CEA) was conducted to compare it to other agents used in the treatment of hypertriglyceridemia.

Results from the fibric acid derivative CMA revealed: 1) gemfibrozil was the most cost-effective fibric acid derivative, and 2) IDD-P fenofibrate (Triglide) was by far the most cost effective fenofibrate. Among the bile acid sequestrants, the CMA showed that colesevelam was not cost-effective in the treatment of hyperlipidemia when compared to other available agents. The results for the prescription omega-3 fatty acids CEA showed that Omacor was not cost effective in the treatment of hypertriglyceridemia when compared to gemfibrozil, fenofibrate, and niacin. At this time, there is insufficient evidence to support a clinical benefit for omega-3 fatty acids in prevention of CHD. For this reason, the cost effectiveness of Omacor was not evaluated for this consequence or clinical outcome.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a budget impact analysis (BIA) of various UF scenarios for the LIP-2s was conducted. The goal of the BIA was to aid the Committee in determining which group of LIP-2s best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The DoD P&T Committee accepted the conclusions from the cost effectiveness analyses stated above. In addition, the Committee concluded that the UF scenario that maintained fenofibrate (Lofibra), IDD-P fenofibrate (Triglide), cholestyramine/aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil on the UF was the most cost effective UF scenario.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the relative CEA of the LIP-2 class.

C. LIP-2s – UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the LIP-2s, and other relevant factors, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) that: 1) fenofibrate (Lofibra, generics), IDD-P fenofibrate (Triglide), cholestyramine/ aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil be maintained as formulary on the UF; 2) micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and prescription omega-3 fatty acids (Omacor) be classified as non-formulary under the UF; and 3) the normal brand formulary cost-share of $9.00 for IDD-P fenofibrate (Triglide) be lowered to the generic formulary cost-share of $3.00.

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate." The objective is to maximize use of IDD-P fenofibrate (Triglide) in the retail network and mail order, given its significantly lower cost relative to other fenofibrate products. Lowering the cost-share for brand name IDD-P fenofibrate (Triglide) will provide a greater incentive for beneficiaries to use the most cost effective fenofibrate formulation in the purchased care arena

D. LIP-2s – MN Criteria

Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and omega-3 fatty acids (Omacor):

1) The use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Formulary alternatives have resulted in therapeutic failure.

The P&T Committee noted that some circumstances under which criterion #2 might be considered to apply may be 1) Omacor for patients who cannot take statins or fibric acid derivatives due to a history of myopathy and who cannot tolerate niacin, or 2) colesevelam for patients with a history of GI obstruction or pregnant patients who require treatment with a bile acid sequestrant.

COMMITTEE ACTION: The P&T Committee voted (13 for, 1 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. LIP-2s – UF Implementation Period

Given the relatively low number of beneficiaries are affected (approximately 83,612 patients (65%) of approximately 127,901 beneficiaries at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, or prescription omega-3 fatty acids (Omacor) on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary LIP-2 agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day

implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. LIP-2s – BCF Review and Recommendation

Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that gemfibrozil and IDD-P fenofibrate (Triglide) be designated as the BCF selections in this class.

7. DRUG CLASS REVIEW – 5-ALPHA REDUCTASE INHIBITORS (5-ARIs)

The P&T Committee evaluated the relative clinical effectiveness of the 5-alpha reductase inhibitor agents (5-ARIs) available in the U.S. The 5-ARI drug class includes finasteride (Proscar, generics) and dutasteride (Avodart). These two agents have been marketed for a number of years; finasteride is available generically. The class review did not include the lower dosage (1 mg) strength of finasteride, which is marketed for alopecia (hair loss) under the brand name Propecia, since this indication is not covered by TRICARE.

The 5-ARI drug class accounted for $31.2 million in the MHS expenditures for the period October 2005 to September 2006 and is ranked #50 in terms of total expenditures during that time period. More than 281,000 prescriptions for 5-ARIs were filled in the MHS during a one-year period (January 2006 to December 2006). Of these, 59% were for finasteride and 41% were for dutasteride.

Pharmacologically, the 5-ARIs reduce prostate volume by inhibiting the conversion of testosterone to dihydrotestosterone (DHT). Finasteride selectively inhibits type I 5-alpha receptors, while dutasteride inhibits both type I and type II receptors; the clinical significance of this difference is unknown. 5-ARIs are used for the treatment of benign prostatic hyperplasia (BPH) in men with an enlarged prostate. Their effect on lower urinary tract symptoms (LUTS) associated with BPH (e.g., urinary frequency, urgency, nocturia, decreased / intermittent force of stream, and the sensation of incomplete bladder emptying) is related to relief of urethral obstruction and may take several months of treatment to become clinically evident. BPH to the point of prostatic obstruction can cause acute urinary retention (AUR), which is considered a medical emergency.

Standard treatments for BPH include watchful waiting (in men with mild symptomatic BPH); alpha blockers (which rapidly relieve symptoms by relaxing prostate and bladder smooth muscle but do not affect prostate volume); 5-ARIs (reduce prostate volume); combination alpha blocker/5-ARI treatment (in men with moderate-to-severe symptomatic BPH); and surgery (in men with severe symptomatic BPH).

A. 5-ARIs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the 5-ARI agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does

not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

1) FDA-approved indications

   Both finasteride and dutasteride are indicated for the treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, reduce the risk of AUR, and reduce the risk of the need for BPH-related surgery. Finasteride is approved for combination therapy with the alpha blocker doxazosin to reduce the risk of symptomatic progression of BPH; labeling for dutasteride does not include an indication for combination therapy. Both are dosed once daily without regard to meals.

2) Efficacy Measures

   The primary outcome measures used to assess efficacy of the 5-ARIs are changes in symptom scores (AUA-SI or IPSS), urinary flow rate (Qmax), reductions in total prostate volume (TPV), and decreased risk of AUR or BPH-related surgery. In trials, a decrease in symptom score of three or more points is generally considered clinically significant; although men rate themselves as slightly improved with a decrease of one to two points. A change in the urinary flow rate of 2 to 3 mL/sec is considered clinically significant.

3) Efficacy

   a) *Long term placebo-controlled trials* – The most extensive data supporting long term efficacy and safety of the 5-ARIs are from two large randomized, double-blind, placebo-controlled trials. The four-year Proscar Long-Term Efficacy and Safety Study (PLESS) [McConnell et al, 1998] showed a significant reduction in symptom scores, Qmax, TPV, risk of AUR, and risk of BPH-related surgery with finasteride, compared to placebo. Data for dutasteride come from pooled analyses of three identical parallel-group trials (ARIA 3001, 3002, 3003) [Roehrborn et al, 2002]. All three trials had a two-year double-blinded phase comparing dutasteride to placebo, followed by a two-year open-label extension phase during which all patients were treated with dutasteride. At the end of the two-year double-blind phase, dutasteride significantly reduced symptom scores, Qmax, TPV, risk of AUR, and risk of BPH-related surgery with finasteride, compared to placebo.

      Reductions in the risk of AUR and BPH-related surgery appeared similar. The calculated risk reduction after two years with finasteride (PLESS) was a 57% reduction in AUR (95% CI 40-69%) and a 58% reduction in BPH-related surgery 58% (95% CI 41-65%), compared with placebo. For dutasteride, the risk reduction after two years (ARIA pooled data) was 57% for AUR (95% CI 38-71%) and 48% for BPH-related surgery (95% CI 26-63%), compared with placebo.

   b) *Systematic reviews and meta-analysis* – Two systematic reviews [Clifford et al, 2000; Edwards et al, 2002] and one meta-analysis [AUA Guideline, 2003] concluded that finasteride offers consistent improvement in terms of symptom

relief, urinary flow rate, and decreased risk of AUR and the need for prostatic surgery, compared to placebo. No systematic reviews or meta-analyses are available for dutasteride.

Head-to-head trials – The only fully published head-to-head trial [Clark et al, 2004] compared effects of finasteride and dutasteride on DHT, testosterone, and leutinizing hormone (LH) levels. This 24-week, Phase II, double-blind, placebo-controlled, dose-ranging trial randomized 399 men with BPH to dutasteride (0.01, 0.05, 0.5, 2.5, or 5.0 mg), 5 mg finasteride, or placebo. The mean percent decrease in DHT with dutasteride was more profound and less variable than with finasteride [dutasteride 0.5 mg (the labeled dose) 94.7 ± 3.3% vs. finasteride 5 mg 70.8 ± 18.3%]. Mean testosterone levels increased but remained in the normal range for all treatment groups. Whether or not differences between finasteride and dutasteride with respect to DHT suppression result in a clinically significant difference in patient outcomes has yet to be determined. Limitations of this trial include its short duration relative to the typical onset of benefits from 5-ARIs and its small sample size, especially given that only one of the dutasteride arms was at the labeled dose (0.5mg).

Unpublished summary data from a second head-to-head trial, the Enlarged Prostate International Comparator Study (EPICS), were furnished by the manufacturer of dutasteride [data on file, GlaxoSmithKline]. EPICS compared dutasteride 0.5 mg and finasteride 5 mg in men with BPH. Following a 4-week placebo run-in period, 1630 men were randomized to dutasteride (n=813) or finasteride (n=817) for twelve months. After one year similar improvements from baseline were seen with dutasteride vs. finasteride, respectively, with respect to changes in symptom scores (-5.8 vs.- 5.5), reductions in TPV (-26.3% vs. -26.7%) and Qmax (2.0 vs. 1.7 mL/sec). No statistically significant differences in outcome measures between treatment groups were reported.

c) *Combination therapy trials* – Three short-term combination trials (finasteride plus an alpha blocker) demonstrated no additional benefit compared to alpha blockers alone. However, the large, long-term Medical Therapy of Prostatic Symptoms (MTOPS) trial demonstrated improvements in LUTS and a greater reduction in overall disease progression (including reduced risk of AUR and need for BPH-related surgery) with combination therapy (finasteride plus doxazosin) versus monotherapy with either agent. The AUA meta-analysis of finasteride trials reported improved AUA-SI scores and Qmax with combination therapy and supported its use in men with LUTS and demonstrable prostate enlargement. There are no published long-term combination trials with dutasteride; therefore, there is insufficient evidence to compare finasteride to dutasteride when used in combination with an alpha blocker.

d) *Prostate cancer* – There is limited evidence concerning the potential use of 5-ARIs for prostate cancer prevention. The only large, long-term trial [Thompson et al, 2003] reported a 24.8% reduction in the prevalence of

prostate cancer in patients receiving finasteride vs. placebo; however, a higher percentage of high-grade prostate cancer tumors was reported with finasteride, compared to placebo. It is not known whether or not dutasteride produces the same effect.

e) Efficacy conclusion – There is insufficient evidence to conclude that there are significant differences in efficacy between finasteride and dutasteride. Indirect comparisons from long-term efficacy trials suggest similar decreases in total prostate volume, increases in urinary flow rate, improvement in symptoms, and similar reductions in the risk of AUR and BPH-related surgery. Summary results from an unpublished head-to-head trial (the Enlarged Prostate International Comparator Study – EPICS) showed similar improvements in symptom scores, TPV, and Qmax; no statistically significant differences in outcome measures were reported. There is insufficient evidence to compare the two agents for use in combination with alpha blockers. More data are available with finasteride than with dutasteride, including a long-term trial with finasteride and doxazosin (the Medical Therapy of Prostatic Symptoms trial – MTOPS); there are no published long-term combination trials with dutasteride. The clinical significance of more profound suppression of DHT with dutasteride than with finasteride is unknown. The overall effect of 5-ARIs on prostate cancer prevention is unclear.

4) Safety and Tolerability

a) Serious adverse events – There have been no notable reports of serious adverse events with either agent.

b) Overall adverse events – The most common adverse effects are related to sexual dysfunction. Similar incidences of sexual adverse events and gynecomastia have been reported with finasteride and dutasteride. In general, clinical trials report rates of decreased libido of 2 to10%, erectile dysfunction 3 to16%, ejaculatory disorders 0 to 8%, and gynecomastia 1 to 2%. The incidence of sexual dysfunction is generally higher during the first six to twelve months of treatment and diminishes with chronic dosing.

c) Withdrawals due to adverse events during clinical trials – With the exception of gynecomastia, adverse effects are generally not severe enough to discontinue use of 5-ARIs. There do not appear to be major differences between the two agents with respect to withdrawal rates due to adverse events. Reported withdrawal rates in clinical trials of finasteride and dutasteride were low overall, similar in the first year of therapy, and decreased further for both agents during continued treatment.

d) Drug interactions – No major comparative disadvantage was noted for either agent based on its potential for drug-drug interactions. Both are metabolized via the cytochrome P450 (CYP) 3A4 enzyme system and should be used cautiously in patients taking potent CYP 3A4 inhibitors.

e) *Special populations* – There are no major differences between finasteride and dutasteride with regard to use in special populations; both are pregnancy category X, contraindicated in children and women, and carry warnings regarding exposure to 5-ARIs of women who are pregnant or may become pregnant, due to the potential risk of transdermal absorption and fetal exposure (feminization of male fetuses is an expected consequence of the inhibition of the conversion of testosterone to DHT by 5-ARIs). Men taking a 5-ARI should defer blood donation for six months from discontinuation of therapy to avoid possible administration of the drug to a pregnant female transfusion recipient. Neither finasteride nor dutasteride requires dosing adjustments or has special dosing requirements, although caution is advised in hepatic dysfunction.

f) *Other factors* – 5-ARIs as a class are associated with a decrease in prostate specific antigen (PSA) concentrations of about 50% after six months of treatment. Neither drug appears to interfere with detection of prostate cancer when PSA values used for prostate cancer screening are appropriately adjusted (they should be doubled in men who have received 5-ARI therapy for at least six months).

g) *Safety and tolerability conclusion* – There appear to be few differences in the incidence of adverse effects with finasteride or dutasteride, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated; with the most common adverse effects related to sexual dysfunction and diminishing with chronic dosing. Reported withdrawal rates due to adverse effects are low overall in clinical trials of finasteride and dutasteride, similar during the first year of therapy, and decrease further with both agents during continued treatment. The two agents appear similar with regard to potential drug interactions and use in special populations (both are contraindicated in women and children and carry special warnings against exposure of women who are or may become pregnant). Neither agent appears to interfere with the prostate cancer detection.

5) Therapeutic Interchangeability

Finasteride and dutasteride appear similar in terms of efficacy, safety, and tolerability, and are used in the same patient population. Neither drug offers a unique benefit, nor is it likely that a patient who did not have an adequate response with one 5-ARI would have a better response with the other. Either finasteride or dutasteride could be expected to meet the needs of the majority of DoD BPH patients.

6) 5-ARIs – Overall Clinical Effectiveness Conclusion

The P&T Committee concluded that:

a) There is insufficient evidence to conclude that there are significant differences in efficacy between finasteride and dutasteride. Indirect comparisons from long-term efficacy trials suggest similar decreases in total prostate volume,

increases in urinary flow rate, improvement in symptoms, and similar reductions in the risk of AUR and BPH-related surgery.

b) The only fully published head-to-head trial suggests that dutasteride therapy reduces serum DHT levels by 95%, compared to 71% with finasteride. The clinical significance of this finding has yet to be determined. This 24-week trial contributes no useful comparative data concerning long-term efficacy. A large but as yet unpublished head-to-head trial (EPICS) reported no differences in efficacy outcomes with finasteride vs. dutasteride after one year of treatment.

c) There is insufficient evidence to compare the two agents when used in combination with alpha blockers. More data are available with finasteride than with dutasteride, including a long-term trial with finasteride and doxazosin (MTOPS); there are no published long-term combination trials with dutasteride.

d) The overall effect of 5-ARIs on prostate cancer prevention is unclear.

e) There appear to be few differences in the incidence of adverse effects with finasteride or dutasteride, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated. The most common adverse effects are related to sexual dysfunction; they diminish with chronic dosing.

f) Reported withdrawal rates due to adverse effects are low in clinical trials of finasteride and dutasteride, similar during the first year of therapy, and decrease further with both agents during continued treatment.

g) There are no major differences between finasteride and dutasteride with regard to use in special populations or drug interactions.

h) Neither agent appears to interfere with prostate cancer detection.

i) Finasteride and dutasteride appear to have a high degree of therapeutic interchangeability; either could be expected to meet the needs of the majority of DoD BPH patients.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. 5-ARIs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the 5-ARIs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the 5-ARI medications differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of BPH. As a result, several CMAs were performed to compare the relative cost effectiveness of the 5-ARIs by condition set. The CMAs compared the weighted average cost per day of treatment

for each drug product across all three points of service. In addition, a CEA was conducted evaluating the cost per BPH surgery avoided for each of the 5-ARIs.

Results from the CMAs showed that finasteride was the most cost effective agent with a lower cost per day of treatment than dutasteride across all conditions sets evaluated. In addition, finasteride was the preferred choice in the CEA with a lower expected cost per BPH surgery averted than dutasteride.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the Committee in determining which group of 5-ARIs best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The P&T Committee accepted the conclusions from the cost effectiveness analyses stated above. In addition, the Committee concluded that the UF scenario that placed finasteride as the sole 5-ARI on the UF was the most cost effective scenario.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, and 2 absent) to accept the 5-ARI relative CEA as presented by the PEC.

C. 5-ARI – UF Recommendations

COMMITTEE ACTION*:* In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the 5-ARIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that finasteride be maintained as formulary on the UF and that dutasteride be classified as non-formulary under the UF.

D. 5-ARI – MN Criteria

Based on the clinical evaluation for dutasteride, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for dutasteride:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. 5-ARI – UF Implementation Period

Because of the relatively few number of beneficiaries affected (approximately 20,917 patients (41%) of approximately 51,017 beneficiaries at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have dutasteride on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary 5-ARI agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. 5-ARIs – BCF Review and Recommendations

Currently there are no 5-ARI agents on the BCF. The P&T Committee had previously determined at the November 2006 meeting that at least one 5-ARI would be placed on the BCF. Finasteride is widely used at MTFs, has clinical data supporting efficacy for decrease in total prostate volume, increase in urinary flow rate, and improvement in symptoms, reductions in risk of acute urinary retention and BPH-related surgery. Finasteride is clinically similar to dutasteride with respect to safety and tolerability, and is the most cost effective 5-ARI. The P&T Committee agreed that finasteride should be placed on the BCF.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend adding finasteride as the BCF selection in this class.

8. DRUG CLASS REVIEW – PROTON PUMP INHIBITORS (PPIs)

The P&T Committee evaluated the relative clinical effectiveness of the PPIs. The PPI drug class includes the following agents: esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec and generics), omeprazole/ sodium bicarbonate (Zegerid), omeprazole magnesium (Prilosec OTC), pantoprazole (Protonix), and rabeprazole (Aciphex). Omeprazole magnesium (Prilosec OTC) was added to the UF for purposes of the OTC Demonstration Project as a result of the February 2007 P&T Committee meeting. The PPI class was previously reviewed by the P&T Committee in February 2005.

As of March 07, about 350,000 MHS prescriptions for PPIs are filled per month. This drug class is now #1 in terms of MHS expenditures: more than $485 million over the 12 months from April 06 to March 07, compared to about $350 million in FY 2005. MTF pharmacies dispense 47% of all PPI tablets, compared to 36% dispensed by retail network pharmacies and 17% dispensed by the TMOP. Across the MHS, rabeprazole is the most commonly prescribed PPI, due mainly to its favorable formulary status and high utilization at MTFs. The next four most-prescribed PPIs – lansoprazole, esomeprazole, pantoprazole, and omeprazole – have similar utilization patterns. Of the PPIs, only prescription omeprazole is generically available.

Pharmacologically, PPIs suppress the final step in gastric acid production. They have become the standard of care for treatment of acid-related disorders, particularly treatment of erosive or ulcerative disease.

Standard practice in the initial management of dyspepsia or gastroesophageal reflux disease (GERD) indicates that if certain "alarm features" (i.e., signs of potential underlying cancer such as melena, persistent vomiting, dysphagia, hematemesis, anemia, or involuntary weight loss) are not present, patients should be treated with an empiric trial of 4 to 8 weeks of PPI therapy. In populations where the prevalence of *H. pylori* is greater than 10%, *H. pylori* testing should occur prior to further evaluation, with subsequent treatment if positive. Patients with inadequate symptom relief after 8 weeks should receive endoscopy and further management based on endoscopy results. GERD is often a relapsing-remitting disease which requires long-term medical maintenance therapy; in many cases PPIs will be continued for an extended period of time.

A. PPIs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the PPIs currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

1) FDA-Approved Indications and Other Uses

All of the PPIs are FDA-approved for the treatment of erosive esophagitis (EE) and maintenance of healed EE. All PPIs except pantoprazole have at least one indication for ulcer treatment (e.g., duodenal or gastric ulcers and/or ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs) or caused by *H. pylori*). All PPIs except pantoprazole and omeprazole/sodium bicarbonate have an FDA indication as part of a multi-drug regimen for the eradication of *H. pylori*. All PPIs except omeprazole/sodium bicarbonate have an indication for the treatment of hypersecretory conditions such as Zollinger-Ellison.

In practice, most of the agents have published data showing effectiveness for use in any of the acid related disorders, and are commonly prescribed to treat all acid related conditions, regardless of FDA indication. Omeprazole, lansoprazole, and esomeprazole are indicated for use in children.

PPIs are also being studied and used outside the area of acid-related disorders (e.g., for surgical procedure prophylaxis, posterior laryngitis, and chronic cough). More data are needed to support broader use of PPIs for these conditions.

2) Efficacy Measures

Comparative efficacy was evaluated on a disease state basis based on FDA indicated uses of the PPIs. The emphasis was on objective clinical endpoints (ulcer healing, esophagitis healing, maintenance of healing / prevention of disease, and symptomatic resolution) rather than surrogate endpoints (such as pH

measurements, supplemental antacid use and serum drug levels), given the uncertain relationship of surrogate endpoints to clinical outcomes.

3) Clinical Evidence

The review focused primarily on randomized, double-blinded trials where one PPI was compared to another (head-to-head or direct comparison trials), or to another active comparator such as histamine-2 receptor antagonists (e.g., ranitidine, cimetidine, etc). Three good quality systematic reviews summarized the available data, supplemented by more recently published trials. The systematic reviews included PPI reviews from the Oregon Health and Science University's Drug Effectiveness Review Project (DERP; July 2006) and the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS; Aug 2005), and the Agency for Healthcare Research and Quality (AHRQ) 2005 Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease guideline.

It should be noted that no published outcomes evidence is available for either omeprazole magnesium (Prilosec OTC) or the immediate release/sodium bicarbonate (Zegerid) formulations of omeprazole. FDA approval of these formulations relied on the original omeprazole data.

4) Efficacy

a) EE healing

Evidence from head-to-head trials suggests the majority of patients obtain complete healing of erosive disease within eight weeks of treatment on any PPI, with most patients achieving symptom relief within four weeks of initiating treatment.

Of the 25 head-to-head trials published in the clinical literature, only six showed a statistically significant difference in healing rates among the PPIs. One of these predictably found omeprazole 20 mg to be more efficacious than lansoprazole 15 mg, but similar to lansoprazole 30 mg, which is the dose typically used for EE healing.

Two trials comparing esomeprazole and lansoprazole reported differences favoring esomeprazole, with one trial reporting statistically significant differences in healing and symptom resolution at four weeks that disappeared by 8 weeks and the other reporting a small but statistically significant difference in healing and symptom resolution at four weeks and healing at eight weeks. Another head-to-head trial of esomeprazole and lansoprazole showed no significant difference in healing or symptom resolution at the same time points.

Two trials comparing esomeprazole and omeprazole reported differences favoring esomeprazole; both trials compared esomeprazole 40 mg to omeprazole 20 mg, which are not equivalent doses. Two adequately powered later trials, one comparing esomeprazole 40 mg to omeprazole 20 mg and one comparing esomeprazole 20 mg to omeprazole 20 mg, failed to show

statistically significant differences in healing rates at four and eight weeks or symptom resolution at 4 weeks.

One trial comparing esomeprazole to pantoprazole reported differences favoring esomeprazole; this trial appears to have some internal validity issues. Another trial comparing esomeprazole 40 mg and pantoprazole 40 mg failed to find any statistically significant differences in healing or symptom relief.

Conclusion – Although some trials appear to demonstrate superior efficacy for healing of EE with esomeprazole, actual differences are small and inconsistent among trials. Evidence for clinical efficacy is similar enough to consider all agents equally effective in healing of EE.

b) Maintenance of healing in erosive esophagitis

The evidence includes six clinical trials comparing various PPIs, along with a placebo-controlled rabeprazole trial and a comparison of pantoprazole and ranitidine. There are substantial methodological differences among trials (e.g., methods of evaluating healing, duration, study populations, and comparators used), as well as internal validity issues and small trial sizes that make it impossible to draw conclusions regarding the superiority of one agent over another.

Conclusion – There is sufficient evidence to support the use of PPIs for maintenance of initial healing and symptomatic relief of EE for as long as five years. However, the evidence is insufficient to conclude that one PPI is superior to others for maintenance of EE healing.

c) Ulcer healing and maintenance of healing

Fifteen head-to-head trials compared efficacy of various PPIs to omeprazole for initial healing and/or maintenance of healing in duodenal, gastric, and NSAID-induced ulcers. No statistically significant differences were found for any comparators versus omeprazole for primary endpoints of ulcer healing and maintenance of healing or for measures of symptom resolution and improvement.

Conclusion – There appear to be no comparative differences among PPIs for healing, maintenance of healing, or symptom improvement in peptic ulcer disease (PUD) and/or NSAID-induced ulcers.

d) Endoscopy negative reflux disease (ENRD)

ENRD is an incompletely understood variant of GERD. It is estimated that as many as half of patients diagnosed with GERD may fall into this category; however, there are few clinical trials specifically focusing on ENRD. Patients with ENRD are generally considered more difficult to treat than patients with positive findings on endoscopy.

Six trials show efficacy of various healing or maintenance doses of PPIs for initial resolution of heartburn (the primary outcome in all of the trials). Three other trials compare on-demand use of a PPI to placebo or an active

comparator (e.g., a histamine-2 blocker) as continuation therapy after initial resolution of symptoms.

Conclusion – Based on available clinical trials, PPIs appear to be similarly efficacious as short-term treatment for ENRD; there are insufficient data to draw conclusions regarding efficacy for long-term or on-demand treatment.

e) H. pylori eradication with multi-drug regimens

There are at least 39 head-to-head trials comparing all of the PPIs in various multi-drug combination regimens with antibiotics. Substantial differences among studies in doses of PPIs and antibiotics, duration of treatment, methods of assessing *H. pylori* eradication, and patient populations make comparisons across studies difficult. A good quality meta-analysis (2003) using omeprazole as the reference for comparison found no difference in eradication rates among PPIs; earlier systematic reviews (1998, 1999) came to similar conclusions.

Conclusion – H. pylori eradication rates appear similar among PPIs when differing doses of antibiotics and treatment duration are taken into account.

f) Efficacy in Pediatric Patients

Omeprazole, lansoprazole and esomeprazole have indications for treatment of symptomatic GERD in pediatric patients, while omeprazole and lansoprazole have indications for treatment and maintenance of healing of EE. Comparisons of PPIs across trials is difficult; most trials in pediatric patients were small, some were open-label or non-controlled, and surrogate endpoints used to assess symptom resolution varied widely. There was no evidence to support greater efficacy for any one PPI compared to others.

Conclusion – There are insufficient data to suggest superiority of one PPI over others for treatment of pediatric patients. Pantoprazole and rabeprazole do not have an FDA-approved pediatric indication.

5) Safety/Tolerability

a) *Serious adverse events* – A long-standing potential safety concern with PPIs is prolonged hypergastrinemia, which can lead to hyperplasia of both normal and neoplastic enterochromaffin-like cells in the GI tract, potentially leading to cancer. However, the precise role of achlorhydria-induced increases in gastrin expression in gastrointestinal carcinogenesis is unknown. Risk of atrophic gastritis and gastric bacterial overgrowth is increased with long-term PPI use, although the clinical significance is unclear.

PPIs have been associated with *C. difficile* infection, especially in patients taking concomitant antibiotics; caution is particularly indicated with *H. pylori* eradication regimens.

Acute interstitial nephritis has been rarely reported with PPIs. In addition, epidemiological data have suggested an association between PPIs and increased risk of fracture; potential study limitations are numerous, and no definitive evidence is available.

b) *Overall adverse events and withdrawal due to adverse events* – In general, adverse effects are similar to placebo, with an overall incidence rate of less than 5%. Most commonly reported are headache, diarrhea, abdominal pain, and nausea. Head-to-head trials have shown no differences in short-term tolerability; withdrawal rates due to adverse events are very low. There are no clear differences among PPIs with respect to adverse effects or withdrawal rates due to adverse events during clinical trials.

c) *Drug interactions* – PPIs have the potential for causing drug interactions based on several mechanisms, including CYP450 inhibition, effects on the P-glycoprotein membrane transport system in columnar cells of the small intestine, and changes in gastric pH, which can affect absorption of other medications. Omeprazole and esomeprazole may have the most potential for CYP450 drug interactions. Increased effects of warfarin have been reported most frequently with omeprazole, lansoprazole, or pantoprazole, although this is a potential interaction for all PPIs. Most drug interactions are minor in nature.

d) *Special populations* – Dosage adjustments for all PPIs, except pantoprazole, should be considered in patients with severe hepatic disease. None of the PPIs require adjustment in patients with chronic renal insufficiency, elderly patients, or based on gender or race. Omeprazole is classified as Pregnancy Category C; other PPIs are Pregnancy Category B. PPIs are excreted in breast milk and are not recommended for use during breastfeeding.

Zegerid contains 300-460 mg of sodium per tablet due to its sodium bicarbonate component; caution is advised for patients who should avoid consumption of large amounts of sodium.

e) *Other factors* – Lansoprazole, esomeprazole and omeprazole/sodium bicarbonate have dosage forms that can be used in pediatric patients or patients with swallowing difficulties. All three are available as packets for oral suspension; lansoprazole is also available as an orally disintegrating tablet. Omeprazole capsules contain enteric-coated granules commonly used to prepare a bicarbonate-based extemporaneous suspension.

Pantoprazole was the only PPI available in intravenous (IV) form for several years; however, both esomeprazole and lansoprazole have recently developed IV formulations. (It should be noted that due to their route of administration and lack of outpatient use, the IV formulations are not eligible for inclusion on the UF and not included in this review.)

f) *Safety and tolerability conclusion* – The class as a whole is well-tolerated, with an adverse effect profile similar to placebo; most drug interactions are minor in nature. There are no clear differences among PPIs with respect to adverse effects or withdrawal rates due to adverse events during clinical trials. In general, agents appear very similar with respect to safety and tolerability. Minor differences include the lack of a requirement to adjust the dose of pantoprazole in patients with severe hepatic disease (unlike other PPIs); a less favorable pregnancy category rating for omeprazole than the more recently

introduced PPIs (C vs. B); and the availability of liquid dosage forms for esomeprazole, lansoprazole, and omeprazole/sodium bicarbonate.

6) PPIs – Overall Clinical Effectiveness Conclusion:

The P&T Committee concluded that:

a) Based on head-to-head and other controlled trials, PPIs have similar efficacy in a wide range of acid related disorders and are highly therapeutically interchangeable.

b) Although some trials appear to demonstrate superior efficacy for healing of EE with esomeprazole, actual differences are small and inconsistent among trials. Evidence for clinical efficacy is similar enough to consider all agents equally effective in healing of EE.

c) There is sufficient evidence to support the use of PPIs for maintenance of initial healing and symptomatic relief of EE for as long as five years. However, the evidence is insufficient to conclude that one PPI is superior to the others for maintenance of EE healing.

d) There appear to be no comparative differences among PPIs for healing, maintenance of healing, or symptom improvement in PUD and/or NSAID-induced ulcers.

e) Based on available clinical trials, PPIs appear to be similarly efficacious in the short-term treatment of ENRD; there are insufficient data to draw conclusions regarding efficacy for long-term or on-demand treatment.

f) *H. pylori* eradication rates appear similar among PPIs when differing doses of antibiotics and treatment duration are taken into account.

g) There are insufficient data to suggest superiority of one PPI over the others for treatment of pediatric patients; omeprazole, lansoprazole, and esomeprazole have FDA indications for use in pediatric patients.

h) The class as a whole is well-tolerated, with an adverse effect profile similar to placebo; most drug interactions are minor in nature. In general, PPIs appear very similar with respect to safety and tolerability.

i) Minor differences include the lack of a requirement to adjust the dose of pantoprazole (Protonix) in patients with severe hepatic disease (unlike other PPIs); a less favorable pregnancy category rating for omeprazole than the more recently introduced PPIs (C vs. B); and the availability of liquid dosage forms for esomeprazole, lansoprazole, and omeprazole/sodium bicarbonate.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. PPIs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the PPIs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class.

Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the PPI medications differed in regard to efficacy, safety, tolerability, or clinical outcomes data in the treatment of EE healing and maintenance of healing, ulcer healing and maintenance of healing, *H. pylori* eradication, and ENRD. As a result, several CMAs were performed to compare the relative cost effectiveness of the PPIs by condition set (the seven condition sets are listed below). The CMAs compared the weighted average cost per day of treatment for each potential UF scenario across all three points of service.

1) C7301: Two or fewer PPIs are selected for the UF and one PPI is selected for the BCF. ($\leq$2 UF, 1 BCF)
2) C7302: Three or four PPIs are selected for the UF and one PPI is selected for the BCF. (3-4 UF, 1 BCF)
3) C7303: Three or four PPIs are selected for the UF and two PPIs are selected for the BCF. (3-4 UF, 2 BCF)
4) C7304: Five or more PPIs are selected for the UF and one PPI is selected for the BCF. ($\geq$5 UF, 1 BCF)
5) C7305: Five or more PPIs are selected for the UF and two PPIs are selected for the BCF. ($\geq$5 UF, 2 BCF)
6) C7306: Two PPIs (generic omeprazole and one other PPI) are selected for the UF and generic omeprazole is the only PPI selected for the BCF. In addition, a PA process requires all new PPI users to complete an adequate trial of generic omeprazole before any other PPI is provided to a new user through an MTF pharmacy, the TMOP, or a TRICARE retail network pharmacy.
7) C7307: Two PPIs (generic omeprazole and one other PPI) are selected for the UF. Generic omeprazole will be selected to the BCF and the other PPI may be selected for the BCF. In addition, a PA process requires all new PPI users to complete an adequate trial of generic omeprazole or the second UF PPI before any third tier PPI is provided to a new user through an MTF pharmacy, the TMOP, or a TRICARE retail network pharmacy.

Results from the PPI CMAs showed three important findings: 1) as expected, the more restrictive the UF scenario, the lower the cost per day of treatment; 2) for the three condition sets that evaluated UF scenarios with two or fewer UF agents (C7301, C7306, and C7307), omeprazole and esomeprazole were the most cost effective agents; and 3) for the two condition sets that evaluated UF scenarios with three to four UF agents (C7302 and C7303), omeprazole, esomeprazole, pantoprazole, and rabeprazole were the most cost effective agents.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the Committee in

determining which group of PPIs best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The DoD P&T Committee accepted the conclusions from the cost effectiveness analyses stated above. In addition, the Committee concluded that the UF scenario (condition set C7307) that maintained omeprazole and esomeprazole as the only two agents on the UF in conjunction with a step therapy PA was the most cost effective scenario.

COMMITTEE ACTION: The DoD P&T Committee voted (14 for, 0 opposed, 0 abstention, and 3 absent) to accept the PPI relative CEA as presented by the PEC.

C. PPIs – UF Recommendations

COMMITTEE ACTION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that: 1) omeprazole and esomeprazole be maintained as formulary on the UF with a PA requiring a trial of either agent for new patients; 2) that rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate be classified as non-formulary under the UF with a PA requiring a trial of either omeprazole or esomeprazole for new patients; and 3) that the normal brand formulary cost-share of $9.00 for esomeprazole be lowered to the generic formulary cost-share of $3.00.

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate." Lowering the cost-share for brand name esomeprazole will provide a greater incentive for beneficiaries to use esomeprazole rather than the less cost effective branded products – rabeprazole, lansoprazole, pantoprazole, or omeprazole/sodium bicarbonate – in the purchased care arena.

D. PPIs – PA Criteria

The P&T Committee agreed that the following PA criteria should apply to PPIs other than omeprazole or esomeprazole. Coverage would be approved if a patient met any of the following criteria:

3) Automated PA criteria:

   a) The patient has received a prescription for any PPI agent at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

4) PA criteria if automated criteria are not met:

   a) The patient has tried omeprazole or esomeprazole and had an inadequate response or was unable to tolerate treatment due to adverse effects.

   b) Treatment with omeprazole or esomeprazole is contraindicated.

The P&T Committee noted that in order for a patient to receive a non-formulary PPI agent at the formulary cost-share, both the PA and MN criteria must be met. If the PA criteria are met without an approved MN determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved PA for rabeprazole, lansoprazole, pantoprazole, or omeprazole/sodium bicarbonate would NOT automatically receive it at the formulary cost-share.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend the PA criteria outlined above.

E. PPIs – MN Criteria

Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.
3) Use of formulary alternatives has resulted in therapeutic failure.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

F. PPIs – UF Implementation Period

Even though a large number of beneficiaries are affected (approximately 453,525 patients [64%] of approximately 702,841 beneficiaries at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The P&T Committee believed the considerable cost avoidance associated with this recommendation warranted a more aggressive implementation period. Furthermore, the P&T Committee was anxious to extend the $3.00 cost-share for esomeprazole to beneficiaries as soon as possible. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have rabeprazole, lansoprazole, pantoprazole, or omeprazole/sodium bicarbonate on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary PPI agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

G. PPIs – BCF Review and Recommendations

Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend designating generic omeprazole (Prilosec 40 mg specifically omitted) and esomeprazole as the BCF selections in this class.

9. DRUG CLASS REVIEW – ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

The P&T Committee evaluated the relative clinical effectiveness of the seven angiotensin receptor blockers (ARBs) marketed in the U.S. The ARB drug class is comprised of losartan (Cozaar), irbesartan (Avapro), valsartan (Diovan), candesartan (Atacand), telmisartan (Micardis), eprosartan (Teveten), olmesartan (Benicar) and their respective combinations with hydrochlorothiazide (HCTZ).

Utilization of the ARBs has been steadily increasing in the MHS. The ARB drug class accounted for $137 million in MHS expenditures in FY 2006, and is ranked #10 in terms of total expenditures during that time period. Approximately 140,000 30-day equivalent ARB prescriptions are dispensed monthly in both retail network pharmacies and MTFs; approximately 80,000 30-day equivalent ARB prescriptions are dispensed monthly in the TMOP. The most frequently dispensed ARBs in the MHS are valsartan at 50,000 prescriptions per month and valsartan at 40,000 prescriptions per month. However, the angiotensin converting enzyme (ACE) inhibitor lisinopril is still by far the most frequently prescribed ACE inhibitor or ARB in the MHS, with over 150,000 prescriptions dispensed monthly.

A. ARB Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the ARBs marketed in the U.S. by considering information regarding their safety, effectiveness, and clinical outcomes. The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 CFR 199.21(e)(1).

The ARB drug class was previously evaluated for UF status in February 2005. The P&T Committee focused on efficacy differences with respect to labeled indications, particularly in those areas where a benefit in clinical outcomes (e.g., death, hospitalization for heart failure, decreased need for dialysis or renal transplantation) was demonstrated. The primary areas evaluated were efficacy for hypertension, chronic heart failure (HF), and type 2 diabetic nephropathy.

Evidence of the ARBs for use in indications other than hypertension is difficult to interpret, due to the lack of head to head trials between the ARBs that assess clinical outcomes. There are no head-to-head trials assessing efficacy of the ARBs compared to ACE inhibitors for reducing cardiovascular outcomes in HF or type 2 diabetic nephropathy.

1) Efficacy

a) Efficacy Measures

The P&T Committee considered evidence of benefit in improving clinical outcomes of greater importance than effects on physiologic endpoints when evaluating relative clinical effectiveness differences among ARBs. Clinical outcomes include all-cause mortality, cardiovascular mortality, hospitalization for HF, stroke, development of end stage renal disease (ESRD), need for dialysis, and need for renal transplant. Examples of physiologic endpoints include reduction in blood pressure (BP), changes in pulmonary capillary wedge pressure, changes in urinary protein excretion rate, reduced rate of decline in glomerular filtration rate (GFR), changes in urinary albumin to creatinine ratio, and changes in urinary albumin excretion rate.

b) Hypertension

All seven ARBs are approved by the FDA for treating hypertension. One meta-analysis evaluating the ARBs (with the exception of olmesartan) examined data from over 51 clinical trials enrolling over 12,000 patients with hypertension. The meta-analysis reported that treatment with any ARB reduced systolic blood pressure by 7.5-10 mm Hg and diastolic blood pressure (DBP) by 4.5 to 6.5 mm Hg, compared to placebo (placebo-corrected values). Pooled clinical trial data from seven studies with olmesartan enrolling over 2,600 patients show similar BP reductions to the other six ARBs.

All of the ARBs combinations with HCTZ are approved solely for treatment of hypertension. Joint National Commission (JNC) guidelines for treating hypertension state that many patients will require more than one drug to reach blood pressure goals. Addition of HCTZ to an ARB increases efficacy. Treatment with an ARB as monotherapy results in a 53-63% response rate, based on a goal DBP < 90 mm Hg. The response rate increases to 56-70% with the addition of HCTZ to the ARB.

c) Hypertension and Clinical Outcomes

The ARBs have been evaluated in four large clinical trials to assess efficacy for reducing the risk of cardiovascular events in patients with hypertension. Based on the results of the LIFE trial, losartan is labeled to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy (LVH), however the benefit does not apply to Africa Americans. The benefits of losartan were likely due to greater reductions in BP compared to that achieved with the comparator drug, atenolol (Tenormin, generics). JNC guidelines mention that several antihypertensive drugs classes, including ACE inhibitors and diuretics, are associated with regression of LVH. Reducing BP is well-proven as an effective mechanism to reduce stroke risk, regardless of the antihypertensive agent administered.

Candesartan was found to reduce non-fatal stroke in the SCOPE trial in elderly patients when compared to placebo. When valsartan was compared to amlodipine (Norvasc) in the VALUE trial, there were no differences noted in

cardiovascular mortality or all-cause mortality between the two drugs, however, there were fewer MIs, fatal strokes, and nonfatal strokes with amlodipine. The beneficial results with amlodipine were attributed to a greater percentage of patients achieving target BP goals vs. valsartan (64% versus 58%). In the Jikei Heart Study, valsartan was found to reduce cardiovascular events and strokes, compared to placebo, in a Japanese population.

Candesartan and valsartan are not currently labeled to reduce cardiovascular outcomes in hypertensive patients. For all four trials (LIFE, SCOPE, VALUE, Jikei Heart Study), differences in blood pressure reduction largely account for reported differences in cardiovascular outcomes of ARBs versus other antihypertensives.

e) Chronic Heart Failure

There are no head to head trials comparing the ARBs for use in chronic heart HF. Two large, randomized, placebo-controlled trials, one each with valsartan and candesartan, demonstrated a reduction in the risk of hospitalization due to chronic HF, a clinically relevant outcome.

Based on the results of the Val-HeFT trial, the FDA approved valsartan for use in patients with heart failure. In the Val-HeFT trial, valsartan treatment resulted in a significant 4.4% absolute risk reduction in HF hospitalizations, vs. placebo. A significant reduction in the primary composite endpoint (all-cause mortality/HF hospitalization) was also seen. The previous limitation in the package insert that valsartan should be restricted for use only in HF patients intolerant of ACE inhibitors has now been removed.

The CHARM trials with candesartan support its use in chronic HF, and it is FDA-approved for this indication. A 4.3% absolute risk reduction in HF hospitalization occurred with candesartan treatment, compared to placebo. A significant reduction in the composite primary endpoint (cardiovascular mortality/HF hospitalization) was also shown.

For the other ARBs, losartan was not superior to captopril in reducing death and HF hospitalization in the ELITE II trial. Two pilot studies are available with irbesartan and telmisartan that show reduction in pulmonary capillary wedge pressure. No trials assessing use of eprosartan or olmesartan in HF have been published.

The P&T Committee agreed that there was no evidence that either valsartan or candesartan were preferable relative to the other for the treatment of chronic HF. Since none of the other ARBs have an indication for HF or evidence showing a reduction in clinically relevant outcomes related to chronic HF, the P&T Committee agreed that valsartan and candesartan were preferable to the other five ARBs for the treatment of HF.

f) Type 2 Diabetic Nephropathy

Patients with type 2 diabetes frequently progress from microalbuminuria to overt proteinuria, with decreasing GFR and eventual development of ESRD.

However, the most common cause of death in diabetic patients is due to cardiovascular complications.

i) Microalbuminuria

Head-to-head trials – Two abstracts noted no difference between telmisartan vs. losartan, and telmisartan vs. valsartan in reducing the rate of decline of renal function, as measured by change in urinary protein excretion ratio. However, neither study has been published in a peer-reviewed journal.

Placebo- or active-controlled trials – Benefits on physiologic outcomes in patients with microalbuminuria have been shown with candesartan, irbesartan, telmisartan and valsartan in small studies with placebo or active comparators (usually an ACE inhibitor or calcium channel blocker). There is no published data evaluating efficacy of eprosartan or olmesartan in either microalbuminuria or nephropathy.

ii) Nephropathy

Two ARBs have shown efficacy in clinical outcomes for patients with overt nephropathy and type 2 diabetes mellitus. Both irbesartan and losartan are labeled for use in patients with type 2 diabetic nephropathy, based on the results of the IDNT and RENAAL trials, respectively.

Treatment with losartan resulted in a significant 16% relative reduction (3.6% absolute risk reduction) in the primary composite endpoint (risk of doubling of serum creatinine, death, and ESRD, defined as the need for dialysis or renal transplant), compared to placebo. In the IDNT trial, a significant 20% relative reduction (6.4% absolute risk reduction) was seen with irbesartan compared to placebo when the same composite endpoint was evaluated.

The P&T Committee agreed that there was no evidence that either irbesartan or losartan were preferable relative to the other in patients with type 2 diabetic nephropathy. Since none of the other ARBs has an indication for HF or evidence showing a reduction in clinically relevant outcomes related to type 2 diabetic nephropathy, the P&T Committee agreed that irbesartan and losartan were preferable to the other five ARBs for reducing the risk of doubling of serum creatinine, death, and ESRD in type 2 diabetic nephropathy.

g) Post MI

Valsartan has an additional indication for use in clinically stable patients with left ventricular systolic dysfunction (LVSD) following an MI, to reduce the risk of MI. FDA approval was based on the VALIANT trial, where valsartan was compared with the ACE inhibitor captopril (Capoten, generics). There was no significant difference between valsartan and captopril in all-cause mortality or cardiovascular mortality post-MI.

Overall, ACE inhibitors have a larger body of evidence supporting a mortality benefit in post-MI patients with LVSD than does valsartan. The aldosterone antagonists spironolactone and eplerenone (Inspra) are also labeled for use or have shown efficacy in the post-MI setting.

2) Safety / Tolerability

The ACE inhibitors and ARBs have similar safety concerns regarding hyperkalemia, elevations of serum creatinine, angioedema, and pregnancy category labeling. The ARBs have an incidence of cough similar to placebo.

These medications are generally well-tolerated, with adverse event rates for all the ARBs similar to placebo in controlled trials. The likelihood of potentially serious adverse events, including hyperkalemia, elevations of serum creatinine, and angioedema, does not appear to differ among agents. Drug interaction profiles are similar. All ARBs are rated pregnancy category C during the first trimester, and pregnancy category D during the second and third trimesters, based on the occurrence of fetal abnormalities with ACE inhibitors. The P&T Committee agreed that there is no evidence that any one ARB is preferable to the others with respect to safety or tolerability.

3) Other Factors

The P&T Committee agreed that although there were no clinically significant differences in minor factors between the ARBs, including twice daily dosing and availability in bulk bottles.

4) DoD Utilization

A data analysis of ARB prescriptions using the Pharmacy Data Transaction Service (PDTS) was conducted to determine DOD ARB utilization by FDA approved indication. FDA-approved indication was based on presence of other background medications in the pharmacy profile, (e.g., evidence of digoxin, a loop diuretic or aldosterone antagonist for HF; and use of insulin, oral diabetic medication or blood glucose test strips for diabetic nephropathy). A two-day cross section of 11,317 patients receiving an ARB or ARB/HCTZ combination on 30-31 Mar 07 found 59% of MHS patients were using the ARB for hypertension, 28% for diabetes, 21% for HF, and 8% for both HF and diabetes.

5) Therapeutic Interchangeability

For hypertension, there is a high degree of therapeutic interchangeability for all seven ARBs. Candesartan and valsartan have a high degree of therapeutic interchangeability for chronic HF. For type 2 diabetic nephropathy, irbesartan and losartan have a high degree of therapeutic interchangeability.

6) Clinical Coverage

To meet the needs of the majority of patients in DoD, ideally the UF would include availability of one ARB with evidence for treating HF, and one ARB with evidence for treating type 2 diabetic nephropathy. A third ARB is not necessarily required, as all the ARBs are effective for hypertension, regardless of whether they have additional labeled indications.

7) ARB Overall Clinical Effectiveness Conclusion

The DoD P&T Committee concluded that:

a) There is no evidence that any one ARB is more efficacious than the others for lowering blood pressure.

b) Although losartan is labeled to reduce the risk of stroke in patients with LVH, JNC guidelines support use of other antihypertensive drugs (e.g., ACE inhibitors, diuretics) in this setting. Differences in blood pressure reduction largely account for differences in cardiovascular outcomes seen in trials comparing ARBs to other antihypertensives.

c) There is no evidence to support clinically significant differences in efficacy between candesartan and valsartan in reducing HF hospitalizations in patients with chronic HF.

d) There is no evidence to support clinically significant differences in efficacy between irbesartan and losartan in improving clinical outcomes (e.g., reducing the risk of doubling of serum creatinine, death, or development of ESRD) in patients with type 2 diabetic nephropathy.

e) Valsartan is the only ARB labeled to reduce death and development of heart failure in post-MI patients with LVSD. However, ACE inhibitors have a larger body of evidence supporting a mortality benefit in post-MI patients with LVSD than valsartan. The aldosterone antagonists spironolactone (Aldactone, generics) and eplerenone are also labeled for use or have shown efficacy in the post-MI setting.

f) There is no evidence that the ARBs differ significantly with regard to safety and tolerability profiles.

g) Based on clinical issues alone, there are no compelling reasons to classify any of the ARBs as nonformulary under the UF.

***COMMITTEE ACTION*:** The P&T Committee voted (15 for, 0 against, 0 abstained, 2 absent) to accept the ARB clinical effectiveness conclusion stated above.

B. ARBs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the ARBs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the ARB medications differed in regards to efficacy, safety, or tolerability in the treatment of hypertension. However, several products did have additional clinical outcomes data and FDA approved indications for the treatment of chronic HF (candesartan and valsartan) and type 2 diabetic nephropathy (losartan and irbesartan). The clinical review determined that a UF scenario with an agent from these two additional subgroups would be clinically advantageous. As a result, several CMAs were performed to determine the relative cost effectiveness of the agents by

condition set (3 or fewer agents on the UF, 4 – 5 agents on the UF, and 6 or more agents on the UF) and by indication (hypertension, chronic HF, and type 2 diabetic nephropathy). The CMAs compared the weighted average cost per day of treatment for each drug product across all three points of service.

Results from the ARB CMA showed several important findings: (1) a UF scenario with three or fewer agents on the UF was the most cost effective condition set; (2) telmisartan was the most cost effective agent for the management of hypertension; (3) among agents for the management of chronic HF, candesartan was more cost effective than valsartan when three or fewer agents were included on the UF; and (4) losartan and irbesartan had similar cost effectiveness profiles for the treatment of type 2 diabetic nephropathy.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the Committee in determining which group of ARBs best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The Committee accepted the conclusions stated above and determined from the BIA that the UF scenario that included candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ was the most cost effective UF scenario.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 0 opposed, 0 abstention, and 2 absent) to accept the ARB relative CEA as presented by the PEC.

C. ARBs – UF Recommendations

COMMITTEE ACTION: In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ARBs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ be maintained as formulary on the UF and that eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ be classified as non-formulary under the UF.

D. ARBs – MN Criteria

Based on the clinical evaluation for eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ:

1) Formulary alternatives are contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.

3) Use of formulary alternatives has resulted in therapeutic failure.

4) The patient previously responded to a nonformulary pharmaceutical agent and changing to a formulary pharmaceutical agent would incur an unacceptable clinical risk.

The P&T Committee specifically noted that some circumstances under which criterion #4 might be considered to apply may be for 1) post-MI patients with previous angioedema or other intolerance to ACE inhibitors, who are stabilized on valsartan or valsartan/HCTZ, or 2) chronic HF patients stabilized on a non-formulary ARB or ARB/HCTZ combination for whom changes in therapy might result in destabilization.

COMMITTEE ACTION: The P&T Committee voted (13 for, 1 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. ARBs – UF Implementation Period

Because of the large number of beneficiaries affected (approximately 228,000 patients (59%) of approximately 387,000 beneficiaries at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan, and valsartan/HCTZ on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary ARB agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. ARBs – BCF Review and Recommendation

COMMITTEE ACTION: Based on the results of the clinical and economic evaluations, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that telmisartan and telmisartan/HCTZ remain on the BCF.

G. Therapeutic Class Reclassification

The Committee agreed that the ARB class should be reclassified and consolidated with other drug classes that affect the renin-angiotensin system. These include ACE inhibitors, ACE/CCB combinations, ARBs, ARB/CCB combinations, and any newly approved antihypertensives affecting the renin-angiotensin system. The new class will be called the Renin-Angiotensin Antihypertensives (RAAs).

10. QUANTITY LIMITS

A. Mometasone nasal spray (Nasonex) – The current QL for mometasone nasal spray is 1 inhaler (17 gm = 120 sprays) per 30 days or 3 inhalers (51 gm) per 90 days. Nasonex, which was previously indicated only for allergic rhinitis at a maximum dose of 2 sprays in each nostril QD (4 sprays per day), received an indication in late 2004 for the treatment of nasal polyps at a maximum dose of 2 sprays in each nostril twice daily (8 sprays per day). TMOP personnel recently reported an increased number of QL override requests for Nasonex, based on dosing consistent with the nasal polyp indication. Accordingly, the P&T Committee recommended an increase in the QL to accommodate the higher maximum dose for nasal polyps.

COMMITTEE ACTION: The Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that the QL for mometasone nasal spray (Nasonex) be increased to 34 gm (2 inhalers) per 30 days (TRRx), 102 gm (6 inhalers) per 90 days (TMOP), based on daily maximum dosing recommended in product labeling.

B. **Ipratropium nasal spray 0.03% and 0.06% (Atrovent Nasal Spray) –** The current QL for Atrovent nasal spray is a collective limit (including both strengths) of 30 mL per 30 days or 90 mL per 90 days. The 0.03% strength, supplied in 30 mL bottles containing 345 sprays per bottle, is indicated for perennial rhinitis in divided doses of up to 12 sprays per day. Taking into account initial priming (7 sprays), 30 mL would equal 28 days supply, assuming consistent use at the maximum recommended dose. The 0.06% strength, supplied in 15 mL bottles containing 165 sprays per bottle, has two indications: 1) rhinorrhea associated with the common cold at divided doses of up to 16 sprays per day; and 2) rhinorrhea associated with seasonal allergic rhinitis at divided doses of up to 16 sprays per day. Based on the indication for seasonal allergic rhinitis and taking into account initial priming, 30 mL would equal 20 days supply, assuming consistent use at the maximum recommended dose.

The P&T Committee also reviewed data concerning QL rejections for Atrovent 0.03% and 0.06%, indicating that approximately 7% of prescriptions for either strength (about 300 prescriptions per month at retail network pharmacies and the TMOP) are initially rejected by the PDTS based on QLs. This is consistent with recent reports from TMOP of an increased number of QL override requests for Atrovent nasal spray.

Based on these data and given that seasonal allergic rhinitis can last considerably longer than 3 weeks, the P&T Committee agreed that the QL for the higher 0.06% strength should be increased. The P&T Committee also agreed that the QL for the lower 0.03% strength should be increased, but requested follow-up monitoring to determine if the change in QLs unduly affected utilization patterns, since the majority of patients should need no more than 1 inhaler per 30 days.

COMMITTEE ACTION: The Committee voted (13 for, 0 opposed, 2 abstained, and 2 absent) to recommend that 1) the QL for ipratropium nasal spray (Atrovent) be changed from a collective limit to a QL by strength; 2) the QL for the 0.03% strength be increased to 2 inhalers (60 mL) per 30 days (TRRx), 6 inhalers (180 mL) per 90 days (TMOP); and 3) the QL for the 0.06% strength be increased to 3 inhalers (45

mL) per 30 days (TRRx), 9 inhalers (135 mL) per 90 days (TMOP), based on daily maximum dosing recommended in product labeling.

11. RE-EVALUATION OF NON-FORMULARY AGENTS

Amlodipine (Norvasc) was designated non-formulary at the August 2005 P&T Committee meeting. In early 2007, the FDA approved Mylan Pharmaceutical's first-time generic for Norvasc (amlodipine, Pfizer). The price of amlodipine remains high enough that the Committee felt that even the generic was not cost effective relative to other drugs in the calcium channel blocker class. However, as part of its re-evaluation of the non-formulary UF status of amlodipine, the P&T Committee recognized that there will be situations in the future in which it would be helpful if a procedure were in place that allowed reclassification of such a drug from non-formulary to generic in a more expeditious manner than can be accomplished through the normal quarterly P&T Committee cycle. Such a procedure would be advantageous for both the MHS and its beneficiaries. The P&T Committee proposed the following process to more expeditiously reclassify non-formulary agents:

1) For each drug class in which such a reclassification is a possibility, the P&T Committee will recommend criteria under which non-formulary agents will be reclassified as generic agents under the UF. These criteria will be reviewed and adopted as a recommendation of the committee. The recommendation will be subject to comment by the BAP), and final decision by the Director, TMA (see recommended criteria below).
2) When the pre-established criteria for reclassification are met, the Chairperson of the P&T Committee will call for an electronic vote by the members of the P&T Committee on the matter.
3) Upon a majority vote affirming that the non-formulary drug should be reclassified as generic, that agent will be changed from non-formulary status to formulary status as a generic.
4) Committee members will be briefed on any reclassification of a non-formulary agent at the next meeting of the P&T Committee. This information will be recorded as an information-only item in the meeting minutes. The item will be included in information provided for the BAP's next meeting; however, since the BAP will have already made any comments on the subject, the item will normally not be subject to further BAP comment.

The DoD P&T Committee recommended the following criteria for the re-evaluation of non-formulary agents for UF status. These criteria would apply only to drug classes in which UF status was NOT awarded based on condition sets that specified the number of similar agents on the UF (i.e., agents in the same class or subclass). All three criteria must be met for the reclassification of a non-formulary agent.

1) The P&T Committee had concluded previously that the non-formulary agent had similar relative clinical effectiveness (i.e., similar efficacy, safety, and tolerability) compared to similar agents on the UF, and that the drug had not been excluded from the UF based on clinical issues alone.

2) The non-formulary agent becomes generically available and:
   a) The generic product is "A-rated" as therapeutically equivalent to the brand name product according to the FDA's classification system
   b) The generic market supply is stable and sufficient to meet DoD MHS supply demands.
3) The non-formulary agent is cost effective relative to similar agents on the UF. A non-formulary agent becomes cost-effective when:
   a) The non-formulary agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the UF class to which they were compared.
   b) The non-formulary agent's total weighted average cost based on an alternate measure used during the previous review is less than or equal to that for the UF class to which they were compared. F or example, antibiotics may be compared on the cost per course of therapy used to treat a particular condition.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 against, 3 absent) that the process and criteria described above should be adopted.

12. CLASS OVERVIEWS

Class overviews for the newer antihistamines, targeted immunomodulatory biologics, leukotriene modifiers, beta/alpha-beta blockers, and alpha blockers for BPH were presented to the P&T Committee. Preliminary information for the technical review for the blood glucose test strips was also presented.

The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed during the August 2007 or November 2007 meetings; no action is necessary.

13. ADJOURNMENT

The second day of the meeting adjourned at 1700 hours on 16 May 2007. The next meeting will be August 14-15, 2007.

_____signed_____

Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	Pending approval	Pending approval
May 07	Antilipidemic Agents II	▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	▪ gemfibrozil ▪ fenofibrate IDD-P (Triglide)	Pending approval	Pending approval
May 07 re-review (Feb 05 original)	ARBs	▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	Pending approval	Pending approval
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	Pending approval	Pending approval
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	NA

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 06	ADHD Agents	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07 (90 days)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06 (updated for new drugs Nov 06)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospironone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			Pending approval	Pending approval
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications)	**Effective Date for Non-Formulary Medications** (Implementation period)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated for new drugs Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
		Recommended Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			Pending approval	Pending approval
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	**-**
Feb 05	ARBs	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary

ER = extended release; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle

ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs = thiazolidinediones

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs. May 2007 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Lapatinib tablets (Tykerb, Glaxo) tyrosine kinase inhibitor	Mar 07 ▪ In combination with capecitabine for treatment of patients with advanced or metastatic breast cancer whose tumors over express HER2, and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.	No UF recommendation at this meeting. Consideration of UF status deferred until oral cancer drugs are reviewed; UF review not anticipated in the next 12 months. Quantity limits recommended: ▪ TMOP o Days supply limit 45 days o 250 mg: 225 tabs per 45 days ▪ Retail Network o Days supply limit 30 days o 250 mg: 150 tabs per 30 days
Vorinostat capsules (Zolinza; Merck) histone deactylase inhibitor	Oct 06 ▪ Treatment of cutaneous manifestations in patients with cutaneous T cell lymphoma (CTCL) who have progressive, persistent, or recurrent disease on or following two systemic therapies.	No UF recommendation at this meeting. Consideration of UF status deferred until oral cancer drugs are reviewed; UF review not anticipated in the next 12 months. Quantity limits recommended: ▪ TMOP o Days supply limit 45 days o 100 mg: 180 caps per 45 days ▪ Retail Network o Days supply limit 30 days o 100 mg: 120 caps per 30 days
Arformoterol inhalation solution (Brovana; Sepracor) inhaled long-acting beta agonist	Oct 06 (launched Apr 07) ▪ Long term twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. For use by nebulization only.	No UF recommendation at this meeting. Consideration of UF status deferred until inhaled long-acting beta agonists are reviewed; UF review anticipated in the next 12 months. Quantity limits recommended: ▪ TMOP o 180 unit dose 15 mcg/2 mL vials per 90 days ▪ Retail Network o 60 unit dose 15 mcg/2 mL vials per 30 days

Appendix C – Table 3. Table of Abbreviations

5-ARI	5-alpha reductase inhibitor
ACE	angiotensin converting enzyme
AERS	adverse event reporting system
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ARB	angiotensin receptor blocker
AUA	American Urological Association
AUA-SI	American Urological Association symptom index
AUR	acute urinary retention
BAP	Beneficiary Advisory Panel
BAS	bile acid sequestrant
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BPA	blanket purchase agreement
BP	blood pressure
BPH	benign prostatic hyperplasia
CAD	coronary artery disease
CCB	calcium channel blocker
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CHD	coronary heart disease
CMA	cost minimization analysis
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CPAP	continuous positive airway pressure
CYP	cytochrome (P450)
DERP	Drug Effectiveness Review Project (state of Oregon)
DHA	docosahexaenoic acid
DHT	dihydrotestosterone
DoD	Department of Defense
DBP	diastolic blood pressure
EE	erosive esophagitis
ENRD	endoscopy-negative reflux disease
EPA	eicosapentaenoic acid
EPICS	Enlarged Prostate International Comparator Study
ESRD	end stage renal disease
ER	extended release
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes trial
FY	fiscal year
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto miocardico (GISSI)-Prevenzione
GFT	glomerular filtration rate
HCTZ	hydrochlorothiazide
HDL	high density lipoprotein
HF	heart failure
HHS	Helsinki Heart Study
IDD-P	Insoluble drug delivery microparticle
IPSS	International Prostate Symptom Score
IV	intravenous

Appendix C – Table 3. Table of Abbreviations (continued)

JNC	Joint National Council
LDL	low density lipoprotein
LH	leutinizing hormone
LIP-2	Antilipidemics II
LRC-CPPT	Lipid Research Clinics – Coronary Primary Prevention Trial
LUTS	lower urinary tract symptoms
LVH	left ventricular hypertrophy
LVSD	left ventricular systolic dysfunction
MHS	Military Health System
MI	myocardial infarction
MN	medical necessity
MTF	military treatment facility
MTOPS	Medical Therapy of Prostatic Symptoms
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Lung, and Blood Institute
NSAIDs	non-steroidal anti-inflammatory drugs
OTC	over-the-counter
PA	prior authorization
PPI	proton pump inhibitor
P&T	Pharmacy and Therapeutics
PDTS	Pharmacy Data Transaction Service
PEC	Pharmacoeconomic Center
PSA	prostate specific antigen
PUD	peptic ulcer disease
QD	once daily
Qmax	urinary flow rate
RAAs	renin-angiotensin antihypertensives
TC	total cholesterol
TG	triglyceride
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TPV	total prostate volume
TRRx	TRICARE Retail Network
UF	Uniform Formulary
UGT	uridine diphosphate glucuronosyl transferase
VA-HIT	Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial
VARR	voluntary agreements for TRICARE retail pharmacy rebates

DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

February 2007

1. **CONVENING**
2. **ATTENDING**
3. **REVIEW MINUTES OF LAST MEETING**
4. **ITEMS FOR INFORMATION**
5. **REVIEW OF RECENTLY APPROVED AGENTS**

A. Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF) – The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee was briefed on two new drugs approved by the Food and Drug Administration (FDA) that did not fall under drug classes previously reviewed for UF consideration: sitagliptin phosphate tablets (Januvia) and paliperidone extended release [ER] tablets (Invega). UF consideration was deferred until drug class reviews are completed. No action is required since the P&T Committee did not recommend a quantity limits (QL) or prior authorization (PA) for either of these drugs.

B. Over-the-Counter Omeprazole Magnesium (Prilosec OTC)

The John Warner National Defense Authorization Act for FY 2007 directed that the Secretary of Defense conduct a demonstration project to assess the impact of authorizing TRICARE coverage for over-the-counter (OTC) agents recommended for inclusion on the UF. The DoD P&T Committee must find that the OTC drug is cost effective and therapeutically equivalent to prescription alternatives. The P&T Committee, after consultation with the TRICARE Management Activity (TMA) Pharmacy Program office, selected the proton pump inhibitor (PPI) omeprazole magnesium as the initial OTC product. It is projected to be available at military treatment facilities (MTFs) and the mail order points of service by 1 May 2007.

The P&T Committee previously reviewed the PPIs in February 2005. PPIs on the UF include prescription omeprazole (Prilosec, generics), rabeprazole (Aciphex), lansoprazole (Prevacid), and pantoprazole (Protonix). Esomeprazole (Nexium), the s-isomer of omeprazole, is non-formulary under the UF. The Basic Core Formulary (BCF) selections in this class are prescription omeprazole and rabeprazole.

Relative Clinical Effectiveness – The P&T Committee concluded (13 for, 0 opposed, 2 abstained, 2 absent) that omeprazole magnesium has similar relative clinical effectiveness compared to other PPIs included on the UF. The P&T Committee also concluded that, while FDA-approved indications differ for the OTC and prescription versions of omeprazole, there is no reason to believe that the clinical effect of omeprazole magnesium, when given to the same patients in the same doses, would differ from the anticipated effects of prescription omeprazole.

Relative Cost Effectiveness – The cost analysis showed that omeprazole magnesium has a cost effectiveness profile similar to prescription omeprazole in the mail order and MTF points of service and a more favorable cost effectiveness profile in the retail sector. Omeprazole magnesium is more cost effective than other products in the PPI class (i.e., esomeprazole, lansoprazole, pantoprazole, and rabeprazole) across all three points of service. Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee voted (13 for, 0 opposed, 2 abstained, 2 absent) that omeprazole magnesium is comparable in cost to prescription omeprazole, and more cost effective than the other PPIs included on the UF.

COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 2 abstained, 2 absent) to recommend that omeprazole magnesium be classified as formulary on the UF (see paragraph 5B on pages 20-22 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

6. DRUG CLASS REVIEW – NEWER SEDATIVE HYPNOTICS (SED-1s)

The P&T Committee evaluated the relative clinical effectiveness of the newer sedative hypnotic agents (SED-1s). The SED-1 drug class includes the following agents: zolpidem immediate release [IR] (Ambien), eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), and zolpidem ER (Ambien CR). All SED-1 agents except ramelteon are classified as benzodiazepine receptor agonists; ramelteon acts as an agonist at melatonin receptors (MT_1 and MT_2) in the suprachiasmatic nucleus of the brain, which is responsible for regulation of the 24-hour sleep-wake cycle (circadian rhythm). All are FDA-indicated for the treatment of insomnia, although specific labeling differs.

As of December 2006, about four million Military Health System (MHS) prescriptions for these agents are filled per month. The SED-1 drug class was ranked #15 in terms of expenditures in FY 2006 ($111 million)—up from #18 in FY 2005 ($72 million), and #20 in FY 2004 ($54 million). Across the MHS, zolpidem IR is the most commonly prescribed SED-1, with about twice as many prescriptions compared to the next most commonly prescribed SED-1 agent, zolpidem ER, followed closely by eszopiclone. Usage of zaleplon is low and stable, while usage of the most recently introduced agent, ramelteon, is low but increasing. All of the SED-1 agents are brand-only; zolpidem IR is expected to become generically available in April 2007.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) Based on placebo-controlled trials, all SED-1 agents decrease sleep latency to a similar degree. Data supporting the effect of ramelteon on sleep latency appears to be the least robust, both in terms of the number of published studies and the amount of improvement demonstrated versus placebo. Zolpidem IR and eszopiclone have evidence indicating consistent and similar increases in sleep

duration. Zaleplon and ramelteon do not appear to consistently increase sleep duration.

2) Based on three comparative trials, zaleplon appears to decrease sleep latency more than zolpidem IR, but zolpidem IR appears to increase total sleep time more than zaleplon. In one comparative trial, very similar results were reported for eszopiclone versus zolpidem IR with respect to measures of sleep latency and sleep duration.

3) Based on comparative trials, SED-1 agents appear to be similar in efficacy and short-term adverse events, compared to benzodiazepines; benzodiazepines may cause more rebound insomnia. Zolpidem IR appears to be similar in efficacy to the sedating antidepressant trazodone (Desyrel, generics), based on one comparative trial in non-depressed patients; trazodone may result in greater daytime somnolence.

4) There are no consistent data to demonstrate that SED-1 agents have beneficial effects on sleep architecture, compared to placebo.

5) There is insufficient evidence to conclude that SED-1 agents have a major beneficial effect on quality of life, although limited data show improvement in certain domains of the SF-36. There are insufficient comparative data to draw conclusions about individual agents.

6) The SED-1 agents appear to have similar adverse effect profiles and to result in similar rates of discontinuation due to adverse events in clinical trials. Eszopiclone is associated with an unpleasant taste. There do not appear to be any major disadvantages for any one agent with respect to drug-drug interactions. Ramelteon may be less effective in smokers.

7) Daytime sleepiness, impairments in psychomotor function and cognitive function, adverse effects on driving safety, and increased risk for falls may occur with any of the benzodiazepine receptor agonists; there are little or no data for the melatonin receptor agonist ramelteon. Agents with longer half-lives tend to pose a greater risk for these effects. The SED-1 agent with the longest half-life is eszopiclone, 6 hours (up to 9 hours in elderly patients); followed by zolpidem (Ambien, Ambien CR), 2.5-2.8 hours; ramelteon, 1-2.6 hours; and zaleplon, 1 hour. Lower starting doses of all SED-1 agents except ramelteon are recommended in elderly patients.

8) The applicability of driving safety studies reporting impaired performance and increased risk of accidents with a 7.5 mg dose of zopiclone (eszopiclone's racemic parent drug) is unclear, since recommended doses of eszopiclone would be equivalent to zopiclone doses lower than 7.5 mg. There was no reported difference between eszopiclone and zolpidem IR on subjective measures of next day effects based on results of an unpublished trial reported in the FDA statistical review of eszopiclone.

9) Because of its very short half-life, zaleplon may be taken in the middle of the night after a patient has had difficulty falling asleep without demonstrating adverse effects on driving performance the next morning. It may have an

advantage in elderly patients, since risk of falls and hip fracture tends overall to increase with increasing half-life (although the relationship between falls and half-life is not straightforward and prescribers must take into account patient activity patterns).

10) No SED-1 agent appears preferable in other special patient populations (hepatic or renal dysfunction, pregnancy, pediatrics); there is some concern about use of ramelteon in pediatric patients due to possible endocrine effects.

11) Rebound insomnia has been reported in clinical trials with all SED-1 agents except ramelteon; more rebound insomnia was noted with zolpidem IR than with zaleplon during comparative trials.

12) All SED-1 agents, with the exception of ramelteon, probably have a small but significant potential for abuse. Ramelteon appears to lack significant abuse potential and may be preferable in patients at high risk for substance abuse. Ramelteon is the only SED-1 agent that is not a Drug Enforcement Agency (DEA) scheduled substance.

13) It is likely that at least two SED-1 agents are needed for adequate clinical coverage, based on provider responses regarding prescribing practices and likely patient response.

Relative Cost Effectiveness Conclusion: Based on the results of the cost minimization analysis (CMA) and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) Eszopiclone was the most cost effective agent until zolpidem IR becomes generically available with competitive pricing.

2) Ramelteon, zaleplon, and zolpidem ER were more costly than eszopiclone and provided no meaningful clinical therapeutic advantage compared to eszopiclone or zolpidem IR.

3) The UF scenario utilizing a prior authorization requiring a trial of zolpidem IR by new SED-1 patients was more cost effective relative to UF scenarios not requiring a trial of zolpidem IR by new SED-1 patients.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the SED-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 2 abstained, 1 absent) to recommend that: 1) eszopiclone and zolpidem IR be maintained as formulary on the UF with a PA requiring a trial of zolpidem IR for new patients and 2) that ramelteon, zaleplon, and zolpidem ER be classified as non-formulary under the UF, with a PA requiring a trial of zolpidem IR for new patients (see paragraphs 6A, 6B, and 6C on pages 23-31 and Appendix D on page 79 of the P&T Committee minutes).

The Committee agreed that the following PA criteria should apply to SED-1 agents other than zolpidem IR. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:

The patient has received a prescription for any SED-1 agent (including zolpidem IR) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2) PA criteria if automated criteria are not met:

The patient has tried zolpidem IR and had an inadequate response or was unable to tolerate it due to adverse effects.

Treatment with zolpidem IR is contraindicated.

In order for a patient to receive a non-formulary SED-1 agent at the formulary cost-share, both the PA and medical necessity (MN) criteria must be met. If the PA criteria are met without an approved MN determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved PA for ramelteon, zaleplon, or zolpidem ER would NOT automatically receive it at the formulary cost-share.

The P&T Committee also noted that the PA is not intended to apply where there are existing policies or protocols in place for operational/readiness situations and that MTFs should make necessary allowances for such use.

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for ramelteon, zaleplon, and zolpidem ER, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) MN criteria for ramelteon, zaleplon, and zolpidem ER (see paragraph 6D on page 31 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 2 abstained, 1 absent) to recommend an effective date of the greater of 1) the first Wednesday following a 90 day implementation period, or 2) the time necessary to complete logistical arrangements to implement the automated PA. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 6E on pages 31-32 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (13 for, 0 opposed, 3 abstained, 1 absent) to recommend adding zolpidem IR as the BCF selection in this class (see paragraph 6F on page 32 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

7. DRUG CLASS REVIEW – NARCOTIC ANALGESICS

The drugs in this class comprise all narcotic analgesics (also referred to as opioids or opiate agonists) used for the treatment of pain on an outpatient basis, including combinations with acetaminophen (APAP), aspirin (ASA), and other non-opioids. Not included in this drug class review are narcotic analgesics given primarily by intravenous injection or infusion, over-the-counter products, products requiring administration by a medical professional, products in which the narcotic component is primarily used as an antitussive, and products indicated solely for the treatment of opioid dependence.

For review purposes, the narcotic analgesics were divided into four categories, based on their potency. Most of these agents are now generically available.

The narcotic analgesics accounted for approximately $153 million dollars in MHS expenditures in FY 2006 and are ranked #8 in terms of total expenditures during that time period. Approximately 437,000 DoD beneficiaries received one or more prescriptions for a narcotic analgesic during FY 2006.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) There is insufficient evidence to support efficacy differences between narcotic analgesics, including high potency long-acting agents for the treatment of chronic cancer or non-cancer pain, high potency IR agents for the treatment of break-through pain, or narcotic analgesics in general for the treatment of neuropathic pain.
2) Strong narcotic analgesics appear to be more effective than non-opioid analgesics (non-steroidal anti-inflammatory drugs [NSAIDs], tricyclic antidepressants [TCAs]) in chronic non-cancer pain.
3) There is no evidence suggesting efficacy differences between long-acting and short-acting formulations of the same agents; however, long-acting products offer greater convenience and may be associated with fewer episodes of breakthrough pain.
4) There is insufficient evidence to support efficacy differences between the 12-hour ER morphine products (e.g., MS Contin and generics) and the 24-hour ER morphine products (Avinza, Kadian), or between the two 24-hour products (Avinza versus Kadian). Avinza is restricted to a maximum dose of 1600 mg daily and cannot be taken with alcohol (including alcohol-containing medications). Kadian has a much longer time to achieve maximum serum levels

(~9.5 hours) compared to Avinza (~0.5 hour) or to 12-hour ER morphine (2-3 hours). Both can be opened and sprinkled on food; Kadian granules can be given via gastrostomy tube.

5) There is insufficient evidence to support efficacy differences between high potency IR agents for the treatment of breakthrough pain in patients with chronic cancer or non-cancer pain, including the newer IR fentanyl products (oral transmucosal lozenges [Actiq, generic] and buccal tablets [Fentora]). Buccal fentanyl is more bioavailable and may offer more consistent dosing; it is also sugar-free. The lack of a 1:1 conversion between the two IR fentanyl products may offer significant potential for medication errors.

6) Narcotic analgesics are rarely considered first line agents for the treatment of neuropathic pain. There is insufficient evidence to support efficacy differences between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.

7) There is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen. The VA/DoD guideline recommends avoiding meperidine for the treatment of postoperative pain.

8) Narcotic analgesics are associated with multiple adverse effects, including nausea, vomiting, constipation, mood changes, somnolence, urinary retention, pruritis, and oral/dental problems. Respiratory depression is uncommon but potentially serious; the risk is generally small when narcotic analgesics are appropriately titrated, as tolerance rapidly develops.

9) A decrease in seizure threshold occurs with the use of all narcotics, but is of particular concern with meperidine (which has a neurotoxic metabolite and should not be used for more than two days in patients with renal impairment, sickle-cell disease, central nervous system [CNS] disease, or in children); propoxyphene (which also has CNS-excitatory metabolites and can cause seizure in high doses, especially in patients with renal disease); and tramadol (which is associated with an increased risk of seizure at higher than recommended doses [300-400 mg daily] or in patients taking other medications or with conditions that increase seizure risk).

10) Propoxyphene is not considered appropriate in elderly patients due to CNS adverse effects, including sedation, confusion, and increased likelihood of falls and fall-related fractures. The consumer watchdog group Public Citizen has petitioned the FDA to phase out propoxyphene from the U.S. market due to the association of excessive doses of propoxyphene with drug-related deaths. Many DoD providers surveyed cited concerns over safety with the use of meperidine and propoxyphene, although others pointed out that they were useful and could be used safely if limited to short-term use in the correct patients.

11) While there are clearly differences among narcotic analgesics with regard to likelihood for abuse (e.g., onset of action and potency), there are no data

supporting differences in potential for abuse among like medications (e.g., high potency long-acting agents) that the P&T Committee considered useful for making any formulary recommendation.

12) In general, drug interactions are relatively similar for all of the drugs in this class and it does not appear that any particular medication offers a substantially higher potential for drug interactions. Two unique considerations are tramadol and meperidine. Because of its dual mechanism of action, tramadol has potential interactions with other medications that increase serotonin and/or norepinephrine levels (e.g., monoamine oxidase inhibitors [MAOIs] and selective serotonin reuptake inhibitors [SSRIs]); meperidine is contraindicated with MAOIs due to the potential for a lethal hyperpyrexic syndrome.

13) There are differences among narcotic analgesics with regard to clinical evidence, extent of clinical experience, and labeling for use in special patient populations (including pediatric and elderly patients, patients who are pregnant or breast-feeding, and patients with renal or hepatic dysfunction). However, the P&T Committee overall did not find sufficient evidence of a unique advantage or disadvantage for specific products that it considered useful for formulary decision-making.

14) Patients with swallowing difficulties may require liquid formulations or products that can be sprinkled on food or administered via a non-oral route. The available narcotic analgesics offer various formulations that meet these needs.

15) Providers surveyed in general emphasized that they require a broad array of narcotic analgesics in their practice to treat their patients and that excessive formulary restrictions would be detrimental to their ability to adequately treat various clinical presentations. They favored ER narcotic analgesics, including the fentanyl transdermal patch, as well as a broad array of strengths of opioid/ acetaminophen combination products. Many pharmacists indicated that centralized contracting for "pre-packed" products in commonly dispensed quantities would facilitate inventory and dispensing at their facilities.

16) Clinical coverage considerations support a broad array of formulary agents and formulations.

Relative Cost Effectiveness Conclusion: Based on the results of the CMAs and other clinical and cost considerations, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 1 absent) that:

1) *High potency long-acting single analgesic agents* – Although the 24-hour ER products (Kadian and Avinza); fentanyl transdermal patch (Duragesic, generics), oxycodone ER (Oxycontin), and oxymorphone (Opana ER) were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin and generics), they possess unique clinical advantages and should be maintained on the UF in order to sufficiently meet the clinical needs of the DoD population.

2) *High potency short-acting single analgesic agents* – Even though fentanyl citrate buccal tablets and fentanyl citrate transmucosal lozenges were more than 40-fold the cost of the two most cost effective agents (morphine sulfate IR and oxycodone

IR), the fentanyl citrate products provide an additional therapeutic alternative for breakthrough pain with novel routes of administration. There was no substantial difference in cost effectiveness between the two fentanyl citrate products.

3) *Low potency single analgesic agents* – Tramadol ER (Ultram ER) was not cost effective relative to other formulations of tramadol (tramadol; tramadol/APAP), which are generically available. All other products in this subclass were cost effective.

4) *Combination agents* – The products within this generic-dominated subclass were all determined to be cost effective relative to their comparators.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the narcotic analgesic drug class, and other relevant factors, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) that tramadol ER be designated non-formulary under the UF, with all other narcotic analgesic agents designated as formulary on the UF. Additionally, the P&T Committee voted to recommend (14 for, 0 opposed, 1 abstained, 1 absent) a QL of 112 tablets/28 days for fentanyl buccal tablets, consistent with established QLs for fentanyl transmucosal lozenges, recommendations in Fentora package labeling recommending a maximum of four tablets per day, and current DoD prescribing patterns for Fentora buccal tablets (see paragraphs 7A, 7B, and 7C on pages 35-51 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for tramadol ER, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) MN criteria for tramadol ER (see paragraph 7D on page 51 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 7E on pages 51-52 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend designating the following medications as the BCF selections in this class: morphine sulfate ER (MS Contin, generics) 15 mg, 30 mg, 60 mg; morphine sulfate IR 15 mg and 30 mg; oxycodone/ APAP 5/325 mg; hydrocodone/APAP 5/500 mg; codeine/APAP 30/300 mg; codeine/ APAP elixir 12/120 mg/5 mL; and tramadol IR 50 mg (see paragraph 7F on page 52 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

8. DRUG CLASS REVIEW – OPHTHALMIC GLAUCOMA AGENTS

The P&T Committee evaluated the relative clinical effectiveness of the ophthalmic glaucoma agents available in the U.S. Based on chemical structure and mechanism of action, the drug class was divided into seven subgroups: ophthalmic prostaglandin analogs; beta blockers; carbonic anhydrase inhibitors and combinations with beta blockers; alpha 2 adrenergic drugs; adrenergics; cholinergics; and cholinesterase inhibitors. The ophthalmic glaucoma agent drug class accounted for $51.1 million in MHS expenditures for the period October 2005 to September 2006, and is ranked #34 in terms of total expenditures during that time period.

Relative Clinical Effectiveness Conclusion – The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) *Prostaglandin analogs* – Bimatoprost (Lumigan), latanoprost (Xalatan), and travoprost (Travatan, Travatan Z) all decrease intraocular pressure (IOP) from baseline by 28% to 33%. A prospectively designed trial assessing efficacy of bimatoprost and travoprost found no difference in efficacy in African Americans; a sub-group analysis from a different trial reported decreased efficacy of latanoprost when compared to travoprost in African Americans versus non-African Americans. Latanoprost has the most favorable ocular adverse event profile of the three prostaglandin analogs, but requires refrigeration prior to opening. The non-benzalkonium (BAK) preservative found in the Travatan Z formulation of travoprost has not shown a major advantage in terms of ocular side effects, compared to the BAK-containing product Travatan.

2) *Beta blockers* – The IOP lowering effects of timolol maleate (Timoptic, generics; Timoptic XE, generics), timolol hemihydrate (Betimol), levobunolol (Betagan, generics), metipranolol (Optipranolol, generics) and carteolol (Ocupress, generics) appear similar based on several head-to-head studies. Timolol maleate solution (Timoptic, generics) and gel-forming solution (Timoptic XE, generics) reduce IOP by 20-35%. The Timoptic XE gel-forming solution has the advantage of once daily dosing, but is associated with transient blurred vision due to the consistency of the gel. There is no evidence that the timolol maleate product Istalol or the timolol hemihydrate product Betimol have additional clinical benefits over other timolol maleate products in IOP lowering or safety profiles.

Betaxolol (Betoptic, generics; Betoptic-S) decreases IOP to a lesser extent than timolol maleate; however, the β1 selectivity of betaxolol may be an advantage in patients with cardiac or pulmonary co-morbidities.

3) *Carbonic anhydrase inhibitors* – The IOP lowering effects of brinzolamide (Azopt) and dorzolamide (Trusopt) appear similar. Dorzolamide/timolol (Cosopt) is the only combination product for glaucoma and offers a convenience to patients. Dorzolamide causes more local ocular irritation than brinzolamide; however the burning and stinging upon instillation lasts less than ten seconds, diminish over time, and has not translated into a higher discontinuation rate due to adverse events.

4) *Alpha 2 adrenergics* – Apraclonidine (Iopidine) is used primarily short-term following ocular surgery, while brimonidine is used chronically for glaucoma. Both apraclonidine and brimonidine lower IOP to similar extent. For brimonidine, changing the BAK preservative (generic) to a purite preservative (Alphagan P) and reducing the concentration from 0.2% to 0.15% or 0.1% does not appear to affect efficacy. There are conflicting data as to whether brimonidine purite 0.15% (Alphagan P) causes less ocular irritation than brimonidine BAK 0.2% (generic). In an unpublished trial, brimonidine purite 0.1% (Alphagan P) demonstrated an improved safety and tolerability profile compared to brimonidine BAK 0.2% (generic).

5) *Adrenergics, cholinergics, and cholinesterase inhibitors* – The cholinergic pilocarpine (Pilocar, generics; Pilopine HS gel) is used for acute angle closure glaucoma and as a miotic agent during ocular surgery. Although not routinely used today, the adrenergic drug dipivefrin (Propine), the cholinergics acetyl-choline (Miochol-E) and carbachol (Isopto Carbachol) and the cholinesterase inhibitor echothiophate (Phospholine Iodide) serve unique niches in therapy.

6) Based on clinical issues alone, there are no compelling reasons to classify any of the glaucoma drugs as non-formulary on the UF.

Relative Cost Effectiveness Conclusion: Based on the results of several CMAs, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) The CMAs compared the weighted average cost per day of treatment for each drug product. For the prostaglandin analogs: a) travoprost (Travatan, Travatan Z) was most cost effective under a scenario where it was the sole agent on the uniform formulary; b) latanoprost and bimatoprost were most cost effective under a scenario where only two prostaglandin products were placed in the UF; and c) an all-on scenario (i.e., all three prostaglandin products were included on the UF) was less cost effective than a scenario where at least one prostaglandin was designated non-formulary.

2) For the other ophthalmic glaucoma agents, only two products were identified as not cost effective in the beta-blocker subclass. Timolol hemihydrate (Betimol) and timolol maleate (Istalol) were both shown to be significantly more costly and no more effective than other agents in the subclass. Similarly, a comparison of the topical carbonic anhydrase inhibitors showed that brinzolamide was not cost

effective compared to dorzolamide. All other medications in the remaining subclasses were determined to be cost effective relative to their comparators.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ophthalmic glaucoma agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that latanoprost, bimatoprost, levobunolol, betaxolol, carteolol, timolol maleate (Timoptic, generics), timolol maleate gel-forming solution, brimonidine, apraclonidine, dorzolamide, dorzolamide/timolol, dipivefrin, acetylcholine, carbachol, pilocarpine, echothiophate be maintained as formulary on the UF and that travoprost (Travatan, Travatan Z), timolol hemihydrate, timolol maleate (Istalol) and brinzolamide be classified as non-formulary under the UF (see paragraphs 8A, 8B and 8C on pages 52-64 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for travoprost, timolol hemihydrate, timolol maleate (Istalol) and brinzolamide, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for travoprost, timolol hemihydrate, timolol maleate (Istalol) and brinzolamide (see paragraph 8D on pages 64-65 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 8E on page 65 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – The P&T Committee considered the BCF status of the ophthalmic glaucoma agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend that the BCF include latanoprost; brimonidine, excluding the 0.1% strength; timolol maleate (Timoptic, generics) 0.25% and 0.5%; timolol maleate gel-forming solution 0.25% and 0.5% (Timoptic XE, generics); and pilocarpine (see paragraph 8F on page 65 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

9. DRUG CLASS REVIEW – MAOI ANTIDEPRESSANTS

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the MAOI antidepressants marketed in the U.S. The drugs in the MAOI antidepressant class include three oral agents, isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate, generics); and one transdermal patch, selegiline (Emsam). Tranylcypromine is the only drug in the MAOI antidepressant class available in a generic formulation. All of the drugs are available in oral dosage forms; however, oral selegiline capsules are excluded from the review, since they are indicated for use in Parkinson's Disease and not depression. The three oral MAOI antidepressants were first introduced to the market in the early 1960s, while transdermal selegiline was launched in 2006. The MAOI antidepressants accounted for approximately $283,000 dollars in expenditures in FY 2006, which comprises less than 1% of total MHS expenditures for all antidepressant drug classes.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) The oral MAOI antidepressants isocarboxazid, phenelzine, and tranylcypromine have been marketed for several decades, but have been replaced by newer drug classes (e.g., SSRIs) with more favorable adverse event profiles.
2) Transdermal selegiline is the newest MAOI antidepressant marketed. The non-oral formulation was developed to reduce the risk of hypertensive crisis from dietary tyramine.
3) There do not appear to be major differences in clinical efficacy between the three oral MAOIs when used for depression, based on the results of one meta-analysis showing response rates ranging between 53% to 61%, and one inpatient clinical trial.
4) Response rates ranging from 27% to 30% were reported with transdermal selegiline in three placebo controlled trials. There are no clinical trials directly comparing the oral MAOI antidepressants with transdermal selegiline. However, there are no data to suggest that treatment with transdermal selegiline would result in improved response rates compared to the oral MAOI antidepressants.
5) The MAOI antidepressants have a safety profile that is well recognized in terms of drug-drug and drug-food interactions, and these adverse events also apply to transdermal selegiline. Local application site reactions are common with transdermal selegiline.
6) The purported benefits of transdermal selegiline in terms of loosened dietary tyramine restrictions have only been shown clinically with the lowest dose (6 mg/24 hour). Dietary precautions are required with oral MAOIs and with the 9 mg/24 hr and 12 mg/24 hr dosages of transdermal selegiline.

7) Off-label usage of transdermal selegiline is anticipated for treating patients with Parkinson's Disease.

8) The primary advantage of transdermal selegiline is for patients unable to swallow oral medications and require a once-daily dosage formulation.

9) There is insufficient evidence to determine whether transdermal selegiline represents a therapeutic advance over isocarboxazid, phenelzine and tranylcypromine.

10) Based on clinical issues alone, there are no reasons to designate any of the MAOI antidepressants (phenelzine, isocarboxazid, or tranylcypromine, and transdermal selegiline) as non-formulary on the UF.

Relative Cost Effectiveness Conclusion - The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) The oral MAOIs demonstrate similar relative cost effectiveness, with phenelzine as the most cost effective agent.

2) Transdermal selegiline is not cost effective relative to the other agents in the class in the treatment of depression and provides no clinically meaningful therapeutic advantage to justify the increased cost.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the MAOI antidepressants, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that isocarboxazid, phenelzine and tranylcypromine be maintained as formulary on the UF, and that transdermal selegiline be classified as non-formulary under the UF (see paragraphs 9A, 9B, and 9C on pages 66-71 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for MN criteria for transdermal selegiline, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for transdermal selegiline (see paragraph 9D on page 71 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation

period will begin immediately following approval by the Director, TMA (see paragraph 9E on pages 71-72 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: EXTENDED CORE FORMULARY (ECF) RECOMMENDATION – The P&T Committee had previously determined at the November 2006 meeting that one MAOI antidepressant should be added to the ECF based on the clinical and cost effectiveness review. The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that phenelzine be classified as the ECF agent (see paragraph 9F on pages 71-72 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

Appendix A – TABLE 1. Implementation Status of UF Recommendations/Decisions
Appendix B – TABLE 2. Newly Approved Drugs
Appendix C – TABLE 3. Abbreviations
Appendix D – FIGURE 1. PA Process for SED-1 Agents Other than Zolpidem IR

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____//signed//_____

MG Elder Granger, USA, MC
Deputy Director, TMA
Date: 02 May 2007

Department of Defense
Pharmacy and Therapeutics Committee Minutes
February 2007

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 13-14 February 2007 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
CAPT Mark Richerson, MSC, USN	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Lt Col Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Lt Col Charlene Reith *for* Lt Col Everett McAllister, BSC	Air Force, Pharmacy Officer
No representative *for* LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatric Physician
CDR David Tanen, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Ted Cieslak, MC	Army, Physician at Large
LTC Peter Bulatao, MSC for COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino, RPh.	Department of Veterans Affairs

B. Voting Members Absent

LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Maj Chang Chinran, NC, USAF	Health Plans Operations, TMA
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CPT Alvin Blackmon, MSC, USA	Defense Supply Center Philadelphia
Mr. Lynn T. Burleson	Assistant General Counsel, TMA
LT Thomas Jenkins, MSC, USN	TMOP/TRRx COR

D. Non-Voting Members Absent

None	

E. Others Present

Col Nancy Misel, BSC, USAF	IMA DoD Pharmacoeconomic Center
CAPT Don Nichols, MC, USN	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
LCDR Joe Lawrence, MSC, USN	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Shana Trice, Pharm.D.	DoD Pharmacoeconomic Center
David Bretzke, Pharm.D.	DoD Pharmacoeconomic Center
Angela Allerman, Pharm.D.	DoD Pharmacoeconomic Center
Eugene Moore, Pharm.D.	DoD Pharmacoeconomic Center
Julie Liss, Pharm.D.	DoD Pharmacoeconomic Center
Elizabeth Hearin, Pharm.D.	DoD Pharmacoeconomic Center
David Meade, Pharm.D.	DoD Pharmacoeconomic Center
Harsha Mistry, Pharm.D.	DoD Pharmacoeconomic Center
Mark Geraci, Pharm.D.	VAPBM
Capt Jeremy King, MC, USAF	WHMC

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – November 2006 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. Approval of November Minutes - Dr. William Winkenwerder, Jr., M.D., approved the minutes of the November 2006 DoD P&T Committee meeting on 17 January 2007.

4. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss and CAPT Richerson briefed the members of the P&T Committee regarding the December 2006 BAP meeting. The P&T Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions – The PEC briefed the members of the P&T Committee on the progress of implementation for drug classes reviewed for UF status since February 2005.

C. Status of Exenatide (Byetta) Prior Authorization (PA) – The PEC briefed the members of the P&T Committee on preliminary results of implementing the PA for exenatide, which went into effect 31 January 2007. The exenatide PA represents the first use of the new automated profile review capability in the Pharmacy Data Transaction Service (PDTS), which enables PA criteria to be automated based on a "look-back" at patient profiles during a given period. The percent of patients automatically approved through the automated process during the first few days the exenatide PA was in place was consistent with previous estimates; the process appears to be functioning as designed.

D. Administrative Action: PA Criteria for Exenatide – The PEC notified the P&T Committee of a December 2006 change in Food and Drug Administration (FDA)-approved labeling for exenatide. The new labeling states that exenatide is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, *a thiazolidinedione,* a combination of metformin and a sulfonylurea, *or a combination of metformin and a thiazolidine-dione*, but have not achieved adequate glycemic control. Italicized text indicates changes in labeling. The P&T Committee ratified the corresponding changes to exenatide PA criteria made under the auspices of the Executive Council, which were accomplished prior to implementation of the PA on 31 January 2007.

E. Status of Fentanyl Patch PA – The P&T Committee discussed implementation of the PA for fentanyl patch recommended at the November 2006 meeting and approved by the Director, TMA in January 2007. The Committee clarified the "look-back" period and definition of prior opioid use that will be used by the automated PA review process. The specific automated PA criteria that will be applied to all fentanyl prescriptions will be the following:

- Patient is likely to be opioid-tolerant based on receiving at least one prescription for one of the following strong opioids (fentanyl patch, morphine, oxycodone (not including combination products), hydromorphone, methadone, or oxymorphone) during the last 60 days.

The P&T Committee reached this conclusion after reviewing estimates of the number and percent of fentanyl patch patients that would be affected by the PA, including the number of patients who had received fentanyl patch prescriptions during the last 120 days, but not within the last 60 days. The P&T Committee agreed that the best trade-

off between ensuring safety and potentially interrupting therapy for established patients would be to allow pharmacists at retail network pharmacies the ability to override the system warning after determining that the patient could be presumed to be opioid tolerant based on information from the patient or the physician. The retail network pharmacist would also have the option of having Express Scripts, Inc. (ESI) handle the PA by advising patients to have their physicians contact ESI.

F. UF Request Process – The P&T Committee approved a request form to be used by military treatment facility (MTF) healthcare providers requesting consideration of potential changes to the Basic Core Formulary (BCF)**,** Extended Core Formulary (ECF), or UF, including changes to medical necessity (MN) criteria for non-formulary medications, prior authorization criteria, or quantity limits. The three general process points previously agreed upon by the P&T Committee will apply:

- Requests will require review and concurrence by the local MTF P&T Committee.
- Requests will be required to contain adequate supporting evidence, including a fair, balanced, and thorough discussion of the relevant clinical literature, and present a rational argument supporting suggested changes.
- Requestors will be required to explain potential conflicts of interest and certify that the request was not initiated or unduly influenced by pharmaceutical industry representatives.

G. Regulatory Status of Pseudoephedrine (PSE) Products – The PEC briefed the committee on the Methamphetamine Anti-Proliferation Act (MAPA), part of the Children's Health Act of 2000; the Combat Methamphetamine Epidemic Act (CMEA) of 2005; and Oregon House Bill 2485 (2005). These three pieces of legislation were enacted to address the diversion of drug products containing PSE, ephedrine and phenylpropanolamine (PPA) for the illicit production of methamphetamine. (PPA has been removed from the human drug market but remains available for veterinary use.)

The CMEA requires pharmacies and other sellers to place PSE products behind the counter; check the identity of purchasers; maintain a log of each sale that includes the purchaser's name and address, signature of the purchaser, product sold, quantity sold, date, and time; maintain the logbook for at least two years; train employees in the requirements of the law; and certify to the Drug Enforcement Agency (DEA) that the training has occurred. Most states have enacted similar legislation.

The State of Oregon passed Oregon House Bill 2485 (2005), which stipulated that the State Board of Pharmacy designate PSE as a Schedule C-III controlled substance. This designation imposed a limit of 90 days supply for a prescription in the State of Oregon. It also requires that refills be filled within 180 days of prescription origin. The bill does not prohibit over-the-counter (OTC) sales, which continue to be subject to requirements of the CMEA. This bill affected 74 individuals in the TRICARE mail order pharmacy and 800 users in the retail point of service. Oregon patients receiving PSE products by prescription are now required to obtain a new prescription every six months.

As part of the review for this presentation, the PEC contacted eight Army and Navy MTFs to determine the regulatory impact on DoD OTC programs. Air Force policy prohibits OTC programs. Directors of four programs previously removed PSE off the drug list for OTC dispensing. Of facilities supplying PSE, all have QLs, require photo identification, and most require a signature. Navy policy requires entry of any of the drugs obtained from an OTC program into the patient's CHCS profile. Army policy does not require CHCS entries. Entry into the patient's CHCS profile would exceed the CMEA logbook requirement. Neither service has a program in place to meet the training requirements specified in the CMEA.

The P&T Committee agreed that there is little chance that large amounts of PSE could be diverted from MTF pharmacies. Mandatory logbook and training requirements are best addressed by the Pharmacy Service consultants/specialty leaders.

5. REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on two new drugs, sitagliptin (Januvia) and paliperidone extended release [ER] tablets (Invega), which were approved by the FDA (see Appendix B). The P&T Committee determined that these two new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed.

B. Over-the-Counter Omeprazole Magnesium (Prilosec OTC)

Section 705 of the John Warner National Defense Authorization Act for Fiscal Year 2007 directs the Secretary of Defense to conduct a demonstration project under section 1092 of title 10, U.S. Code, to allow particular OTC drugs to be included on the UF under section 1074g of such title. For an OTC drug to be included as part of the OTC Demonstration Project, the P&T Committee must find that the OTC drug is cost effective and therapeutically equivalent to a prescription drug. Beneficiaries will be required to have a prescription for the OTC product.

OTC drugs provided under the demonstration project shall be made available through MTFs and the TRICARE mail order pharmacy. The demonstration will begin no later than 1 May 2007, and will last for a time period at least as long as the current contract, but no longer than five years.

Omeprazole magnesium is the first medication proposed for inclusion in the OTC Demonstration Project. Since this is the first opportunity for omeprazole magnesium to be considered for inclusion on the UF, it was reviewed as a new drug in a class already reviewed.

The P&T Committee previously reviewed the proton pump inhibitors (PPIs) in February 2005. These medications suppress secretion of gastric acid by irreversibly inhibiting H+, K+ ATPase (the proton pump) in gastric parietal cells. PPIs on the UF include prescription omeprazole (Prilosec, generics), rabeprazole (Aciphex), lansoprazole (Prevacid), and pantoprazole (Protonix). Esomeprazole (Nexium), the s-

isomer of omeprazole, is non-formulary under the UF. The BCF selections in this class are prescription omeprazole and rabeprazole.

1) *Relative Clinical Effectiveness* – Prescription omeprazole, first approved in 1987, is indicated for short-term treatment of active duodenal ulcer, benign gastric ulcer, and endoscopically-diagnosed erosive esophagitis; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease; maintenance of healing of erosive esophagitis; long-term treatment of pathological hypersecretory conditions such as Zollinger-Ellison Syndrome; and for eradication of *H. pylori* infection (in combination with clarithromycin). Recommended doses range from 20 mg to 60 mg per day. It is available in 10-, 20-, and 40-mg delayed release capsules.

   Omeprazole magnesium was approved as an OTC medication in June 2002 based on placebo-controlled trials that found it to be effective in the treatment of recurring heartburn. It is labeled as a 14-day once-daily course of treatment for frequent heartburn (occurring two or more times per week), which may be repeated every four months. Each 20.6 mg delayed release tablet of omeprazole magnesium is equivalent to 20 mg of omeprazole. There is no reason to believe that the pharmacology or pharmacokinetics of omeprazole magnesium differ from prescription omeprazole.

   Common adverse events reported with the use of omeprazole magnesium include headache, diarrhea, and elevations in liver enzymes. Rare but severe adverse events include liver injury, bone marrow suppression, Stevens-Johnson syndrome, and hypersensitivity. Omeprazole magnesium is Pregnancy Category C. It is not recommended for patients under 18 years of age.

   Conclusion: The P&T Committee concluded that omeprazole magnesium has similar relative clinical effectiveness compared to other PPIs included on the UF. The P&T Committee also concluded that, while Food and Drug Administration (FDA)-approved indications differ for the OTC and prescription versions of omeprazole, there is no reason to believe that the clinical effect of omeprazole magnesium, when given to the same patients in the same doses, would differ from the anticipated effects of prescription omeprazole.

2) *Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the PPI class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

   Based on the information reported from the relative clinical effectiveness evaluation, there was evidence to suggest that omeprazole magnesium has similar efficacy, safety, tolerability, and clinical outcomes compared to the existing drugs in the PPI class.

   The cost review for omeprazole magnesium compared the cost per unit across all three points of service to the other PPIs.

Conclusion: The results of the cost review showed that omeprazole magnesium is cost effective on a per unit basis when compared to generic prescription omeprazole in the mail order and MTF points of service. Omeprazole magnesium is more cost effective when compared to generic prescription omeprazole in the retail point of service. Omeprazole magnesium is more cost effective when compared to other products in the PPI class (i.e., esomeprazole, lansoprazole, pantoprazole, and rabeprazole) across all three points of service.

3) *Clinical and Cost effectiveness Conclusions* – The P&T Committee voted (13 for, 0 opposed, 2 abstained, 2 absent) to accept the clinical and cost effectiveness conclusions stated above.

   COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 2 abstained, 2 absent) to recommend that omeprazole magnesium be classified as formulary under the UF.

4) *MN Criteria* – Since omeprazole magnesium was not recommended for non-formulary status under the UF, establishment of MN criteria is not applicable.

5) *UF Implementation Period* – Since omeprazole magnesium was not recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

6. DRUG CLASS REVIEW – NEWER SEDATIVE HYPNOTICS (SED-1s)

The P&T Committee evaluated the relative clinical effectiveness of the newer sedative hypnotic agents (SED-1s). The SED-1 drug class includes the following agents: zolpidem immediate release [IR] (Ambien), eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), and zolpidem ER (Ambien CR).

All SED-1 agents except ramelteon are classified as benzodiazepine receptor agonists; they bind to benzodiazepine gamma-aminobutyric acid (GABA) receptors in the brain, but at a different site than the benzodiazepines. Ramelteon is mechanistically different; it acts as an agonist at melatonin receptors (MT_1 and MT_2) in the suprachiasmatic nucleus of the brain, which is responsible for regulation of the 24-hour sleep-wake cycle (circadian rhythm). All are FDA-indicated for the treatment of insomnia, although specific labeling differs.

The newer sedative hypnotics are preferred to benzodiazepines (the second most commonly used drug for insomnia) primarily due to a more favorable adverse effect profile and lower potential for abuse. They are widely used worldwide. Other medications for insomnia include sedating antidepressants such as trazodone, sedating antihistamines such as diphenhydramine, and other rarely used medications (e.g., chloral hydrate).

Utilization of the SED-1 agents is increasing rapidly in DoD. As of Dec 2006, about four million Military Health System (MHS) prescriptions for these agents are filled per month; the drug class was ranked #15 in terms of expenditures in FY 2006 ($111 million) – up from #18 in 2005 ($72 million), and #20 in 2004 ($54 million). Retail network

pharmacies dispense about three times more tablets than do MTFs and approximately five times more than mail order. Across the MHS, zolpidem IR is the most commonly prescribed SED-1, with about twice as many prescriptions compared to the next most commonly prescribed agent, zolpidem ER. Zolpidem ER is followed closely by eszopiclone. Usage of zaleplon is low and stable, while usage of the most recently introduced agent, ramelteon, is low but increasing. All of the SED-1 agents are brand-only; zolpidem IR is expected to become generically available in April 2007.

A. SED-1s – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the SED-1 agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

Insomnia is the most common sleep complaint across all stages of adulthood. Prevalence increases with age, from an estimated 10% of the younger adult population to up to 50% of elderly adults. Treatment includes both pharmacologic and non-pharmacologic approaches; however, non-pharmacologic treatments such as cognitive behavioral therapy are often not available to patients due to the need for extensive clinical contact. Patients should receive instruction on sleep hygiene measures (such as removing distractions from the sleeping area and avoiding stimulants at bedtime).

1) Efficacy

Many clinical trials compare the newer sedative hypnotic agents to placebo; some of these trials include an active comparator (most commonly zolpidem IR in addition to placebo. There are also many published trials comparing these agents to benzodiazepines. Two studies compare zolpidem IR to trazodone (Desyrel, generics), an antidepressant commonly used for insomnia.

In addition to measures of sleep onset and duration, the Committee also reviewed data assessing effect on quality of life, since the ultimate goal of treating insomnia is to improve overall health and well-being, not merely to increase the number of minutes spent asleep.

Based on this information, the P&T Committee came to the following conclusions:

- All SED-1 agents improve sleep latency (the amount of time it takes to fall asleep) compared to placebo, based on both polysomnographic measures (monitoring performed in a sleep lab) and subjective measures (as reported by patients). The amount of improvement compared to placebo appears similar among all of the agents. Data supporting the effect of ramelteon on sleep

latency appear to be the least robust, both in terms of the number of published studies and the amount of improvement demonstrated versus placebo. Published data with zolpidem ER are also limited, with a single published trial, but sleep latency data appear similar to the IR formulation and pharmacokinetic studies show little or no difference in initial drug concentrations.

- Zolpidem IR and eszopiclone appear to consistently improve total sleep time and awake time after sleep onset (or the amount of time spent awake after initially falling asleep) to a similar degree versus placebo. Zaleplon and ramelteon do not consistently demonstrate increases in measures of sleep duration.
- Zolpidem ER is a controlled release version of zolpidem consisting of a two-layer tablet providing an IR phase followed by a prolonged release phase. The formulation is intended to retain the onset and elimination characteristics of zolpidem IR while maintaining plasma concentrations three to six hours post-dose. Time versus concentration curves comparing zolpidem ER to zolpidem IR show comparable initial concentrations followed by higher concentrations of zolpidem ER during this time period. However, it is unclear whether this is associated with a clinically significant increase in sleep duration, as clinical trial data comparing zolpidem IR and ER are not available and reported effects on sleep duration with zolpidem ER do not appear markedly different from results from zolpidem IR trials.
- Trials including two or more SED-1 agents (usually compared to placebo) include three published trials comparing zaleplon and zolpidem IR to placebo and one unpublished trial obtained from the FDA statistical review of eszopiclone that included eszopiclone and zolpidem IR. Based on these trials, zaleplon decreased sleep latency to a greater degree than zolpidem IR (8-24 minutes for zaleplon versus 6-13 minutes for zolpidem IR, but zolpidem IR increased total sleep time more than zaleplon (28-42 minutes for zolpidem IR versus 7-27 minutes for zaleplon). More rebound insomnia was noted with zolpidem IR on the first night after discontinuation. The FDA statistical review for eszopiclone reported very similar results for eszopiclone versus zolpidem IR with respect to sleep latency, total sleep time, and awake time after sleep onset.
- Based on trials comparing zolpidem IR and zopiclone (eszopiclone's racemic parent drug) to benzodiazepines, the newer sedative hypnotics appear to be similar in efficacy to the benzodiazepines. Short-term adverse events appear similar based on published trials; however, there appears to be more rebound insomnia with benzodiazepines than with the newer sedative hypnotics.
- A single comparative trial of zolpidem IR versus trazodone in adult insomnia sufferers without co-morbid depression demonstrated similar efficacy during the two weeks of the study; although trazodone may result in greater daytime somnolence than zolpidem IR.

- In regard to improvement of sleep architecture, there are no consistent data to demonstrate that the newer sedative hypnotics increase the length of time spent in the stages of sleep associated with restorative sleep to a degree that is clinically significant, compared to placebo.
- The most extensive data supporting long-term efficacy and safety are for eszopiclone, which has data from a 6-month randomized controlled trial (RCT) and open label data out to one year. Zolpidem IR has data from RCTs indicating continued efficacy and safety over 35 nights of nightly use and 84 nights of non-nightly use, with open label data out to one year. No long-term data are available for zolpidem ER, which was only tested in short-term trials (three weeks), although it is probably reasonable to expect long-term results similar to zolpidem IR (Ambien). Zaleplon RCT data are limited to 4-week trials, although open label data supporting efficacy and safety for up to one year are available in elderly patients. Ramelteon has shown sustained efficacy and safety for up to five weeks in RCTs, with open label data out to one year.
- Improvement in overall quality of life as a function of improved sleep was not usually addressed in either short- or long-term clinical trials. However, a few trials employed quality of life assessment tools, with one of the most useful measures being the standardized short-form 36 (SF-36) questionnaire. Two non-nightly zolpidem IR studies demonstrated a minimal improvement on certain aspects of the SF-36 after treatment, but no difference from placebo on other aspects. Two eszopiclone studies that included pre and post-treatment questionnaires addressing improvement in overall sense of well-being showed no significant improvement versus placebo. The Committee concluded that there is insufficient evidence to conclude that SED-1 agents have a major beneficial effect on quality of life, although there limited are data showing improvement in certain aspects of quality of life. There are insufficient comparative data to draw conclusions about individual agents.

2) Safety / Tolerability

- The SED-1 agents, including both the benzodiazepine receptor agonists and ramelteon, appear to have similar adverse effect profiles, most commonly drowsiness, dizziness, and headache. Rates of discontinuation due to adverse events during clinical trials were similar among the SED-1 agents, ranging from about 2-6% in short-term trials. Adverse effects and discontinuation rates due to adverse events were similar in comparative trials (zolpidem IR versus zaleplon; eszopiclone versus zolpidem IR). An unpleasant taste was consistently reported with eszopiclone during clinical trials, occurring in about 26.1% of patients receiving eszopiclone versus 5.6% with placebo over the course of a 6-month trial.
- Daytime sleepiness, impairments in psychomotor function and cognitive function, adverse effects on driving safety, and increased risk for falls may occur with any of the benzodiazepine receptor agonists; there are little or no data for the melatonin receptor agonist ramelteon. Agents with longer elimination half-lives tend to pose a greater risk for these effects. Particularly

notable is the 6-hour half-life of eszopiclone, which may extend to nine hours in elderly patients, compared to half-lives of about one hour for zaleplon, 1-2.6 hours for ramelteon and 2.5-2.8 hours for zolpidem (Ambien, Ambien CR). Lower starting doses of all SED-1 agents except ramelteon are recommended in elderly patients.

- Driving safety studies report impaired performance and increased risk of accidents with eszopiclone's racemic parent drug zopiclone (widely used outside the U.S.) at a 7.5 mg daily dose. The applicability of these data to eszopiclone is unclear, since the usual younger and elderly adult dosing strengths of eszopiclone (3 and 2 mg, respectively) would be equivalent to zopiclone doses lower than 7.5 mg. Product labeling and marketing for eszopiclone advises against taking the product unless the patient is able to get eight or more hours of sleep; adherence to this warning is advisable. There was no reported difference between eszopiclone and zolpidem IR on subjective measures of next day effects (morning sleepiness, daytime alertness, daytime ability to function), based on results of one unpublished trial reported in the FDA statistical review of eszopiclone.
- Because of its very short half-life, a repeat dose of zaleplon may be taken after the patient has had difficulty falling asleep, as long as the patient is able to sleep for four or more hours. Driving studies with zaleplon 10 and 20 mg showed no significant effects on morning driving even after middle-of-the-night administration. Since the risk of falling and hip fracture tend overall to increase with increasing half-life, zaleplon may have an advantage in elderly patients. However, this is not a simple relationship and prescribers must take into account patient activity patterns; short half-life agents may be more likely to cause falls during the early part of the night.
- In other special patient populations, it is difficult to see major advantages or disadvantages for any one agent. All are hepatically metabolized and carry warnings about use and/or recommendations for dose adjustment in patients with hepatic dysfunction; pharmacokinetic parameters do not appear to be substantially affected by renal dysfunction. All are Pregnancy Category C. Little data is available concerning use in pediatric patients; there is some concern about chronic or chronic intermittent use of ramelteon in pediatric patients due to effects on prolactin and testosterone levels that are not felt to be clinically significant in adults.
- The most prominent withdrawal symptom upon discontinuation of the SED-1 agents is probably rebound insomnia, or worsening of insomnia compared to the patient's pre-treatment baseline; other withdrawal symptoms may also occur. Rebound insomnia typically occurs only in the first night after discontinuation. Occurrence of rebound insomnia has been reported in clinical trials with all of the SED-1 agents except ramelteon. Based on three trials, more rebound insomnia on the first night after discontinuation was noted with zolpidem IR versus zaleplon.

- All of the newer sedative hypnotics, with the exception of ramelteon, probably have a small, but significant potential for abuse, although this is likely to be rare in patients without psychiatric disorders or previous history of substance abuse. Ramelteon appears to lack significant abuse potential and may be preferable in patients with a high risk of substance abuse. Ramelteon is the only agent in this class that is not a DEA scheduled substance.
- No major comparative disadvantages were noted among the agents based on potential for drug-drug interactions. All are affected by potent CYP 3A4 inducers or inhibitors and have predictable additive effects if given with alcohol or other medications that can impair psychomotor performance. Cimetidine (Tagamet, generics) markedly increases levels of zaleplon due to inhibition of two metabolic pathways (CYP 3A4 and aldehyde oxidase); the initial dose of zaleplon should be decreased. The major metabolic route for ramelteon is CYP 1A2; ramelteon is contraindicated with the potent 1A2 inhibitor fluvoxamine (Luvox, generics) and may be less effective in smokers, since smoking is a 1A2 inducer.

3) Other Uses

Based on its effects on the sleep-wake cycle, ramelteon may have a niche in therapy for time zone shifting in travelers, or for phase shifting in shift workers, but data at this point are limited.

4) Provider Opinion

A total of 173 DoD healthcare providers responded to a survey regarding the SED-1 agents; 72% of responders were physicians, 22% pharmacists, 5% physician assistants or advanced practice nurses, and 1% other. The most common specialties were psychiatry (25%), pharmacists (22%), and family practice, internal medicine, or general practice (21%). The vast majority of responders (97%) indicated that they had zolpidem IR on their local formulary, but relatively few indicated that other SED-1 agents were on formulary (zolpidem ER 18%, ramelteon 3%, eszopiclone and zaleplon 0%).

The majority of responders estimated that between 40 and 79% of patients could be successfully treated with their first choice of agents. Most (71%) would treat patients failing the first agent with another SED-1 agent; the majority estimated that between 20 and 59% of patients could be successfully treated with the second agent. The majority of responders estimated that fewer than 20% of patients discontinue therapy due to adverse events.

5) Clinical Effectiveness Conclusion

The P&T Committee concluded that:

a) Based on placebo-controlled trials, all SED-1 agents decrease sleep latency to a similar degree. Data supporting the effect of ramelteon on sleep latency appear to be the least robust, both in terms of the number of published studies and the amount of improvement demonstrated versus placebo. Zolpidem IR and eszopiclone have evidence indicating consistent and similar increases in

sleep duration. Zaleplon and ramelteon do not appear to consistently increase sleep duration.

b) Based on three comparative trials, zaleplon appears to decrease sleep latency more than zolpidem IR, but zolpidem IR appears to increase total sleep time more than zaleplon. In one comparative trial, very similar results were reported for eszopiclone versus zolpidem IR with respect to measures of sleep latency and sleep duration.

c) Based on comparative trials, SED-1 agents appear to be similar in efficacy and short-term adverse events, compared to benzodiazepines; benzodiazepines may cause more rebound insomnia. Zolpidem IR appears to be similar in efficacy to the sedating antidepressant trazodone, based on one comparative trial in non-depressed patients; trazodone may result in greater daytime somnolence.

d) There are no consistent data to demonstrate that SED-1 agents have beneficial effects on sleep architecture, compared to placebo.

e) There is insufficient evidence to conclude that SED-1 agents have a major beneficial effect on quality of life, although limited data show improvement in certain domains of the SF-36. There are insufficient comparative data to draw conclusions about individual agents.

f) The SED-1 agents appear to have similar adverse effect profiles and to result in similar rates of discontinuation due to adverse events in clinical trials. Eszopiclone is associated with an unpleasant taste. There do not appear to be any major disadvantages for any one agent with respect to drug-drug interactions. Ramelteon may be less effective in smokers.

g) Daytime sleepiness, impairments in psychomotor function and cognitive function, adverse effects on driving safety, and increased risk for falls may occur with any of the benzodiazepine receptor agonists; there are little or no data for the melatonin receptor agonist ramelteon. Agents with longer half-lives tend to pose a greater risk for these effects. The SED-1 agent with the longest half-life is eszopiclone, six hours (up to nine hours in elderly patients); followed by zolpidem (Ambien, Ambien CR), 2.5-2.8 hours; ramelteon, 1-2.6 hours; and zaleplon, one hour. Lower starting doses of all SED-1 agents except ramelteon are recommended in elderly patients.

h) The applicability of driving safety studies reporting impaired performance and increased risk of accidents with a 7.5 mg dose of zopiclone (eszopiclone's racemic parent drug) is unclear, since recommended doses of eszopiclone would be equivalent to zopiclone doses lower than 7.5 mg. There was no reported difference between eszopiclone and zolpidem IR on subjective measures of next day effects based on results of an unpublished trial reported in the FDA statistical review of eszopiclone.

i) Because of its very short half-life, zaleplon may be taken in the middle of the night after a patient has had difficulty falling asleep without demonstrating adverse effects on driving performance the next morning. It may have an

advantage in elderly patients, since risk of falls and hip fracture tends overall to increase with increasing half-life (although the relationship between falls and half-life is not straightforward and prescribers must take into account patient activity patterns).

j) No SED-1 agent appears preferable in other special patient populations (hepatic or renal dysfunction, pregnancy, pediatrics); there is some concern about use of ramelteon in pediatric patients due to possible endocrine effects.

k) Rebound insomnia has been reported in clinical trials with all SED-1 agents except ramelteon; more rebound insomnia was noted with zolpidem IR than with zaleplon during comparative trials.

l) All SED-1 agents, with the exception of ramelteon, probably have a small but significant potential for abuse. Ramelteon appears to lack significant abuse potential and may be preferable in patients at high risk for substance abuse. Ramelteon is the only SED-1 agent that is not a DEA scheduled substance.

m) It is likely that at least two SED-1 agents are needed for adequate clinical coverage, based on provider responses regarding prescribing practices and likely patient response.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

B. SED-1s – Relative Cost Effectiveness

In considering the relative cost effectiveness of agents within this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2). Given the overall clinical conclusion that the agents within the SED-1 class have similar relative clinical effectiveness, a cost-minimization analysis (CMA) was employed to assess the relative cost effectiveness of the agents within this therapeutic class. The agents were evaluated on their weighted average cost per day of therapy across all three points of service.

The CMA for the SED-1 class revealed the following cost effectiveness rank-order (from most to least cost effective): 1) eszopiclone; 2) ramelteon; 3) zaleplon; 4) zolpidem IR; and 5) zolpidem ER. Although zolpidem IR was not as cost effective as eszopiclone in this CMA, the P&T Committee noted that zolpidem IR is scheduled to become generically available on 21 April 2007 and will likely become the most cost effective agent within the class shortly thereafter.

A budget impact analysis (BIA) of various UF formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, and non-formulary cost-shares). The goal of the BIA was to aid the P&T Committee in determining which group of SED-1 agents best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS.

The BIA also considered the cost effectiveness of implementing a prior authorization (PA) that requires a trial of zolpidem IR for patients starting treatment with a SED-1 agent. This PA would incorporate the automated PA capability in PDTS in order to "look-back" at the patient's profile during the last 180 days. Based on this automated review, TRICARE would cover prescriptions for a SED-1 agent other than zolpidem IR if the patient had received a prescription for any SED-1 agent (including zolpidem IR) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during this previous 180 days. Patients who had not received a SED-1 agent prescription during the last 180 days would be required to meet PA criteria for any SED-1 agent other than zolpidem IR (Ambien). (See Appendix D.)

Cost Effectiveness Conclusion

The P&T Committee concluded that:

1) Eszopiclone was the most cost effective agent until zolpidem IR becomes generically available with competitive pricing.
2) Ramelteon, zaleplon, and zolpidem ER were more costly than eszopiclone and provided no meaningful clinical therapeutic advantage compared to eszopiclone or zolpidem IR.
3) The UF scenario utilizing a prior authorization requiring a trial of zolpidem IR by new SED-1 patients was more cost effective relative to UF scenarios not requiring a trial of zolpidem IR by new SED-1 patients.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to accept the cost effectiveness conclusion stated above.

C. SED-1s – UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the SED-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 2 abstained, 1 absent) to recommend that: 1) zolpidem IR and eszopiclone be maintained as formulary on the UF with a prior authorization requiring a trial of zolpidem IR for new patients and 2) that ramelteon, zaleplon, and zolpidem ER be classified as non-formulary under the UF with a PA requiring a trial of zolpidem IR for new patients.

The P&T Committee agreed that the following PA criteria should apply to SED-1 agents other than zolpidem IR. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:

   The patient has received a prescription for any SED-1 agent (including zolpidem IR) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2) PA criteria if automated criteria are not met:

   The patient has tried zolpidem IR and had an inadequate response or was unable to tolerate it due to adverse effects.

Treatment with zolpidem IR is contraindicated.

The P&T Committee noted that in order for a patient to receive a non formulary SED-1 agent at the formulary cost-share, both the PA and MN criteria must be met. If the PA criteria are met without an approved MN determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved PA for ramelteon, zaleplon, or zolpidem ER would NOT automatically receive it at the formulary cost-share.

The P&T Committee also noted that the PA is not intended to apply where there are existing policies and protocols in place for operational/readiness situations and that MTFs should make necessary allowances for such use.

D. SED-1s – MN Criteria

Based on the clinical evaluation for ramelteon, zaleplon, and zolpidem ER, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for ramelteon, zaleplon, and zolpidem ER:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Use of formulary alternatives has resulted in therapeutic failure.

The P&T Committee noted that while zolpidem IR and eszopiclone would both be considered formulary alternatives, a trial of zolpidem IR would be required for patients who had not received a SED-1 prescription in the last 180 days at an MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order).

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to approve the MN criteria outlined above.

E. SED-1s – UF Implementation Period

Approximately 40,447 patients (21% of all SED-1 patients) would be affected by the recommended non-formulary selections in this drug class. This figure includes both patients who have previously received SED-1 agents, as well as new users starting on SED-1 agents. Based on the number of new users and the current percentage of new users receiving SED-1 agents other than zolpidem IR in retail (50%) and mail (40%), the prior authorization for SED-1 agents other than zolpidem IR would affect approximately 12,500 users per quarter, or 50,000 annually.

The P&T Committee noted that this would be the first time a PA including the newly available automated review process had been established in a class also including non-formulary agents and that many operational details of the process had yet to be worked out. Accordingly, the P&T Committee voted to recommend an implementation period of the greater of 1) the first Wednesday following a 90-day implementation period or 2) the time necessary to complete logistical arrangements to implement the automated PA.

MTFs will not be allowed to have ramelteon, zaleplon, or zolpidem ER on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary SED-1 agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 2 abstained, 1 absent) to recommend an implementation period of the greater of 1) the first Wednesday following 90 day implementation period or 2) the time necessary to complete logistical arrangements to implement the automated PA.

F. SED-1s – BCF Review and Recommendations

The P&T Committee considered the BCF status of the SED-1 Agents. Currently there are no SED-1 agents on the BCF; the P&T Committee had previously determined at the August 2006 meeting that at least one SED-1 agent would be placed on the BCF. Zolpidem IR is widely used at MTFs, has clinical data supporting efficacy both for decreasing sleep latency and increasing sleep duration, is clinically similar to other SED-1 agents with respect to safety and tolerability, and is expected to become the most cost effective SED-1 agent after it becomes generically available (anticipated date: 21 April 2007). The P&T Committee agreed that zolpidem IR should be placed on the BCF.

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 3 abstained, 1 absent) to recommend adding zolpidem IR as the BCF selection in this class.

7. DRUG CLASS REVIEW – NARCOTIC ANALGESICS

The drugs in this class comprise all narcotic analgesics (also referred to as opioids or opiate agonists) used for the treatment of pain on an outpatient basis, including combinations with acetaminophen (APAP), aspirin (ASA), and other non-opioids. Not included in this drug class review are narcotic analgesics given primarily by intravenous injection or infusion, over-the-counter products, products requiring administration by a medical professional, products in which the narcotic component is primarily used as an antitussive, and products indicated solely for the treatment of opioid dependence.

For review purposes, the narcotic analgesics were divided into the following categories, based on their potency (as reflected by their DEA status) and whether or not they are combined with a non-opioid analgesic, as outlined in Table 1. These categories do not take into account all differences among agents, but serve to reduce the large number of available agents into manageable categories. Most of these agents are now generically available.

The narcotic analgesics accounted for approximately $153 million dollars in MHS expenditures in FY 2006 and are ranked #8 in terms of total expenditures during that time period. Approximately 437,000 DoD beneficiaries received one or more prescriptions for a narcotic analgesic during FY 2006.

By category, the majority of MHS narcotic analgesic prescriptions during FY 2006 (59%) were for the lower potency opioid combinations, which are widely prescribed following

Table 1: Narcotic Analgesic Categories & BCF Listings as of Feb 2007

Category	Medications	BCF Agents (Feb 07)
High potency Opioids (Schedule II Agents) – Single Analgesic Ingredient	▪ Codeine* - tablets, solution, injection ▪ **Fentanyl** – transdermal (Duragesic), transmucosal lozenges (Actiq), buccal tablets (Fentora) ▪ Hydromorphone – injection, tablets, liquid ▪ Levorphanol – tablets, injection ▪ Meperidine – tablets, solution, injection ▪ Meperidine / promethazine – capsules ▪ Methadone – oral concentrate, solution, tablet, injection ▪ **Morphine –** IR tablets, 12-hr ER tablets (MS Contin, generics; Oramorph SR), 24-hr ER capsules (Avinza, Kadian), solution, suppositories, injection ▪ Opium - tincture; opium / belladonna alkaloids – suppositories ▪ **Oxycodone –** IR capsules, oral concentrate, solution, 12-hr ER tablets (Oxycontin), IR tablets ▪ Oxymorphone – IR tablets (Opana); 12-hr ER tablets (Opana ER)	Morphine sulfate 15 mg, 30 mg and 60 mg 12-hour extended release tablets (MS Contin, generics; excludes 100 and 200 mg strengths)
High potency (Strong) Opioids (Schedule II Agents) – Analgesic Combos	▪ **Oxycodone/** APAP – tablets, capsules, solution ▪ Oxycodone / ASA – tablets	Oxycodone 5 mg/APAP 325 mg and/or 500 mg oral
Lower-Potency (Mild) Opioids (Schedule III, IV, V & Non-Controlled Agents) – Single Analgesic Ingredient Agents	▪ Buprenorphine – injection (sublingual tablets not included in class) ▪ Butorphanol – nasal spray, injection ▪ Pentazocine / naloxone – tablets ▪ Propoxyphene – capsules, tablets ▪ Nalbuphine (not controlled) – injection ▪ **Tramadol** (not controlled) **–** IR tablet, 24-hr ER tablets (Ultram ER)	None
Lower-Potency (Mild) Opioids (Schedule III, IV, V & Non-Controlled Agents) – Analgesic Combos	▪ **Codeine / APAP –** tablets, elixir, oral suspension ▪ Codeine / ASA – tablets ▪ Codeine / ASA / carisoprodol - tablets ▪ Codeine / caffeine / butalbital / APAP – capsules ▪ Codeine / caffeine / butalbital / ASA – capsules ▪ Dihydrocodeine / caffeine / APAP – capsules, tablets ▪ Dihydrocodeine / caffeine / ASA – capsules ▪ **Hydrocodone / APAP** – capsules, solution, tablets ▪ Pentazocine / APAP – tablets ▪ **Propoxyphene / APAP** – tablets ▪ Propoxyphene / ASA / caffeine – capsule ▪ **Tramadol / APAP** (not controlled) – tablets	Codeine/APAP oral

* Pharmacologically and therapeutically, codeine is usually referred to as a weak opioid; however, single ingredient codeine formulations are classified by the DEA as Schedule II medications (C-IIs) and are so classified in this table. The most commonly used medications are bolded.
APAP = acetaminophen; ASA = aspirin; ER = extended release; IR = immediate release

injuries or medical / dental procedures; followed by high potency opioid combos (19%); high potency single analgesic products (13%); and lower potency opioid single analgesic products (9%). The majority of expenditures during this time period, however, were for the high potency single analgesic products (67%), followed by the lower-potency opioid combinations (20%), the high potency opioid combinations (8%), and the lower-potency single analgesic products (5%). This reflects the relatively higher cost and more intensive treatment regimens associated with the high potency single analgesic products used for chronic treatment of pain, some of which are still brand-only medications.

Pharmacologically, the narcotic analgesics act at opioid receptors (mu, kappa, and delta), inhibiting excitatory neurotransmission of substance P, acetylcholine, norepinephrine, dopamine, and GABA by blocking voltage-dependent calcium channels. Analgesia is mediated through changes in the perception of pain at the spinal cord (mu_2, delta, kappa receptors) and higher levels in the central nervous system (CNS) (mu_1 and kappa

receptors). Narcotic analgesics also have effects on the endocrine and immune systems. Stimulation at the mu receptor produces euphoria, respiratory depression, and physical dependence. In addition to acting at mu receptors, tramadol is also a weak inhibitor of norepinephrine and serotonin reuptake, resulting in inhibition of pain transmission in the spinal cord (similar to monoamine oxidase inhibitors [MAOIs] or tricyclic antidepressants [TCAs]).

Narcotic analgesics are primarily indicated for the treatment of mild, moderate and severe pain. Use correlates with potency, with the higher potency agents (e.g., morphine, oxycodone, fentanyl) used in more severe pain and lower potency agents and combinations with non-opioids used for less severe pain. Some narcotic analgesics have specific clinical niches:

- Opium is used in combination with the anticholinergic belladonna for the treatment of pain caused by ureteral spasm; more effective and/or safer agents have largely replaced the use of opium tincture for diarrhea.
- Use of meperidine, a short-acting narcotic analgesic primarily given parenterally due to poor oral absorption, is limited to acute pain situations due to a neurotoxic metabolite that can cause anxiety, tremors, myoclonus, and generalized seizures with repetitive dosing.
- Methadone is used for detoxification and maintenance treatment of narcotic addiction, but also for chronic pain.
- The nasal formulation of butorphanol is used primarily for migraine headache; this product was initially released as a non-scheduled product, but was subsequently scheduled as a C-IV controlled substance following multiple reports of abuse.
- Tramadol has a lower potential for abuse or respiratory depression than other narcotic analgesics, lacks significant cardiac effects, and is not associated with peptic ulcer disease, making it an alternative in patients who cannot tolerate non-steroidal anti-inflammatory drugs (NSAIDs). Due to its dual mechanism of action, tramadol may have a more prominent place in the treatment of neuropathic pain than other narcotic analgesics.

The majority of the narcotic analgesics are IR and/or short-acting medications most commonly used on an every four to six hour basis. Longer duration products include fentanyl transdermal patches (Duragesic, generics), which are applied every 72 hours; morphine, which is available in 12-hour (MS Contin, generics; Oramorph SR) and 24-hour ER formulations (Avinza, Kadian); oxycodone, which is available in a 12-hour ER formulation (Oxycontin); oxymorphone, which was recently approved as a 12-hour ER formulation (Opana ER), tramadol, which is available in a once daily ER formulation (Ultram ER), and methadone, which may be dosed less frequently when given chronically, due to a depot effect. Levorphanol has a long half-life and an extended duration of action (four to eight hours), but its use is limited by sedation and concerns about drug accumulation.

Pure opiate agonists may be categorized by their chemical structure as phenanthrenes (codeine, hydromorphone, morphine, and oxycodone; phenylpiperidines (fentanyl, meperidine); or diphenylheptanes (methadone, propoxyphene). They are therapeutically

classified as either strong opiates (hydromorphone, morphine, methadone, and oxycodone) or weak opiates (codeine, hydrocodone, and propoxyphene). Use of mixed agonist antagonists (e.g., buprenorphine, nalbuphine, butorphanol, and pentazocine) is limited by ceiling analgesia effects and the risk of inducing withdrawal symptoms and recurrence of pain in patients taking chronic opioids.

Tolerance to the adverse effects of narcotic analgesics, including respiratory depression, occurs with chronic use. Tolerance to therapeutic effects requiring dose escalation also occurs; some patients may require very large doses of narcotic analgesics to control their pain. Patients often require changes in chronic opioid therapy to address adverse effects or lack of efficacy; switching or rotating different opioids (opioid rotation) has been proposed as a strategy to obtain optimal pain control with minimum adverse effects.

Combination products including both a narcotic analgesic and non-opioid analgesic (most commonly acetaminophen) provide additive analgesic effects, but also limit the possible dose of the narcotic analgesic due to potential toxicity and dosing limits associated with the non-opioid component (e.g., no more than 4 grams of acetaminophen daily). They are not well suited for the treatment of chronic pain.

Standard tables of equianalgesic doses are available to assist clinicians in safely switching between long-acting opioids, typically by converting the total 24-hour dose to an equivalent amount of morphine and from there to the appropriate 24-hour dose of the new opioid. This process is complicated by wide intra-patient variability in response and incomplete cross-tolerance among opioids; for this reason, recommended conversions are usually conservative and titration of the new opioid is likely to be required. Disparate methodologies in calculating equianalgesic doses for transdermal fentanyl, levorphanol and methadone exist; these agents may be more difficult to titrate than other narcotic analgesics.

A. Narcotic Analgesics – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the narcotic analgesics class. Narcotic analgesics were divided into the categories outlined in Table 1, based on DEA schedule, potency, and whether or not the analgesic is a combination agent. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

The clinical efficacy review was divided into two major areas: chronic pain (cancer, non-cancer, or neuropathic) and acute pain (post-operative or non-specific). Because ample information is available for most of these agents, the review focused primarily on published meta-analyses, systematic reviews, and well-accepted tertiary literature sources, including clinical practice guidelines. A more detailed review of the literature was performed for specific issues affecting potential formulary decisions.

No single systematic review, meta-analysis, or clinical practice guideline addresses the use of narcotic analgesics to treat all types of chronic and acute pain. Sources included:

- *Chronic cancer pain* – Available cancer pain studies are in general too heterogeneous to conduct systematic reviews. The review included applicable conclusions from a 2001 Agency for Healthcare Research and Quality (AHRQ) technical report, a meta-analysis of four evaluable trials comparing long-acting oxycodone to morphine and hydromorphone [Reid *et al.*, 2006], and head-to-head trials and data analyses comparing two or more narcotic analgesics published since the AHRQ report. Sources of clinical practice guidelines for the treatment of cancer pain include the World Health Organization, the American Pain Society, and the University of Texas MD Anderson Cancer Center.
- *Chronic non-cancer pain* – The most useful reference for the treatment of chronic non-cancer pain was the Drug Effectiveness Review Project (DERP) review of long-acting opioid analgesics for non-cancer pain, last updated July 2006 [Chou *et al.*, 2006]. This review included all drugs reviewed here except for hydrocodone, levorphanol, and the agonist-antagonist agents. In addition, the review included a meta-analysis [Furlan *et al.*, 2006] comparing "weak" opioids (tramadol, propoxyphene, codeine) and "strong" opioids (morphine, oxycodone) to other agents in chronic pain patients primarily suffering from chronic non-cancer pain (osteoarthritis, rheumatoid arthritis, or low back pain), as well as clinical trials assessing the efficacy of the two available fentanyl formulations for breakthrough pain (buccal tablets and transmucosal lozenges). Sources of clinical practice guidelines for the treatment of chronic non-cancer pain included the American Society of Interventional Pain and VA/DoD.
- *Chronic neuropathic pain* – Clinical evidence specifically addressing the use of narcotic analgesics in chronic neuropathic pain is limited; the most useful review was considered to be the one conducted by Finnerup *et al.* (2005) in an attempt to construct an evidence-based algorithm for the treatment of neuropathic pain. The review also included a meta-analysis of trials assessing the efficacy of morphine, methadone, and oxycodone for neuropathic pain and published treatment recommendations from an expert panel group.
- *Acute pain* – There is little literature addressing the use of narcotic analgesics for non-specific acute pain. Consensus statements from the American Pain Society and the American Society for Pain Management Nursing support the appropriate use of "as needed" dosage range orders for narcotic analgesics in the treatment of acute pain. With respect to postoperative pain, the review relied heavily on the Bandolier Oxford League Table of Analgesic Efficacy, which is based on data compiled from single-dose studies in patients with moderate to severe pain. The review also provided clinical trial data or the results of Cochrane reviews for agents not included in the League table and recommendations from the VA/DoD Clinical Practice Guideline for the Management of Postoperative Pain.

1) Efficacy

a) Chronic pain

The clinical review divided chronic pain into three types, based on etiology: cancer pain, non-cancer pain, and neuropathic pain (considered separately from other causes of non-cancer chronic pain).

Treatment algorithms for chronic cancer pain typically start with non-opioids (e.g., NSAIDs, acetaminophen); progress to weak opioids such as codeine or hydrocodone, normally in combination with the non-opioid (some algorithms skip this step depending on pain severity); and then progress to around-the-clock treatment with long-acting high potency single analgesic agents plus IR opioids for breakthrough pain.

There is less consensus about the use of chronic opioids in patients with non-cancer pain (e.g., low back pain, rheumatoid arthritis, osteoarthritis), although various professional organizations have endorsed judicious use of opioids in patients with refractory chronic non-cancer pain. Recommended treatment algorithms are similar to chronic cancer pain.

The categories of drugs most pertinent to treatment of chronic pain are likely the high potency long-acting agents used on an around-the-clock basis for the treatment of constant pain, and the high potency IR agents, which are used for the treatment of breakthrough pain occurring despite treatment with long-acting agents. The most commonly used medications are long-acting and IR formulations of morphine, oxycodone, and fentanyl.

The placement of narcotic analgesics in treatment guidelines for neuropathic pain appears controversial; discussion of the topic is complicated by the fact that some authors consider tramadol to be an opioid and some do not. In general, narcotic analgesics are regarded as third-line agents after TCAs and gabapentin/pregabalin, although at least one set of treatment recommendations lists them among other agents as potential first-line choices.

iii) Clinical evidence in constant cancer pain

Available cancer pain studies are in general too heterogeneous to conduct systematic reviews and many are small and of poor quality. The 2001 AHRQ technical report provided an extensive review of cancer pain literature that served to highlight the limited data available. Out of nine trials, one reported oxycodone to be less effective than morphine, but equally or more often preferred by patients; one reported tramadol to be similar to morphine in efficacy and patient preference (nurses thought pain control was better with morphine but tramadol more tolerable); two reported methadone to be as effective as morphine; one reported buprenorphine as effective as morphine; and one reported propoxyphene to be more effective than low-dose morphine. Eight studies comparing sustained (12-hour formulations) and IR morphine found no difference in efficacy.

Head-to-head comparative trials, one meta-analysis, and a pooled analysis of transdermal fentanyl data published since the AHRQ report add little additional information. A meta-analysis of four randomized double-blind controlled trials found no differences in mean pain scores between oxycodone and either morphine or hydromorphone. An open-label trial comparing transdermal fentanyl to sustained release (every 12-hour) morphine found no differences in efficacy; the percentage of patients reporting constipation and withdrawals due to adverse effects favored transdermal fentanyl. A pooled analysis of transdermal fentanyl data reported similar results, with withdrawals due to adverse effects of 16% with transdermal fentanyl versus 23% with morphine ($p<0.001$). A 4-week trial comparing methadone and morphine reported similar efficacy, but a higher withdrawal rate with methadone (22% versus 6%, $p=0.019$). Two open-label crossover trials involving oxymorphone (Opana ER) versus morphine or oxycodone sustained release reported similar efficacy and concluded that patients could safely be switched from these medications to ER oxymorphone.

The 24-hour ER morphine products (Avinza and Kadian) are purported to have distinct advantages compared to 12-hour ER morphine products, including continuous pain relief, reduced sleep disturbance, ease of use, and fewer reported side effects. These benefits have not been shown to be statistically or clinically significant based on head-to-head trials with 12-hour ER morphine. Trials comparing Kadian or Avinza to 12-hour ER morphine have demonstrated bioequivalence (i.e., 12-hour ER morphine given as 45 mg every 12 hours = 90 mg of Avinza every 24 hours). There are no published trials directly comparing the two 24-hour ER products.

The two products do have some differences. Avinza is a capsule containing both IR and ER beads of morphine sulfate. Therapeutic serum levels are achieved rapidly (~0.5 hour) and then maintained for 24 hours. At steady state, plasma concentrations remain constant (no peak-trough phenomenon). Avinza is restricted to a maximum dose of 1600 mg daily, since it contains fumarate and can cause renal toxicity. Alcohol, including alcohol-containing medications, cannot be taken with Avinza, since this can lead to a rapid dissolution of the ER granules and premature release of morphine.

Kadian capsules contain polymer-coated ER pellets of morphine sulfate, which release morphine slowly within the gastrointestinal tract. The time to achieve maximum serum levels (~9.5 hours) is much longer than with 12-hour ER morphine (2-3 hours) or Avinza (~0.5 hours).

Both products can be opened and sprinkled onto applesauce for patients who have trouble swallowing pills. Kadian granules can also be suspended in water and administered down a large bore (≥16 French) gastrostomy tube, which is not possible with 12-hour ER morphine or oxycodone products.

iv) Clinical evidence in constant non-cancer pain

The DERP report on long-acting narcotic analgesics for non-cancer pain included products requiring dosing three or fewer times per day, including transdermal fentanyl and oral oxycodone, morphine, methadone, levorphanol, codeine, dihydrocodeine, and oxymorphone.

- Based on direct evidence from head-to-head studies, the report found no differences between agents overall. Evidence included three RCTs comparing transdermal fentanyl and long-acting morphine (two fair-quality trials showed similar efficacy, one poor quality trial showed greater efficacy for transdermal fentanyl); one RCT showing similar efficacy for long-acting morphine once-daily versus twice daily; and one RCT showing equal efficacy between long-acting oxymorphone and long-acting oxycodone.
- Reviewers found no useful indirect evidence concerning comparative efficacy based on 20 clinical trials comparing narcotic analgesics to other agents or placebo; withdrawal rates did not suggest tolerability advantages for any one product.
- Reviewers further found no evidence to suggest greater efficacy for long-acting versus short-acting opioids, based on seven fair-quality trials. Based on three of these trials, they concluded that there was fair evidence that long- and short-acting oxycodone were equally effective for pain control.

A 2006 systematic review [Furlan *et al.*, 2006] included data from 41 trials of opioids (codeine, morphine, oxycodone, tramadol, or propoxyphene) for the treatment of chronic non-cancer pain. Results from a meta-analysis of 28 placebo-controlled trials favored opioids. A meta-analysis of eight trials comparing opioids to other agents (NSAIDs, TCAs) found no significant difference overall, although strong opioids (oxycodone, morphine) were significantly more effective than other agents. The review outlined adverse effect rates with opioids but did not provide useful detail regarding comparison of different agents.

A systematic review of eight trials [Devulder *et al.*, 2005] assessing functional and quality of life outcomes in patients with chronic non-cancer pain in general reported favorable results with opioids, but studies were too heterogeneous to allow comparison of agents.

v) Clinical evidence in breakthrough pain

Historically, the standard practice has been to use the same opioid for treatment of baseline and breakthrough pain (e.g., sustained release and IR morphine), although fentanyl patches are commonly used along with morphine IR for breakthrough pain. Narcotic analgesics offering both a long-acting formulation and a short-acting formulation include morphine, oxycodone, fentanyl, and oxymorphone.

Recent trials primarily focus on the newer fentanyl products: oral transmucosal lozenges (Actiq, generic) and buccal tablets (Fentora). There is insufficient comparative evidence to directly compare the two formulations. Buccal fentanyl is more bioavailable and may therefore offer more consistent dosing; it is also sugar-free, unlike the transmucosal lozenges. The two products cannot be switched at a 1:1 conversion due to the difference in bioavailability (for example, patients receiving 200 to 400 mcg of Actiq should start on 100 mcg of Fentora). A specific regimen is provided in Fentora labeling for converting from Actiq to Fentora (but not vice versa). From a safety standpoint, there is probably a significant potential for medication errors related to this conversion.

vi) Clinical evidence in neuropathic pain

Authors of a systematic review of double-blinded, placebo-controlled trials in neuropathic pain conditions [Finnerup *et al.*, 2005] attempted to use numbers-needed-to-treat (NNTs) to achieve one patient with 50% pain relief and numbers-needed-to-harm (NNHs) for one patient to drop out due to adverse effects to construct a treatment algorithm for neuropathic pain. The systematic review included 11 trials comparing opioids (morphine, oxycodone, methadone, or tramadol) to placebo. These trials showed evidence of efficacy for morphine in post-herpetic neuralgia and mixed neuropathic pain; oxycodone and tramadol in post-herpetic neuralgia and polyneuropathy, and methadone in post-herpetic neuralgia.

Authors concluded that if the proposed algorithm was based solely on NNTs for pain relief, it should place TCAs first, followed by opioids or gabapentin/pregabalin. However, taking into account quality of life measures and NNHs, the authors proposed an algorithm placing opioids as third-line therapy, following TCAs and gabapentin/pregabalin. A 2005 meta-analysis [Eisenberg *et al.*, 2005] that included most of the same trials but excluded tramadol found overall efficacy for opioids in neuropathic pain, compared to placebo.

Overall, while there is evidence that opioids are effective for neuropathic pain, there is insufficient evidence to conclude that there are differences in efficacy between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.

b) *Acute pain*

The clinical review divided acute pain into two types, based on etiology: non-specific pain (e.g., low back, neck, shoulder, arm, or extremity pain) and post-operative pain.

Data in acute pain consist primarily of a plethora of very small, short-term (including single-dose) trials, most commonly in patients with post-op pain, and meta-analyses of these trials. There is little clinical evidence specifically addressing non-specific acute pain.

The most coherent approach to making sense of the available data appears to be the Oxford League Table of Analgesic Efficacy, a resource maintained by the evidence-based medicine journal/site Bandolier. The "League Table" aggregates data from randomized, double-blind, single-dose studies in patients with moderate to severe pain, using the NNT to achieve at least 50% pain relief over 4 to 6 hours as a common measure. Despite reliability issues (confidence intervals are broad for agents with relatively small datasets and probably unreliable for datasets representing fewer than 250 patients), some tentative conclusions can be drawn:

- For the combination agents, the League table generally supports the common perception of relative efficacy (oxycodone/APAP > hydrocodone/APAP > codeine or propoxyphene/APAP).
- Overall, both opioid combination agents and tramadol compare relatively poorly with NSAIDs.

Sources addressing agents not included in the League table did not add substantially to available data. One double-blind RCT [White *et al.*, 1997] found similar efficacy with hydrocodone 7.5 mg/APAP 750 mg and ketorolac 10 mg given every 6 hours for up to 3 days following tubal ligation (although neither agent was regarded by authors as very effective). Ketorolac appeared to be more tolerable. A Cochrane review of 16 poor quality studies [Elbourne and Wiseman, 2006] comparing IM meperidine to tramadol or pentazocine concluded there was insufficient evidence to evaluate comparable efficacy and safety. More vomiting and drowsiness was noted with meperidine.

The VA/DoD guideline for postoperative pain draws few specific conclusions, but does advise against use of meperidine.

Overall, there is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain, although the League table does give an overall impression of relative potency. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen.

c) *Efficacy conclusion*

The DoD P&T Committee concluded that:

a) All of the reviewed narcotic analgesics appear to be effective at providing analgesia when used in equipotent dosing. There is insufficient evidence to conclude that there are differences in efficacy between narcotic analgesics, including high potency long-acting agents for the treatment of chronic cancer or non-cancer pain, high potency IR agents for the treatment of breakthrough pain, or narcotic analgesics in general for the treatment of neuropathic pain.

b) Strong narcotic analgesics appear to be more effective than non-opioid analgesics (NSAIDs, TCAs) in chronic non-cancer pain.

c) There is no evidence suggesting efficacy differences between long-acting and short-acting formulations of the same agents; however, long-acting products offer greater convenience and may be associated with fewer episodes of breakthrough pain.

d) There is insufficient evidence to support efficacy differences between the 12-hour ER morphine products (e.g., MS Contin and generics) and the 24-hour ER morphine products (Avinza, Kadian), or between the two 24-hour products (Avinza versus Kadian). Avinza is restricted to a maximum dose of 1600 mg daily and cannot be taken with alcohol (including alcohol-containing medications). Kadian has a much longer time to achieve maximum serum levels (~9.5 hours) compared to Avinza (~0.5 hour) or to 12-hour ER morphine (2-3 hours). Both Avinza and Kadian capsules can be opened and sprinkled on food; Kadian granules can be given via gastrostomy tube.

e) Historically, the standard practice has been to use the same opioid for treatment of baseline and breakthrough pain (e.g., sustained release and IR morphine), although fentanyl patches are commonly used along with morphine IR for breakthrough pain. There is insufficient evidence to conclude that there are differences in efficacy between IR agents for the treatment of breakthrough pain in patients with chronic cancer or non-cancer pain. Trials focusing on the newer IR fentanyl products—oral transmucosal lozenges and buccal tablets—do not supply sufficient evidence to directly compare efficacy. Buccal fentanyl is more bioavailable and may therefore offer more consistent dosing; it is also sugar-free, unlike the transmucosal lozenges. The lack of a 1:1 conversion between the two formulations may offer significant potential for medication errors.

f) Narcotic analgesics are rarely considered first-line treatment for the treatment of neuropathic pain. There is insufficient evidence to conclude that there are differences in efficacy between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.

g) There is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain, although the League table does give an overall impression of relative potency. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen.

2) Safety and Tolerability

a) General adverse effects

Narcotic analgesics are associated with an increased risk of nausea, vomiting and constipation. Other prominent adverse effects include mood changes (dysphoria, euphoria), somnolence, urinary retention (associated with increased sphincter tone), and urticaria/pruritis (associated with histamine

release). Respiratory depression is uncommon but potentially serious. Death secondary to opiate overdose is nearly always due to respiratory depression. When these agents are appropriately titrated, the risk of severe respiratory depression is generally small, as tolerance rapidly develops to this effect.

A decrease in seizure threshold occurs with the use of all narcotics and is of particular concern when these medications are given with other agents that lower seizure threshold or used in patients predisposed to seizure.

Codeine is often associated with gastrointestinal intolerance, which some patients incorrectly identify as an allergic reaction. True allergy to opiate agonists is uncommon. Narcotic analgesics may also decrease or inhibit salivary flow, contributing to oral/dental problems.

b) Drug-specific adverse effects

Meperidine – Neurotoxicity (anxiety, tremors, myoclonus, and generalized seizures) has been observed with repeated use of meperidine due to accumulation of a metabolite, normeperidine, which functions as a CNS excitotoxin. Patients using meperidine for more than two days, with pre-existing renal impairment, sickle-cell disease, or CNS disease, or receiving meperidine doses greater than 600 mg/24 hours are at particularly high risk for normeperidine toxicity. Use in children is not recommended.

Propoxyphene – Like meperidine, propoxyphene has CNS-excitatory metabolites and can cause CNS disturbances including seizure when administered in high doses, especially in patients with renal disease. Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants (including alcohol), are a major cause of drug-related deaths (many of them in patients with histories of emotional disturbance, suicidal ideation or attempts, or misuse of tranquilizers, alcohol, and other CNS-active drugs). The consumer watchdog group Public Citizen petitioned the FDA in February 2006 to phase out propoxyphene from the U.S. market. Propoxyphene overdoses can be more difficult to reverse than with other opioids. Propoxyphene is not considered appropriate in elderly patients due to CNS adverse effects, including sedation, confusion, and increased likelihood of falls and fall-related fractures. It is one-half to two-thirds as potent an analgesic as codeine.

Many DoD providers surveyed cited concerns for safety with the use of meperidine and propoxyphene, although others pointed out that they were useful and could be used safely if limited to short-term use in the correct patients.

Tramadol – Doses of tramadol are limited by its association with an increased risk of seizure at higher than recommended doses. Per labeling, total dose should not exceed 300 mg of tramadol per day for the ER tablets (Ultram ER) and tramadol/APAP combination (Ultracet, generics), or 400 mg per day for tramadol IR tablets (Ultram, generics). Tramadol may increase seizure risk in

patients with a history of seizures, conditions with a recognized risk of seizure, or taking other medications that increase seizure risk.

Oral transmucosal and buccal fentanyl citrate are IR, high potency products indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and tolerant of opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who have been taking morphine 60 mg/day or more, transdermal fentanyl 50 mcg/h, or an equianalgesic dose of another opioid for a week or longer. These products should not be used in opioid non-tolerant patients because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates. They are contraindicated in the management of acute or postoperative pain. Patients requiring more than four doses per day should have their maintenance analgesic reevaluated; use of round-the-clock oral transmucosal or buccal fentanyl citrate is not recommended.

Transdermal fentanyl is indicated for management of persistent, moderate to severe chronic pain requiring continuous, around-the-clock administration for an extended period of time, that cannot be managed by other means, and ONLY in patients who are already receiving opioids, have demonstrated opioid tolerance, and require a total daily dose at least equivalent to fentanyl 25 mcg/hr. It should not be used for management of acute pain or short periods of opioid analgesia; post-op pain, including outpatient/day surgeries; mild pain; or intermittent pain. The DoD P&T Committee agreed in November 2006 that a PA was needed for transdermal fentanyl; the recommendation was approved by the Director, TMA in January 2007. Please see the November 2006 DoD P&T minutes for more information.

c) Potential for abuse

Numerous factors determine how and whether a drug is abused. It is generally accepted that rapidly acting medications (or ER dosage systems that can be compromised to cause drug to become rapidly available) are more prone to abuse than slow-acting or ER medications. Factors such as availability, local market conditions, drug popularity, and drug abuse culture may very greatly among geographic areas. Prescriptions for C-III to C-V controlled medications can generally be phoned in to pharmacies, written with refills, and are not tracked in statewide databases. This makes them easier to obtain through fraudulent activity (e.g., forging prescriptions). Prescriptions for C-II controlled medications, which have restrictions on telephone orders, cannot be refilled, and are usually tracked at the state level, are more difficult to obtain but are also more desirable to addicts due to their higher potency. Clearly there are differences among narcotic analgesics with regard to these factors; however, there were no data supporting differences in potential for abuse among like medications (for example, comparing the various long-acting high potency formulations) that the P&T Committee considered useful for making formulary recommendations.

d) Drug interactions

A large number of medications may interact with the narcotic analgesics. In general, these drug interactions are relatively similar for all of the drugs in this class and do not suggest that any particular medication offers a substantially higher potential for drug interactions. One unique consideration arises due to the dual mechanism of action of tramadol, leading to potential interactions (including increased risk of seizures or serotonin syndrome) with other medications that increase levels of serotonin and/or norepinephrine (e.g., MAOIs and selective serotonin reuptake inhibitors [SSRIs]). Another is the potential for a lethal hyperpyrexic syndrome with delirium if meperidine is administered to patients receiving MAOIs; this combination is contraindicated.

e) Special populations

There are differences among narcotic analgesics with regard to clinical evidence, extent of clinical experience, and labeling for use in special patient populations (including pediatric and elderly patients, patients who are pregnant or breast-feeding, and patients with renal or hepatic dysfunction). However, the P&T Committee overall did not find sufficient evidence of a unique advantage or disadvantage for specific products that it considered useful for formulary decision-making.

Patients with swallowing difficulties may require liquid formulations or products that can be sprinkled on food or administered via a non-oral route (e.g., as a transdermal patch, nasal spray, buccal tablet, transmucosal lozenge, or rectal suppository). The available narcotic analgesics offer various formulations that meet these needs (see Table 1).

3) Provider Opinion

The P&T Committee reviewed survey responses from 342 MHS healthcare providers with experience in prescribing narcotic analgesics for the treatment of pain. Responders represented more than 40 specialties (including a number of dental specialties), reflecting the ubiquity of use of the narcotic analgesics in clinical practice; however, the majority of responders were from Family Practice, Internal Medicine, and General Surgery. Overall, providers emphasized that they require a broad array of narcotic analgesics in their practice to treat their patients and that excessive formulary restrictions would be detrimental to their ability to adequately treat various clinical presentations. They favored ER narcotic analgesics, including the fentanyl transdermal patch, as well as a broad array of strengths of opioid/acetaminophen combination products.

The P&T Committee also reviewed comments from MTF pharmacists regarding the ability of their facilities to accommodate additional controlled substances if placed on the BCF, which would require additional vault space and increase administrative burden (i.e., performing narcotic counts) for MTFs that did not already have the additional medications on formulary. Many pharmacists indicated that centralized contracting for “pre-packed” products in commonly-

dispensed quantities would facilitate inventory and dispensing requirements at their facilities.

4) Clinical Coverage Considerations

The issue of clinical coverage, or "how many agents do we need on formulary to meet the majority of patients' needs," is dependent on multiple factors, including the efficacy, safety, and tolerability of individual agents for the treatment of conditions in which they are used, the needs of specific subpopulations, how interchangeable the medications are, the degree of intra-patient variability, and whether or not patients failing one agent (due to lack of efficacy, adverse effects, or hypersensitivity) typically respond to or tolerate another. In the case of the narcotic analgesics, several factors support availability of multiple agents and formulations.

- There is evidence that patients failing one narcotic analgesic due to lack of efficacy may respond better to another.
- Patients allergic to medications in one chemical class may be able to tolerate another without cross-sensitivity (i.e., may be able to take a phenylheptane [e.g., methadone] if allergic to a phenanthrene [e.g., morphine]).
- As with other pain medications, there is substantial intra-patient variability in response. Rotation of different narcotic analgesics has been proposed as a strategy to increase efficacy and decrease adverse effects, although clinical data are limited.
- Alternative formulations (e.g., liquids, suppositories, or patches) are needed in some patient populations. Long-acting products may be desirable not only for convenience, but to provide more blood concentrations and reduce the number of episodes of breakthrough pain.
- Utilization of these agents spreads across the entire population and touches virtually every disease state and professional specialty. Differences in clinical practice exist both locally and by specialty (e.g., products typically used in dental practice).

5) Narcotic Analgesics – Overall Clinical Effectiveness Conclusion

The P&T Committee concluded that:

a) There is insufficient evidence to support efficacy differences between narcotic analgesics, including high potency long-acting agents for the treatment of chronic cancer or non-cancer pain, high potency IR agents for the treatment of breakthrough pain, or narcotic analgesics in general for the treatment of neuropathic pain.

b) Strong narcotic analgesics appear to be more effective than non-opioid analgesics (NSAIDs, TCAs) in chronic non-cancer pain.

c) There is no evidence suggesting efficacy differences between long-acting and short-acting formulations of the same agents; however, long-acting products

offer greater convenience and may be associated with fewer episodes of breakthrough pain.

d) There is insufficient evidence to support efficacy differences between 12-hour (e.g., MS Contin and generics) and 24-hour ER morphine products (Avinza, Kadian), or between the two 24-hour products (Avinza versus Kadian). Avinza is restricted to a maximum dose of 1600 mg daily and cannot be taken with alcohol (including alcohol-containing medications). Kadian has a much longer time to achieve maximum serum levels (~9.5 hours) compared to Avinza (~0.5 hour) or to 12-hour ER morphine (2-3 hours). Both can be opened and sprinkled on food; Kadian granules can be given via gastrostomy tube.

e) There is insufficient evidence to support efficacy differences between IR agents for the treatment of breakthrough pain in patients with chronic cancer or non-cancer pain, including the newer IR fentanyl products (oral transmucosal lozenges and buccal tablets). Buccal fentanyl is more bioavailable and may offer more consistent dosing; it is also sugar-free. The lack of a 1:1 conversion between the two IR fentanyl products may offer significant potential for medication errors.

f) Narcotic analgesics are rarely considered first line agents for the treatment of neuropathic pain. There is insufficient evidence to support efficacy differences between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.

g) There is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen. The VA/DoD guideline recommends avoiding meperidine for the treatment of postoperative pain.

h) Narcotic analgesics are associated with multiple adverse effects, including nausea, vomiting, constipation, mood changes, somnolence, urinary retention, pruritis, and oral/dental problems. Respiratory depression is uncommon but potentially serious; the risk is generally small when narcotic analgesics are appropriately titrated, as tolerance rapidly develops.

i) A decrease in seizure threshold occurs with the use of all narcotics, but is of particular concern with meperidine (which has a neurotoxic metabolite and should not be used for more than two days, in patients with renal impairment, sickle-cell disease, or CNS disease, or in children); propoxyphene (which also has CNS-excitatory metabolites and can cause seizure in high doses, especially in patients with renal disease); and tramadol (which is associated with an increased risk of seizure at higher than recommended doses [300-400 mg daily] or in patients taking other medications or with conditions that increase seizure risk).

j) Propoxyphene is not considered appropriate in elderly patients due to CNS adverse effects, including sedation, confusion, and increased likelihood of

falls and fall-related fractures. The consumer watchdog group Public Citizen has petitioned the FDA to phase out propoxyphene from the U.S. market due to the association of excessive doses of propoxyphene with drug-related deaths. Many DoD providers surveyed cited concerns for safety with the use of meperidine and propoxyphene, although others pointed out that they were useful and could be used safely if limited to short-term use in the correct patients.

k) While there are clearly differences among narcotic analgesics with regard to likelihood for abuse (e.g., onset of action and potency), there are no data supporting differences in potential for abuse among like medications (e.g., high potency, long-acting agents) that the P&T Committee considered useful for making any formulary recommendation.

l) In general, drug interactions are relatively similar for all of the drugs in this class and it does not appear that any particular medication offers a substantially higher potential for drug interactions. Two unique considerations are tramadol and meperidine. Because of its dual mechanism of action, tramadol has potential interactions with other medications that increase serotonin and/or norepinephrine levels (e.g., MAOIs, SSRIs); meperidine is contraindicated with MAOIs due to the potential for a lethal hyperpyrexic syndrome.

m) There are differences among narcotic analgesics with regard to clinical evidence, extent of clinical experience, and labeling for use in special patient populations (including pediatric and elderly patients, patients who are pregnant or breast-feeding, and patients with renal or hepatic dysfunction). However, the P&T Committee overall did not find sufficient evidence of a unique advantage or disadvantage for specific products that it considered useful for formulary decision-making.

n) Patients with swallowing difficulties may require liquid formulations or products that can be sprinkled on food or administered via a non-oral route. The available narcotic analgesics offer various formulations that meet these needs.

o) Providers surveyed in general emphasized that they require a broad array of narcotic analgesics in their practice to treat their patients and that excessive formulary restrictions would be detrimental to their ability to adequately treat various clinical presentations. They favored ER narcotic analgesics, including the fentanyl transdermal patch, as well as a broad array of strengths of opioid/ acetaminophen combination products. Many pharmacists indicated that centralized contracting for “pre-packed” products in commonly-dispensed quantities would facilitate inventory and dispensing requirements at their facilities.

p) Clinical coverage considerations support a broad array of formulary agents and formulations.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to accept the clinical effectiveness conclusions stated above.

B. Narcotic Analgesics – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the agents in the narcotic analgesic therapeutic class in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analyses (CMAs) were conducted for four subclasses of the narcotic analgesics, which differed slightly from the categories used during the clinical review: (1) long-acting high potency single analgesic agents; (2) short-acting high potency single analgesic agents; (3) low potency single analgesic agents; and (4) combination products. The conclusion of the relative clinical effectiveness evaluation was that there was insufficient evidence to suggest that the narcotic analgesics differed within the defined subclasses (long-acting high potency agents, short-acting high potency agents, low potency agents, and combination products) in regards to efficacy, safety, tolerability, or clinical outcomes in the treatment of pain. As a result, several CMAs were performed to determine the relative cost effectiveness of the agents within each subclass. The CMAs compared the agents based on their weighted average cost per equianalgesic dose.

The results of the CMA for the high potency long-acting single analgesic agents showed that the 12-hour morphine sulfate ER product (MS Contin, generics) was the most cost effective agent. This result was anticipated since this product is generically available at a significantly discounted cost relative to brand name MS Contin. The other long-acting high potency single analgesic agents—the 24-hour ER morphine products (Kadian, Avinza), fentanyl patch, oxycodone ER, and oxymorphone ER—were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin, generics). Two of these products, fentanyl patch and oxycodone ER only recently became generically available. The cost of these generics is only slightly lower than their respective brand name products. The other three long-acting high potency single analgesic agents—the 24-hour ER morphine products (Kadian, Avinza) and oxymorphone ER—are brand-only products. There was no substantial difference in cost effectiveness between Kadian and Avinza.

The results of the CMA for the high potency short-acting single analgesic agents showed that morphine sulfate IR and oxycodone IR had similar relative cost effectiveness and were the most cost effective agents. Once again, this result was anticipated since morphine sulfate IR and oxycodone IR are now generically available at a significantly discounted cost relative to the their respective brand name products. The other two agents, fentanyl citrate buccal tablets and fentanyl citrate transmucosal lozenges, were 40-fold the cost of the two most cost effective agents. Fentanyl citrate transmucosal lozenges only recently became generically available. There was no substantial difference in cost effectiveness between the two fentanyl citrate products (Fentora versus Actiq or its generic equivalent).

The results of the CMA for the low potency single analgesic agents showed that tramadol ER was not cost effective relative to other formulations of tramadol (tramadol; tramadol/APAP), which are generically available.

The CMA for the combination agents showed that the agents within this generic-dominated class were all similar in terms of relative cost effectiveness.

The P&T Committee's discussion primarily focused on the relative clinical and cost effectiveness of the high potency long-acting and high potency short-acting single analgesic agents. The general consensus of the P&T Committee was that the UF should provide a broad array of these agents sufficient to meet the clinical needs of the DoD population. The P&T Committee made the following conclusions for each of these two subclasses:

1) *High potency long-acting single analgesic agents* – Although the 24-hour ER products (Kadian and Avinza); fentanyl transdermal patch, oxycodone ER, and oxymorphone ER were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin and generics), these agents should be maintained on the UF in order to sufficiently meet the clinical needs of the DoD population. This conclusion was based on the following factors:

    a. The 24-hour ER morphine products (Kadian and Avinza) provide more consistent levels of medication throughout a 24-hour period, which may reduce the number and/or severity of breakthrough pain episodes. Both products can be sprinkled on food to ease administration for patients who cannot swallow oral solid dosage forms. There was no substantial difference in cost effectiveness between Kadian and Avinza.

    b. Oxycodone ER provides an alternative for patients who cannot tolerate morphine sulfate.

    c. Transdermal fentanyl provides a unique dosage form for patients who are unable to swallow.

    d. Oxymorphone ER provides an additional long-acting oral alternative for patients who cannot tolerate morphine sulfate or oxycodone. The place of oxymorphone in therapy relative to other long-acting narcotic analgesics with much longer periods of clinical experience is not yet clear.

2) *High potency short-acting single analgesic agents* – Even though fentanyl citrate buccal tablets and fentanyl citrate transmucosal lozenges were more than 40-fold the cost of the two most cost effective agents, morphine sulfate IR and oxycodone IR, the fentanyl citrate products provide an additional therapeutic alternative for breakthrough pain with novel routes of administration. There was no substantial difference in cost effectiveness between the two fentanyl citrate products.

Cost Effectiveness Conclusion

1) *High potency long-acting single analgesic agents* – Although the 24-hour ER products (Kadian and Avinza); fentanyl transdermal patch, oxycodone ER, and oxymorphone ER were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin and generics), they have unique clinical

advantages and should be maintained on the UF in order to sufficiently meet the clinical needs of the DoD population.

2) *High potency short-acting single analgesic agents* – Even though fentanyl citrate buccal tablets and fentanyl citrate transmucosal lozenges were more than 40-fold the cost of the two most cost effective agents, morphine sulfate IR and oxycodone IR, the fentanyl citrate products provide an additional therapeutic alternative for breakthrough pain with novel routes of administration. There was no substantial difference in cost effectiveness between the two fentanyl citrate products.

3) *Low potency single analgesic agents* – Tramadol ER was not cost effective relative to other formulations of tramadol (tramadol; tramadol/APAP), which are generically available. All other products in this subclass were cost effective.

4) *Combination agents* – The products within this generic-dominated subclass were all determined to be cost effective relative to their comparators.

The P&T Committee agreed (14 for, 0 opposed, 1 abstained, 2 absent) with the relative cost effectiveness analysis of the narcotic analgesic agents.

C. Narcotic Analgesics – UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the narcotic analgesic drug class, and other relevant factors, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) that tramadol ER tablets be designated non-formulary under the UF, with all other narcotic analgesic agents designated as formulary on the UF. Additionally, the P&T Committee voted to recommend (14 for, 0 opposed, 1 abstained, 1 absent) a QL of 112 tablets/28 days for fentanyl buccal tablets, consistent with established quantity limits for fentanyl transmucosal lozenges, recommendations in Fentora package labeling, and current DoD prescribing patterns for Fentora buccal tablets.

D. Narcotic Analgesics – MN Criteria

Based on the clinical evaluation for tramadol ER and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for tramadol ER:

1) Use of formulary alternatives is contraindicated.

2) The patient previously responded to tramadol ER and changing to a formulary alternative would incur unacceptable clinical risk.

The P&T Committee did not agree that other MN criteria were likely to apply, given the UF status of tramadol IR.

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to approve the MN criteria outlined above.

E. Narcotic Analgesics – UF Implementation Period

Because of the small number of unique utilizers affected (approximately 6500 patients [~1.5%] out of approximately 437,000 unique utilizers at all three points of

service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have tramadol ER on their local formularies. MTFs will be able to fill non-formulary requests for this medication only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary narcotic analgesic written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. Narcotic Analgesics – BCF Review and Recommendation

The P&T Committee considered the BCF status of the narcotic analgesics. Currently the only narcotic analgesic agents on the BCF are the 15 mg, 30 mg, and 60 mg strengths of morphine sulfate ER (MS Contin, generics); codeine/APAP oral (formulations not specified), and oxycodone/APAP 5/325 mg or 5/500 mg tablets. In addition to the medications already on the BCF, the P&T Committee agreed that morphine sulfate IR 15 and 30 mg and tramadol IR 50 mg should be added to the BCF and that the listings for hydrocodone/APAP and codeine/APAP should be clarified to specify the most commonly used and clinically necessary formulations and strengths (hydrocodone / APAP 5/500 mg; codeine/APAP 30/300 mg, and codeine/APAP elixir 12/120 mg per 5 mL). All of these drugs are cost effective, widely used agents in the MTF setting.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend the following agents be designated as the BCF selections in this class: morphine sulfate ER 15 mg, 30 mg, 60 mg; morphine sulfate IR 15 mg and 30 mg; oxycodone/APAP 5/325 mg; hydrocodone/ APAP 5/500 mg; codeine/APAP 30/300 mg; codeine/APAP elixir 12/120 mg per 5 mL; and tramadol IR 50 mg.

8. DRUG CLASS REVIEW – OPHTHALMIC GLAUCOMA AGENTS

The P&T Committee evaluated the relative clinical effectiveness of the ophthalmic glaucoma agents. Based on chemical structure and mechanism of action, the drug class was divided into seven categories as outlined in Table 2. The seven categories include ophthalmic prostaglandin analogs; beta blockers; carbonic anhydrase inhibitors; alpha 2 adrenergics; adrenergics; cholinergics; and cholinesterase inhibitors. The glaucoma drug class accounted for $51.1 million in MHS expenditures in FY 2006, and is ranked #34 in terms of total expenditures during that time period.

A. Ophthalmic Glaucoma Agents – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the ophthalmic glaucoma agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical

review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

Table 2: Ophthalmic Glaucoma Agents Available in the U.S.

Subclass	Generic Name	Brand Name
Prostaglandin Analogs	Bimatoprost Latanoprost Travoprost	Lumigan Xalatan Travatan; Travatan Z
Beta Blockers	Betaxolol Carteolol Levobunolol Metipranolol Timolol maleate solution Timolol maleate gel-forming solution Timolol maleate with potassium sorbate Timolol hemihydrate	Betoptic, generics; Betoptic-S Ocupress, generics Betagan, generics Optipranolol, generics Timoptic, generics Timoptic XE, generics Istalol Betimol
Carbonic Anhydrase Inhibitor; Combination Drug	Brinzolamide Dorzolamide Dorzolamide / timolol	Azopt Trusopt Cosopt
Alpha 2 adrenergics	Brimonidine BAK 0.2% Brimonidine Purite 0.15%/ 0.1% Apraclonidine	Generic (Alphagan brand discontinued) Alphagan P Iopidine
Adrenergics	Dipivefrin	Propine, generics
Cholinergics (miotics)	Acetylcholine Carbachol Pilocarpine	Miochol-E Isopto Carbachol Pilocar, generics; Pilopine HS gel
Cholinesterase Inhibitors	Echothiophate	Phospholine iodide

1) Efficacy Measures

The primary outcome measure used to assess efficacy of the glaucoma drugs is the change in intraocular pressure (IOP) as compared to baseline, expressed as an absolute value in mm Hg or as a relative percentage change from baseline.

2) Efficacy

a) Prostaglandin analogs

i) Products – The prostaglandins available on the market include bimatoprost (Lumigan), latanoprost (Xalatan), and travoprost (Travatan). These three products contain benzalkonium chloride (BAK) as a preservative, which has been associated with local ocular irritation. Travoprost is also available with a non-BAK preservative under the trade name of Travatan Z. None of the products are available in generic formulations.

ii) Meta-analyses – The efficacy of the ophthalmic prostaglandin analogs was evaluated in two meta-analyses. At peak levels, the mean differences from baseline IOP were similar; -33% (95% CI -29% to -27%) with bimatoprost,

-28% (95% CI -30% to -26%) with latanoprost, and -29% (95% CI -32% to -25%) with travoprost [Van der Valk *et al.*, 2005].

Ni Li *et al.* in 2006 found no difference in the IOP lowering effects when travoprost was compared to bimatoprost (weighted mean difference 0.08, 95% CI -0.62 to 0.79; p=0.8), or to latanoprost (weighted mean difference 0.57, 95% CI -1.18 to 0.04; p = 0.07). The IOP lowering efficacy of bimatoprost was not directly compared to latanoprost.

iii) Head-to-head trials – Two RCTs that evaluated the prostaglandin analogs in a head-to-head manner did not find significant differences in the efficacy of the drugs. Parrish *et al.* in 2003 found no difference among all comparison groups (p = 0.128), while Orzalesi *et al.* in 2006 reported that the performance of all three drugs was statistically identical within the 1.5 mmHg power of the trial.

iii) Racial differences in efficacy – Travoprost was more effective than latanoprost at lowering IOP in African Americans than non-African Americans in one sub-analysis [Netland *et al.*, 2001]. The difference of up to 1.5 mm Hg was statistically significant (p = 0.04) in favor of travoprost. However, this was a post-hoc analysis that was not prospectively designed to evaluate racial differences in efficacy.

No significant differences between bimatoprost and travoprost in mean IOP-lowering were found in one prospectively designed trial involving ninety-four African American patients [Noecker *et al.*, 2006]. Both drugs resulted in a statistically significant reduction from baseline IOP at all study visits ($p < 0.001$). There were no statistically significant between-group differences in IOP-lowering ($p \geq 0.130$).

b) Beta blockers

i) Products – Six ophthalmic beta blockers are included in the class; one β1 selective product, betaxolol (Betoptic-S, Betoptic); and five non-selective products, levobunolol (Betagan), metipranolol (OptiPranolol), timolol hemihydrate (Betimol), timolol maleate (Timoptic, Istalol, Timoptic Ocudose and Timoptic XE, a gel-forming solution), and carteolol (Ocupress).

ii) Generics – Several beta blockers are available in generic formulations, with the exception of betaxolol suspension 0.25% (Betoptic-S), timolol hemihydrate (Betimol), the branded timolol maleate product Istalol, and preservative free unit dose timolol maleate (Timoptic Ocudose).

iii) Timolol – Timolol was the first beta blocker marketed and is the gold standard to which other ophthalmic glaucoma agents are compared. On average, timolol reduces IOP by 20% to 35%. Several different formulations and salts are available:

- *Timolol maleate solution (Timoptic, generics) versus timolol maleate gel-forming solution* – Timolol maleate solution requires twice daily

dosing. Timolol maleate gel-forming solution is dosed once daily, and potentially has increased ocular penetration and duration of action compared to the solution, but causes transient blurred vision. One study comparing the solution with the gel-forming solution found no difference in IOP-lowering from baseline; both products lowered IOP by 30% to 31%.

- *Timolol hemihydrate* – The timolol hemihydrate salt theoretically enhances ocular drug availability, due to increased solubility compared to timolol maleate. The hemihydrate formulation is dosed twice daily, as is timolol maleate. Two comparative studies of timolol hemihydrate with timolol maleate solution or timolol maleate gel-forming solution showed similar reductions in IOP from baseline by about 22%. One study [Mundorf *et al.*, 1998] found there was no change in IOP after three months when patients previously receiving timolol maleate solution were switched to timolol hemihydrate.
- *Timolol maleate (Istalol)* – The timolol maleate branded product Istalol is dosed once daily. Potassium sorbate is incorporated into the formulation, which purportedly enhances ocular penetration into the eye. However, a clinical trial comparing Istalol to timolol maleate (Timoptic, generics) dosed twice daily demonstrated no efficacy differences between the products, both drugs reduced IOP by 23% to 24% [Mundorf *et al.*, 2004].

iv) Levobunolol, metipranolol, carteolol – Comparative trials with the non-selective beta blockers levobunolol, metipranolol, and carteolol each with timolol maleate (Timoptic, generics) show similar reductions in IOP.

vi) Betaxolol – Betaxolol is the sole β_1 selective ophthalmic beta blocker. It is available in two strengths, a 0.25% suspension (Betoptic-S) that is not available in a generic formulation, and a 0.5% solution (Betoptic, generics). Clinical trial data suggest that timolol maleate may decrease IOP to a greater extent than betaxolol. Due to betaxolol's β_1 selectivity, patients with respiratory or reactive airway diseases may not experience adverse pulmonary effects seen with non-selective beta blockers. However, there is only one published study enrolling nine subjects demonstrating a lack of adverse effect on pulmonary function tests.

c) Carbonic anhydrase inhibitors; combinations with beta blockers

i) Products – The ophthalmic carbonic anhydrase inhibitors include brinzolamide (Azopt), and dorzolamide (Trusopt). The branded product Cosopt consists of dorzolamide and timolol maleate and is the only combination glaucoma product marketed. Generic formulations of the three products are not available. The carbonic anhydrase inhibitors are used in patients with contraindications to other glaucoma drugs, and can be used concomitantly with other drugs that lower IOP. Brinzolamide and dorzolamide both decrease intraocular pressure by 15%-26%.

ii) Meta-analysis – One meta-analysis included an indirect comparison of brinzolamide and dorzolamide. Both drugs significantly reduced IOP, compared with placebo. At trough levels, the mean differences from baseline IOP were similar; -17% (95% CI -19% to -15%) for both drugs [Van der Valk *et al.*, 2005].

Head-to-head trials – One randomized trial reported similar reductions in IOP with brinzolamideand dorzolamide (-17% to -20% for both), compared to increases in IOP of 8% to 19% with placebo [Sall *et al.*, 2000]. When brinzolamide and dorzolamide were given with timolol maleate, similar IOP reductions were also seen (-14% to -21% for both) [Michaud *et al.*, 2001]. Similar absolute reductions in IOP of 0.1 to 0.3 mm Hg were reported with brinzolamide and dorzolamide when the carbonic anhydrase inhibitor was added on to a regimen of latanoprost and timolol (Timoptic, generics) [Tsukamoto *et al.*, 2005].

iii) Dorzolamide/timolol (Cosopt) – Clinical trials sponsored by the manufacturer lasting 3 to 15 months found the combination of dorzolamide with timolol produced similar reductions in IOP as the two separate components administered together. The net effect of administering the Cosopt combination is an absolute IOP reduction of 3-4 mm Hg below that seen with timolol (Timoptic, generics).

d) Alpha 2 adrenergics

i) Products – The alpha 2 adrenergic agents include the parent compounds of apraclonidine (Iopidine) and brimonidine. Brimonidine is available in three formulations: a 0.2% concentration with BAK as a preservative (available only as a generic, as the proprietary product has been discontinued); a 0.15% solution with purite as a preservative (Alphagan P), and a 0.1% solution with purite as a preservative (also called Alphagan P). Apraclonidine and brimonidine reduce intraocular pressure by 18% to 27% two to five hours after dosing and by 10% at 8 to 12 hours after administration.

ii) FDA Indications – There are differences in the FDA-approved indications for apraclonidine and brimonidine. All formulations of brimonidine BAK 0.2% (generic) and brimonidine purite 0.15% and 0.1% (Alphagan P) are indicated to reduce IOP in patients with glaucoma. Apraclonidine is approved for use following laser procedures to control post-surgical IOP elevations (1% concentration), or for short-term use in patients receiving maximally tolerated medical therapy who require additional IOP reductions prior to surgery (0.5% concentration).

iii) Apraclonidine – Apraclonidine is primarily used short-term, as it is associated with tachyphylaxis and diminished intraocular pressure lowering effect over time. DoD utilization of apraclonidine represents a small percentage of overall alpha 2 adrenergic drug use (0.5%).

iv) Apraclonidine versus brimonidine 0.2% BAK – Head-to-head studies of brimonidine BAK 0.2% and apraclonidine demonstrated similar intraocular

pressure lowering effects, both in patients with glaucoma, and in laser surgery. Both agents lower intraocular pressure by 17 to 26% in this setting.

v) Brimonidine – One meta-analysis reported that brimonidine reduced intraocular pressure by 25% at peak and 18% at trough, but to a lesser extent than the prostaglandins (25% to 35%) [Van der Valk *et al.*, 2005].

Brimonidine formulations – Two head-to-head trials comparing brimonidine BAK 0.2% formulation (generic) with brimonidine purite 0.15% (Alphagan P) did not show differences in IOP lowering [Katz *et al.*, 2002; Mundorf *et al.*, 2003]. One comparative trial with brimonidine purite 0.1% (Alphagan P) reported similar efficacy with brimonidine BAK 0.2% (generic), but few details were provided [package insert]. Product labeling states that the brimonidine purite 0.15% (Alphagan P) and brimonidine purite 0.1% (Alphagan P) both lower IOP by 2-6 mmHg; no corresponding percentage reduction in intraocular pressure was provided.

e) Adrenergics, cholinergics, and cholinesterase inhibitors

i) Products – Dipivefrin (Propine, generic) is the only ophthalmic adrenergic, and echothiophate (Phospholine iodide) is the only ophthalmic cholinesterase inhibitor. The cholinergics include acetylcholine (Miochol-E), carbachol (Isopto Carbachol), and pilocarpine gel (Pilopine HS) and pilocarpine solution (Pilocar, generics). The adrenergics, cholinergics, and cholinesterase inhibitors were introduced in the early 1980s, and were the first agents used to treat glaucoma, but have been replaced by newer therapies, due to adverse effects. They are now third-line treatments for glaucoma, but do fulfill unique niches in therapy.

ii) Dipivefrin – Dipivefrin is a pro-drug that has improved lipophilicity and enhanced corneal penetration compared to the parent compound epinephrine. IOP reduction with dipivefrin ranges from 15% to 25%.

iii) Cholinergics – The direct-acting cholinergics or miotics are used for glaucoma to decrease IOP via increased aqueous outflow, or are used to induce miosis during surgery. Acetylcholine, carbachol and pilocarpine solution are all dosed four times daily; only pilocarpine solution is available generically.

Acetylcholine – Acetylcholine is used intraocularly to constrict the pupil during cataract surgery, or after placement of the intraocular lens following cataract removal.

Carbachol – Carbachol has two mechanisms to decrease IOP; it directly stimulates muscarinic receptors in the eye, and indirectly inhibits acetylcholinesterase.

Pilocarpine – Pilocarpine lowers IOP by 22% to 30%. It is dosed four times daily in the treatment of open-angle glaucoma. In acute angle closure glaucoma, pilocarpine is used as monotherapy or in combination with other cholinergic agents or with a carbonic anhydrase inhibitor to relieve IOP prior to ocular surgery. Pilocarpine gel is a sustained release formulation

that is applied at bedtime to provide 24-hour control of IOP; pilocarpine gel reduces the adverse effects of myopia.

iv) Echothiophate – Echothiophate is dosed twice daily for glaucoma. It has a role for the treatment of aphakia or pseudophakia (patients with their lens replaced by artificial lens). The drug is poorly absorbed due to its quaternary structure, but has similar IOP reductions as pilocarpine.

3) Safety / tolerability

a) Prostaglandin analogs

i) Serious adverse events – Overall the ophthalmic prostaglandins have a low incidence of systemic adverse effects, which has contributed to their use as first-line therapy for glaucoma.

ii) Minor adverse events

- *Hyperemia* is the most common minor adverse event reported with the ophthalmic prostaglandins. A comparison of package insert data shows a higher incidence of hyperemia with bimatoprost (15-45%) and travoprost (30-50%), as compared to latanoprost (5-15%). In one head-to-head trial, hyperemia occurred in 69% of patients receiving bimatoprost, 58% of travoprost-treated patients, and 47% of latanoprost-treated patients [Parrish *et al.*, 2003]. Significantly fewer patients experienced an ocular adverse event with latanoprost in this trial. Hyperemia appears to be more of a cosmetic issue and is noted to generally be mild in severity and transient in nature.
- *Increased pigmentation* occurs more frequently with latanoprost (5-15%) than either bimatoprost (1-3%) or travoprost (1-4%). The pigmentation changes may be permanent.
- *Preservatives (Travatan versus Travatan Z)* – Products with preservatives that do not contain BAK are purported to have a favorable adverse event profile over products with BAK-based preservatives. A randomized trial in 700 patients evaluated the adverse events of the BAK-containing travoprost product (Travatan) with the non-BAK preservative formulation (Travatan Z). Hyperemia occurred in 9% of patients receiving Travatan, compared to 6.4% with Travatan Z (no p value provided) [Lewis 2007]. The adverse events in this trial were not serious and did not interrupt treatment.

iii) Drug discontinuations due to adverse effects

The prostaglandins are well tolerated. Discontinuation rates noted in package labeling due to conjunctival hyperemia were 3% for both travoprost and bimatoprost, and <1% for latanoprost. The discontinuation rates due to adverse events in one head to head trial were 0.7% with travoprost, 1.4% with bimatoprost, and zero with latanoprost [Parrish *et al.*, 2003].

b) Beta blockers

i) Serious adverse events – As a class, the ophthalmic beta blockers are associated with systemic adverse effects that limit their use for glaucoma, including bradycardia, arrhythmia, cardiac block, congestive heart failure, and bronchospasm. Betaxolol is the only β1 selective ophthalmic beta blocker; however bronchospasm has occurred in patients with asthma and chronic obstructive pulmonary disease. Both selective and non-selective beta blockers are contraindicated for use in patients with severe cardiovascular disease including sinus bradycardia, second and third degree heart block, cardiogenic shock, or patients with overt cardiac failure.

ii) Minor adverse events – Local adverse events of the beta blockers include stinging, itching, redness and blurred vision, which may be due to the preservative and pH of the solutions. Overall, stinging is most commonly associated with betaxolol and metipranolol. Timoptic maleate gel-forming solution is associated with transient blurry vision due to its thick consistency upon instillation.

Timolol maleate (Istalol) – A higher incidence of burning and stinging was associated with the once daily branded formulation of timolol maleate (Istalol) compared to timolol maleate (Timoptic, generics) in one trial (41.6% versus 22.9%) [Mundorf *et al.*, 2004].

c) Carbonic anhydrase inhibitors; and combinations with beta blockers

i) Serious adverse events – Brinzolamide and dorzolamide both have similar contraindications (hypersensitivity to the individual components). Brinzolamide/timolol (Cosopt) contains precautions regarding pulmonary and cardiovascular function seen with other ophthalmic beta blockers, due to the timolol component. Rare effects with dorzolamide include altered cornea endothelial cell function, renal calculi, and thrombocytopenia.

ii) Minor adverse effects – The most common adverse effects of the ophthalmic carbonic anhydrase inhibitors include local burning and stinging upon drug instillation, and taste perversion. In head-to-head-trials comparing brinzolamide with dorzolamide, dorzolamide was associated with a higher incidence of burning/stinging (12-16% versus 2-3%). The higher incidence of ocular discomfort with dorzolamide may be due to the acidic pH of the product (5.6) versus the more physiologic pH of brinzolamide (7.5). However, the ocular discomfort with dorzolamide appears transient, lasts about 10 seconds, is characterized as mild and diminishes with continued therapy [Stewart *et al.*, 2004]. The incidence of taste perversion appears similar between the two products, based on head-to-head clinical trials.

iii) Discontinuations due to adverse effects – It is difficult to determine differences in tolerability between brinzolamideand dorzolamide, as only a few patients discontinued therapy due to adverse events in the head-to-head clinical trials.

d) Alpha 2 adrenergics

i) Serious adverse effects – Both apraclonidine and brimonidine are contraindicated in patients with hypersensitivity to the individual agents, patients taking clonidine, and patients taking MAOIs. The alpha 2 adrenergics as a class may reduce pulse and blood pressure. Apraclonidine penetrates the blood brain barrier to a lesser extent than brimonidine, and is less likely to reduce heart rate and blood pressure.

ii) Minor adverse effects – Overall, the alpha 2 adrenergics are associated with a relatively high incidence of minor adverse events, including fatigue and local allergic reactions, compared to other glaucoma drug classes. As a class, the alpha 2 adrenergic agents can cause ocular intolerance (allergy leading to conjunctival erythema and potential periorbital infection) in 13% to 36% of patients. Apraclonidine can cause dry nose and mouth and upper eyelid retraction, and follicular conjunctivitis has occurred frequently. Brimonidine has a higher incidence of dry mouth (33%) than apraclonidine, but is associated with less frequent ocular side effects.

iii) Brimonidine formulations –There are three concentrations of brimonidine marketed; a 0.2% concentration with BAK as a preservative, and two products (0.15% and 0.1%) containing a purite preservative. There is only limited data comparing the safety differences between the three products. There are conflicting data as to whether brimonidine purite 0.15% (Alphagan P) causes less ocular irritation than brimonidine BAK 0.2%. A statistically significant 41% reduction in reports of allergic conjunctivitis, oral dryness, conjunctival hyperemia, and eye discharge with brimonidine purite 0.15% compared to brimonidine BAK 0.2% was found in one head-to-head trial, [Katz *et al.*, 2002], while another study noted no significant differences between the two drugs in the overall incidence of adverse events [Mundorf *et al.*, 2003)]. Indirect comparison of the trials does not suggest any difference in the incidence of discontinuation due to adverse drug reactions between the two agents.

Data from an unpublished study cited in product labeling found a significantly lower frequency of treatment-related adverse events with brimonidine purite 0.1% (Alphagan P) versus brimonidine BAK 0.2%. More patients (34%) discontinued treatment due to adverse events with brimonidine BAK 0.2% than with brimonidine purite 0.1% (21%).

e) Adrenergics, cholinergics, and cholinesterase inhibitors

i) Dipivefrin – Today dipivefrin is rarely used due to adverse effects such as conjunctival hyperemia, hypersensitivity and ocular irritation. It is contra-indicated in patients with narrow-angle glaucoma, since any dilation of the pupil may predispose the patient to an exacerbation of closed-angle glaucoma.

ii) Cholinergics – Retinal detachment and tearing may occur if the cholinergic drugs are used in patients with pre-existing retinal disease. Miotics may

also cause angle closure in patients with narrow angle glaucoma due to increased resistance to aqueous flow from the posterior to the anterior eye chamber.

Acetylcholine – Safety concerns with acetylcholine include infrequent corneal edema, corneal clouding, and corneal decompensation. Major adverse events are rare, but include bradycardia, hypotension, flushing, breathing difficulties, and sweating.

Carbachol – Carbachol is more potent than pilocarpine, and can induce significant adverse effects. Transient stinging and burning, in addition to corneal clouding have been reported. Brow ache is the most frequent patient-reported adverse effect, due to stimulation of the ciliary muscle, which exerts a physical pull on the trabecular mesh network. Older patients with cataracts often complain of dimmed vision caused by miosis. Severe but rare systemic effects include headache, sweating, epigastric distress, nausea, vomiting, and diarrhea.

Pilocarpine – Pilocarpine is associated with miosis or accommodative spasm, which may cause blurred vision and night blindness. Long-term use is limited by loss of visual field, due to the decreased amount of light entering the eye. Systemic adverse effects include atrioventricular block and other cardiovascular effects.

iii) Echothiophate – Echothiophate frequently causes blurred vision, brow ache, eyelid fasisculation, and watery eyes. Rarely, burning or stinging has been reported. Rare but serious adverse effects are similar to those of the miotics, but also include punctul stenosis of the nasolacrimal system. Organo-phosphate pesticides should be used with caution, as echothiophate activity may increase, raising the potential for adverse effects.

4) Other Factors

a) Prostaglandin analogs

Storage and stability – Latanoprost requires refrigeration prior to opening, to maintain a 36-month shelf life; it does not require refrigeration once opened. Bimatoprost and travoprost (Travatan, Travatan Z) do not require refrigeration.

Special populations – There are no differences between the prostaglandin analogs in their pregnancy category rating (all are pregnancy category C) or labeling for pediatric use (none are FDA-approved).

b) Beta blockers

Special populations – The ophthalmic beta blockers are rated a pregnancy category C. Timolol crosses into breast milk, so it should be avoided in lactating women. Safety and efficacy of ophthalmic beta-blockers have not been established in pediatrics. The majority of published information in children has been with timolol maleate. Topical application of timolol 0.5% can cause cardiac blockade in infants younger than 2 years of age.

Frequency of dosing – Patient convenience is an advantage of once daily ophthalmic beta blockers, particularly if multiple ophthalmic drugs are required. The branded timolol maleate product Istalol, and timolol maleate gel-forming solution are dosed once daily.

c) Carbonic anhydrase inhibitors; combinations with beta blockers

Dosing dispenser – The dosing dispenser of dorzolamide is specifically designed to deliver a controlled pre-measured drop, and will not operate unless the instructions are followed correctly.

Patient convenience – The primary advantage of the combination of dorzolamide with timolol (Cosopt) is patient convenience in reducing the number of bottles and daily ophthalmic drops required, potentially improving compliance.

d) Adrenergics, cholinergics, and cholinesterase inhibitors

i) Dipivefrin – The adrenergic dipivefrin still has a place in therapy as adjunctive therapy to beta blockers, pilocarpine and carbachol.

ii) Cholinergics – The cholinergics are usually reserved for patients who have not responded to other topical glaucoma treatments.

Pilocarpine – Pilocarpine is used to treat acute angle closure glaucoma and as a miotic during ocular surgery.

iii) Echothiophate – The cholinesterase inhibitor echothiophate has fallen out of favor, due to four times daily dosing, compared to newer agents.

Overall Clinical Effectiveness Conclusion – The P&T Committee concluded that:

1) *Prostaglandin analogs* – Bimatoprost, latanoprost, and travoprost all decrease IOP from baseline by 28% to 33%. A prospectively designed trial assessing efficacy of bimatoprost and travoprost found no difference in efficacy in African Americans; a sub-group analysis from a different trial reported decreased efficacy of latanoprost when compared to travoprost in African Americans versus non-African Americans. Latanoprost has the most favorable ocular adverse event profile of the three prostaglandin analogs, but requires refrigeration prior to opening. The non-BAK preservative found in the Travatan Z formulation of travoprost has not shown a major advantage in terms of ocular side effects, compared to the BAK-containing product Travatan.

2) *Beta blockers* – The IOP-lowering effects of timolol maleate (Timoptic, generics; Timoptic XE, generics), timolol hemihydrate, levobunolol, metipranolol and carteolol appear similar, based on several head-to-head studies. Timolol maleate solution (Timoptic, generics) and gel-forming solution reduce IOP by 20-35%. The Timoptic XE gel-forming solution has the advantage of once daily dosing, but is associated with transient blurred vision due to the consistency of the gel. There is no evidence that the timolol maleate product Istalol or the timolol hemihydrate product Betimol have additional clinical benefits over other timolol maleate products in IOP lowering or safety profiles. Betaxolol decreases IOP to a lesser

extent than timolol maleate; however, the β1 selectivity of betaxolol may be an advantage in patients with cardiac or pulmonary co-morbidities.

3) *Carbonic anhydrase inhibitors* – The IOP lowering effects of brinzolamideand dorzolamide appear similar. Dorzolamide/timolol (Cosopt) is the only combination product for glaucoma and offers a convenience to patients. Dorzolamide causes more local ocular irritation than brinzolamide; however, burning and stinging upon instillation last 10 seconds, diminish over time, and have not translated into a higher discontinuation rate due to adverse events.

4) *Alpha 2 adrenergics* – Apraclonidine is used primarily short-term following ocular surgery, while brimonidine is used chronically for glaucoma. Both apraclonidine and brimonidine lower IOP to a similar extent. For brimonidine, changing the BAK preservative (generic) to a purite preservative (Alphagan P) and reducing the concentration from 0.2% to 0.15% or 0.1% does not appear to affect efficacy. There are conflicting data as to whether brimonidine purite 0.15% (Alphagan P) causes less ocular irritation than brimonidine BAK 0.2% (generic). Brimonidine purite 0.1% (Alphagan P) may have an improved safety and tolerability profile compared to brimonidine BAK 0.1% (generic), but the one supportive study has not been published in a peer-reviewed journal.

5) *Adrenergics, cholinergics, and cholinesterase inhibitors* – The cholinergic pilocarpine is used for acute angle closure glaucoma and as a miotic agent during ocular surgery. Although not routinely used today, the adrenergic drug dipivefrin, the cholinergics acetylcholine and carbachol and the cholinesterase inhibitor echothiophate serve unique niches in therapy.

6) Based on clinical issues alone, there are no compelling reasons to classify any of the glaucoma drugs as non-formulary on the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to accept the clinical effectiveness conclusions state above.

B. Ophthalmic Glaucoma Agents – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the ophthalmic glaucoma agents in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The ophthalmic glaucoma agents were classified and compared within subgroups based on mechanism of action. The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the glaucoma medications differed within subclasses in regards to efficacy, safety, tolerability, or clinical outcomes in the treatment of glaucoma. As a result, several CMAs were performed to determine the relative cost effectiveness of the agents within each subclass. The CMAs compared the weighted average cost per day of treatment for each drug product.

Results from the CMA of the prostaglandin subclass included three key findings: (1) travoprost (Travatan, Travatan Z) was most cost effective under a scenario where it was the sole agent on the uniform formulary; (2) Latanoprost and bimatoprost were most cost effective under a scenario where only two prostaglandin products were placed in the UF; and (3) an all on scenario (i.e., all three prostaglandin products included on the UF) was less cost effective than a scenario where at least one prostaglandin was designated non-formulary.

The results from the CMA of the topical beta-blockers showed that the majority of these products were cost effective. Only two products were identified as not cost effective in the beta-blocker subclass. Timolol hemihydrate and timolol maleate (Istalol) were both shown to be significantly more costly and no more effective than other agents in the subclass. Similarly, a comparison of the topical carbonic anhydrase inhibitors showed that brinzolamide was not cost effective compared to dorzolamide. All other medications in the remaining subclasses were determined to be cost effective relative to their comparators.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the P&T Committee in determining which group of ophthalmic glaucoma agents would best meet the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to accept the cost effectiveness conclusions stated above.

C. Ophthalmic Glaucoma Agents – UF Recommendations

COMMITTEE ACTION: In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ophthalmic glaucoma agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend that latanoprost, bimatoprost, levobunolol, betaxolol (Betoptic, generics; Betoptic-S), carteolol, metipranolol, timolol maleate (Timoptic, generics), timolol maleate gel-forming solution (Timoptic XE, generics), brimonidine (generics; Alphagan P), apraclonidine, dorzolamide, dorzolamide/timolol (Cosopt), dipivefrin (Propine), acetylcholine (Miochol-E), carbachol (Isopto Carbachol), pilocarpine (Pilopine HS gel; Pilocar, generics), echothiophate (Phospholine Iodide) be maintained as formulary on the UF and that travoprost (Travatan, Travatan Z), timolol hemihydrate (Betimol), timolol maleate (Istalol) and brinzolamidebe classified as non-formulary under the UF.

D. Ophthalmic Glaucoma Agents – MN Criteria

Based on the clinical evaluation for travoprost (Travatan, Travatan Z), timolol hemihydrate, timolol maleate (Istalol) and brinzolamide, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T

Committee recommended the following general MN criteria for travoprost (Travatan, Travatan Z), timolol hemihydrate, timolol maleate (Istalol) and brinzolamide:

1) Formulary alternatives are contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Use of formulary alternatives has resulted in therapeutic failure.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. Ophthalmic Glaucoma Agents – UF Implementation Period

Because of the small number of unique utilizers affected (approximately 17,000 patients [15%] of approximately 111,000 unique utilizers at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have travoprost (Travatan, Travatan Z), timolol hemihydrate, timolol maleate (Istalol) and brinzolamide on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary glaucoma agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. Ophthalmic Glaucoma Agents – BCF Review and Recommendations – The P&T Committee considered the BCF status of the ophthalmic glaucoma agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that the BCF include latanoprost; brimonidine, excluding the 0.1% strength; timolol maleate (Timoptic, generics) 0.25% and 0.5%; timolol maleate gel-forming solution 0.25% and 0.5%; and pilocarpine.

9. DRUG CLASS REVIEW – MAOI ANTIDEPRESSANTS

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the MAOI antidepressants marketed in the U.S. The drugs in the MAOI antidepressant class include three oral agents, isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate, generics); and one transdermal patch, selegiline (Emsam). Tranylcypromine is the only drug in the MAOI antidepressant class available in a generic formulation. All of the drugs are available in oral dosage forms; however, oral selegiline capsules are excluded from the review, since they are indicated for use in Parkinson's disease and not depression. The three oral MAOI antidepressants were first introduced to

the market in the early 1960s, while transdermal selegiline was launched in 2006. The MAOI antidepressants accounted for approximately $283,000 dollars spent in FY 2006 wresp, which amounts to less than 1% of total MHS expenditures for all antidepressant drug classes.

A. MAOI Antidepressants – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the MAOI antidepressant agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

1) Pharmacology

There are two MAOI enzymes. Inhibition of MAO-B enzyme in the CNS leads to decreased metabolism of norepinephrine, dopamine and serotonin. Inhibition of MAO-A enzyme in the gastrointestinal tract results in decreased catabolism of tyramine, which can increase blood pressure. Patients taking MAOI anti-depressants who do not restrict dietary sources of tyramine can potentially develop hypertensive crisis. Theoretically, administering an MAOI anti-depressant via the transdermal route would obviate the need for strict dietary precautions.

2) Efficacy for Atypical Depression and Major Depressive Disorder (MDD)

a) FDA-approved indications

The three oral MAOI antidepressants, isocarboxazid, phenelzine, and tranylcypromine, are FDA-approved to treat either atypical depression or MDD. The selegiline transdermal patch is indicated only for treatment of MDD.

b) Efficacy measures

The Hamilton Rating Scale for Depression (HAM-D) is the most widely used observer-rated scale that assesses the symptoms and severity of depression. In efficacy trials for the MAOI antidepressants, a 50% reduction in the HAM-D from baseline was considered a response to treatment. Remission refers to reduction in the HAM-D score below a specific cut-off score.

c) Efficacy of oral MAOI antidepressants

i) Meta-analysis – One meta-analysis [Thase *et al.*, 1995] evaluated 55 RCTs (published from 1959 through 1992) that focused on depressive disorders in adults in the outpatient setting. The trials evaluated the efficacy of isocarboxazid, phenelzine, and tranylcypromine.

There were no apparent differences in the overall efficacy between isocarboxazid (60% ± 7%), phenelzine (58% ± 4%), and tranylcypromine (53% ± 12%). Limitations to the meta-analysis included differences in trial methodologies and patient populations between trials and the fact that evaluated studies were from approximately 30 years ago.

ii) Head-to-head clinical trial – One head-to-head trial compared the efficacy of phenelzine and tranylcypromine in 77 inpatients with antidepressant-refractory depression [Birkenhager *et al.*, 2004]. A response to therapy occurred in 44% (17/39) of the patients receiving tranylcypromine, and 47 % (18/38) of the patients randomized to phenelzine (p=0.82). Only 18% (7/39) of the tranylcypromine-treated patients and 11% (4/38) of the phenelzine-treated patients met criteria for remission (p=0.52). This trial had limited power to detect a difference between the two drugs and was conducted in the inpatient setting.

d) Efficacy of transdermal selegiline

Three published placebo-controlled trials lasting six to eight weeks and one open-label trial lasting 52 weeks evaluate the efficacy of the transdermal selegiline formulation. There are no comparative trials evaluating efficacy differences between transdermal selegiline and any of the three oral MAOI antidepressant or other antidepressants (e.g., TCAs, SSRIs).

i) Placebo-controlled trials – In the first trial, a response to therapy occurred in 38% of patients receiving transdermal selegiline 6 mg/24 hr, compared to 23% receiving placebo (p=0.01); remission occurred in 23% of the patients treated with the patch compared to 11 % with placebo (p=0.05) [Bodkin *et al.*, 2002]. In the second trial, response rates ranged from 32% to 33% with transdermal selegiline 6 mg/24 hr, versus 21% to 30% with placebo [Amsterdam *et al.*, 2003]. In the third trial [Fieger *et al.*, 2006], the response rate was 40% with transdermal selegiline (flexible dosing up to 12 mg/24 hr) versus 30% with placebo (p value not significant)

ii) Open label extension trial – In an open label extension trial enrolling 600 patients who had previously responded to transdermal selegiline, 17% of patients randomized to the patch relapsed after one year, compared to 31% of placebo-treated patients (p=0.003).

e) Clinical efficacy conclusion

A meta-analysis comparing the three oral MAOIs reported similar overall efficacy rates of 58% with phenelzine, 60% with isocarboxazid, and 53% with tranylcypromine in the outpatient setting. One trial conducted in an inpatient population found no statistically significant difference between phenelzine and tranylcypromine in response or remission rates. For transdermal selegiline, three placebo controlled trials are available. The response rates with transdermal selegiline ranged from 30% to 40%, compared to 21% to 30% with placebo.

3) Safety and Tolerability

a) *Minor adverse events* – The most common adverse effects of the oral MAOI antidepressants are orthostatic hypotension, dizziness, edema, tremor, insomnia, mydriasis, and anorgasmia. There are no data to suggest that one oral MAOI antidepressant is more likely than another to be associated with minor adverse effects.

Mild to moderate local irritation at the application site occurred in 15% to 36% of patients receiving transdermal selegiline in the placebo controlled trials. As with the oral MAOI antidepressants, insomnia and orthostatic hypotension are also concerns, with higher incidences reported with the 9 mg/24 hr and 12 mg/24 hr strengths.

b) *Serious adverse events* – As a class, the MAOI antidepressants have the potential for causing serotonin syndrome when administered with other serotonergic drugs or when dietary precautions are not followed. Deaths have been reported with the oral MAOI antidepressants due to both drug-drug and drug-food interactions. The MAOI antidepressants are considered third-line agents due to their adverse effect profile. To date there have been no deaths or other life-threatening events including hypertensive crisis attributed to transdermal selegiline in the controlled setting of the clinical trials.

c) *Drug-food interactions* – Consumption of tyramine-containing foods (e.g., aged meats, aged cheeses) and beverages (e.g., non-pasteurized beers) while taking any MAOI may result in hypertensive crisis. The lowest dosage strength of transdermal selegiline (6 mg/24 hr) is the only dosage where dietary tyramine restrictions are not required in the product labeling. A tyramine-restricted diet is required with all oral MAOIs and with the 9 mg/24 hr and 12 mg/24 hr strengths of transdermal selegiline. Most patients are likely to require the higher strengths of transdermal selegiline for MDD.

d) *Drug-drug interactions* – As a class, the oral MAOI antidepressants are associated with several well known and clinically important drug-drug interactions. The same extensive list of drug-drug interactions also applies to transdermal selegiline. Concomitant use of any MAOI antidepressant, including transdermal selegiline, is contraindicated with meperidine, tramadol, methadone, propoxyphene, dextromethorphan, cyclobenzaprine, carbamazepine, other MAOIs, SSRIs, and amphetamine derivatives.

e) *Withdrawal due to adverse events* – Differences in tolerability profiles between the three oral MAOI antidepressants are difficult to determine, as the available clinical trials used less rigorous study design than is standard today.

In the three short-term (6- to 8-week) placebo controlled trials evaluating transdermal selegiline, 6% (23/370) of patients randomized to the patch discontinued therapy due to an adverse event, compared to 4% (16/373) of subjects in the placebo groups. Application site reactions were the most common reason for discontinuation. In the 52-week open label trial,

discontinuation rates due to application site reactions were 15% with transdermal selegiline versus 4% with placebo.

f) Safety and tolerability conclusion – The MAOI antidepressants as a class are associated with several serious adverse events. Hypertensive crisis and risk of death due to dietary and drug-drug interactions are well-publicized. In the placebo controlled trials with transdermal selegiline, a high incidence of local patch irritation was reported. Dietary restrictions are required with all oral MAOIs and with the 9 mg/24 hr and 12 mg/24 hr strengths of transdermal selegiline. There are no head-to-head trials comparing the safety and tolerability profiles of transdermal selegiline versus the oral MAOIs.

4) Other factors

a) Available dosage formulations – Transdermal selegiline is the only MAOI antidepressant available in a non-oral dosage formulation. Transdermal selegiline would be preferred over the oral MAOI antidepressants in patients with dysphagia.

b) Dosing frequency – Transdermal selegiline and tranylcypromine are the only MAOI antidepressants that are dosed once daily. Isocarboxazid and phenelzine require dosing twice to three times daily.

c) Potential for off-label uses – The oral MAOI antidepressants have many off-label uses other than depression, including panic disorder and social anxiety disorder. Oral selegiline is currently used in conjunction with carbidopa-levodopa in Parkinson's Disease. Transdermal selegiline is currently undergoing Phase II trials to evaluate efficacy for depression in patients with Parkinson's Disease, but no peer-reviewed studies have been published.

d) Pregnancy – The oral MAOI antidepressants and transdermal selegiline are contraindicated for use during pregnancy; however, there are published reports of the use of phenelzine and tranylcypromine in pregnant patients with severe depression.

e) Pediatrics – The three oral MAOI antidepressants and transdermal selegiline are not approved for use in children younger than 16 years of age.

f) Other factors conclusion – There are only minor differences in other factors for the MAOIs, including dosing frequency, availability of non-oral dosage formulations, and potential for off-label uses.

MAOI Antidepressant Overall Clinical Effectiveness Conclusion – The P&T Committee concluded that:

1) The oral MAOI antidepressants isocarboxazid, phenelzine, and tranylcypromine have been marketed for several decades, but have been replaced by newer drug classes (e.g., SSRIs) with more favorable adverse event profiles.

2) Transdermal selegiline is the newest MAOI antidepressant marketed. The non-oral formulation was developed to reduce the risk of hypertensive crisis from tyramine.

3) There do not appear to be major differences in clinical efficacy between the three oral MAOIs when used for depression, based on the results of one meta-analysis showing response rates ranging between 53% to 61%, and one inpatient clinical trial.

4) Overall, response rates ranging from 27% to 30% were reported with transdermal selegiline in three placebo controlled trials. There are no clinical trials directly comparing the oral MAOI antidepressants with transdermal selegiline However, there are no data to suggest that treatment with transdermal selegiline would result in improved response rates compared to the oral MAOI antidepressants.

5) The MAOI antidepressants have a safety profile that is well recognized in terms of drug-drug and drug-food interactions, and these adverse events also apply to transdermal selegiline. Local application site reactions are common with transdermal selegiline.

6) The purported benefits of transdermal selegiline in terms of loosened dietary tyramine restrictions have only been shown clinically with the lowest dose (6 mg/24 hr). Dietary precautions are required with oral MAOIs and with the 9 mg/24 hr and 12 mg/24 hr dosages of transdermal selegiline.

7) Off-label usage of transdermal selegiline is anticipated for treating patients with Parkinson's Disease.

8) The primary advantage of transdermal selegiline is for patients unable to swallow oral medications and require a once-daily dosage formulation.

9) There is insufficient evidence to determine whether transdermal selegiline represents a therapeutic advance over isocarboxazid, phenelzine and tranylcypromine.

10) Based on clinical issues alone, there are no reasons to designate any of the MAOIs (phenelzine, isocarboxazid, or tranylcypromine, and transdermal selegiline) as non-formulary on the Uniform Formulary.

COMMITTEE ACTION – The P&T Committee voted (16 for, 0 opposed, 1 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

B. MAOI Antidepressants – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the MAOI antidepressants in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e) (2). Given the overall clinical conclusion that the agents within the MAOI class have similar relative clinical effectiveness, a CMA was employed to assess the relative cost effectiveness of the agents within this therapeutic class. The agents were evaluated on their weighted average cost per day of therapy across all three points of service.

Results of the CMA for the MAOI class showed that:

1) Among the oral agents, phenelzine was the most cost effective agent, followed closely by tranylcypromine and isocarboxazid.

2) Transdermal selegiline was the least cost effective MAOI for the treatment of depression. The weighted average cost per day of treatment with transdermal selegiline was four-fold higher than the most costly oral MAOI, isocarboxazid.

Cost Effectiveness Conclusion

1) The oral MAOIs demonstrate similar relative cost effectiveness, with phenelzine as the most cost effective agent.

2) Transdermal selegiline is not cost effective relative to the other agents in the class in the treatment of depression and provides no clinically meaningful therapeutic advantage to justify the increased cost.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the cost effectiveness conclusions stated above.

C. MAOI Antidepressants – UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the MAOIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that phenelzine, tranylcypromine and isocarboxazid be maintained as formulary on the UF and that transdermal selegiline be classified as non-formulary under the UF.

D. MAOI Antidepressants – MN Criteria

Based on the clinical evaluation for transdermal selegiline and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for transdermal selegiline:

1) Use of formulary alternatives is contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.

3) Use of formulary alternatives has resulted in therapeutic failure.

4) The patient previously responded to a *non-formulary* pharmaceutical agent and changing to a formulary pharmaceutical agent would incur an unacceptable clinical risk.

5) No formulary alternative is available.

The P&T Committee noted that criterion #5 would only apply to patients unable to take oral medications.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. MAOI Antidepressants – UF Implementation Period

Because of the small number of unique utilizers affected (approximately 135 patients per quarter at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The

implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have transdermal selegiline on their local formularies. MTFs will be able to fill non-formulary requests for this agent only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary MAOI antidepressant agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. MAOI Antidepressant – ECF Review and Recommendations

The P&T Committee had previously determined at the November 2006 P&T Committee meeting that one MAOI antidepressant should be added to the ECF based on the clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that phenelzine be classified as the ECF agent. Phenelzine was determined to be the most cost effective MAOI and currently has the greatest utilization across the MHS.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend phenelzine be classified as the ECF agent.

10. CLASS OVERVIEWS

Portions of the clinical reviews for the ophthalmic non-steroidal anti-inflammatory agents (Ophthalmic NSAIDs) and erythropoiesis stimulating agents (ESAs) were presented to the P&T Committee.

The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed during the May 2007 or August 2007 meetings; no action is necessary.

11. ADJOURNMENT

The second day of the meeting adjourned at 1430 hours on 14 February 2007. The next meeting will be 13-15 May 2007.

_____//signed//_____

Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem)	BCF	▪ zolpidem IR (Ambien)	Pending approval	Pending approval
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	Pending approval	Pending approval
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	Pending approval	Pending approval
Feb 07	MAOI Antidepressants	▪ transdermal selegiline (Emsam)	ECF	▪ phenelzine (Nardil)	Pending approval	Pending approval
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	NA
Nov 06	ADHD	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR	17 Jan 07	18 Apr 07 (90 days)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
May 06 (updated for new drugs Nov 06)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospironone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	24 Jan 07 (to coincide with May 06 meeting decision)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide / Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated for new drugs Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
		Recommended Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			17 Jan 07	21 Feb 07 (30 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications)	**Effective Date for Non-Formulary Medications** (Implementation period)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-
Feb 05	ARBs	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary

ER = extended release; IR = immediate release; SR = sustained release

ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs = thiazolidinediones

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs. February 2007 DoD P&T Committee Meeting

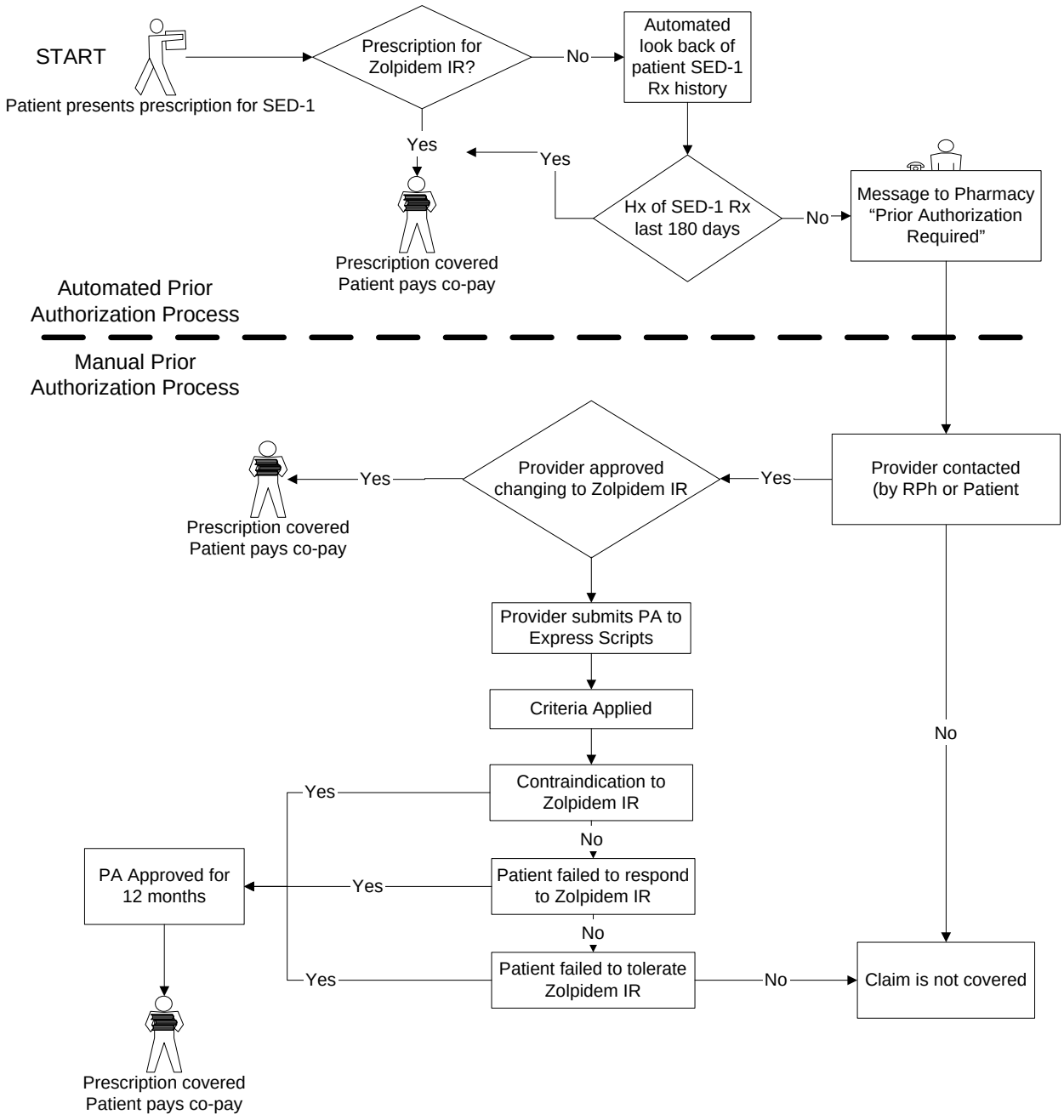
Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Sitagliptin phosphate tablets (Januvia ;Merck) Oral hypoglycemic drug (dipeptidyl peptidase IV [DPP4] inhibitor)	Oct 06 (launched Nov 06) ▪ For use as monotherapy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus ▪ For use in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, or a thiazolidinediones when the single agent alone, with diet and exercise, does not provide adequate glycemic control. ▪ Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings	No UF recommendation at this meeting. Consideration of UF status deferred until oral hypoglycemic drugs are reviewed; UF review not anticipated for 12 months.
Paliperidone extended release tablets (Invega; Janssen/ALZA)) Atypical antipsychotic	Dec 06 (launched Jan 07) ▪ Treatment of schizophrenia ▪ Efficacy in acute treatment of schizophrenia established in three 6-week, placebo controlled, fixed-dose trials in subjects with schizophrenia. ▪ Efficacy not evaluated in placebo-controlled trials for longer than six weeks; physicians electing to use paliperidone for extended periods should periodically re-evaluate long-term usefulness	No UF recommendation at this meeting. Consideration of UF status deferred until atypical antipsychotics are reviewed; UF review not anticipated for 12 months.

Appendix C – Table 3. Table of Abbreviations

AHRQ	Agency for Healthcare Research and Quality
APAP	acetaminophen
ASA	aspirin
BAK	benzalkonium chloride
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
CFR	Code of Federal Regulations
CMA	cost minimization analysis
CNS	central nervous system
CYP	cytochrome P450
DEA	Drug Enforcement Agency
DERP	Drug Effectiveness Review Project
DoD	Department of Defense
ECF	Extended Core Formulary
ER	extended release
ESA	erythropoiesis stimulating agents
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FY	fiscal year
GABA	gamma-aminobutyric acid
HAM-D	Hamilton Rating Scale for Depression
IOP	intraocular pressure
IR	immediate release
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MHS	Military Health System
MTF	military treatment facility
NNH	number-needed-to-harm
NNT	number-needed-to-treat
NSAIDs	non-steroidal anti-inflammatory drugs
OTC	over-the-counter
PA	prior authorization
P&T	Pharmacy and Therapeutics
PDTS	Pharmacy Data Transaction Service
PEC	Pharmacoeconomic Center
PPI	proton pump inhibitor
RCT	randomized controlled trial
SED-1s	newer sedative hypnotics
SSRIs	selective serotonin reuptake inhibitors
TCAs	tricyclic antidepressants
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
UF	Uniform Formulary

Appendix D – Figure 1. Prior Authorization Process for SED-1 Agents Other than Zolpidem IR (Ambien)

Figure 1. TRICARE Pharmacy Network Step Therapy Process
Newer Sedative Hypnotics (SED-1)



DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

November 2006

1. **CONVENING**
2. **ATTENDING**
3. **REVIEW MINUTES OF LAST MEETING**
4. **ITEMS FOR INFORMATION**
5. **REVIEW OF RECENTLY APPROVED AGENTS**

Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF): The P&T Committee was briefed on four new drugs approved by the Food and Drug Administration (FDA) that did not fall under drug classes previously reviewed for UF consideration. The committee discussed the need for quantity limits and prior authorization (PA) for two of the new drugs, human insulin inhalation powder (Exubera) and fentanyl buccal tablets (Fentora); there are existing quantity limits for other inhaled products and fentanyl lozenges. No recommendations were made for human insulin inhalation powder, as typical dosage requirements and utilization are unclear at this time. The Committee deferred a decision on quantity limits for fentanyl buccal tablets until the narcotic analgesic class is reviewed at an upcoming meeting.

Contraceptive Agents 30/10 mcg ethinyl estradiol (EE)/0.15 mg levonorgestrel for extended use, (Seasonique), and 20 mcg ethinyl estradiol (EE)/1 mg norethindrone acetate – 24 day regimen, (Loestrin 24 Fe).

Background: Two new contraceptive products, Seasonique and Loestrin 24 Fe, have been marketed since the contraceptive drug class was reviewed in May 2006.

Seasonique - Seasonique is a monophasic oral contraceptive with 30 mcg of EE specifically packaged and labeled for extended cycle use (84 days of 30 mcg EE/0.15 mg levonorgestrel, followed by seven days of low-dose estrogen [10 mcg EE]). The rationale for providing seven days of 10 mcg EE instead of placebo is to reduce symptoms associated with estrogen withdrawal, including dysmenorrhea, menstrual migraine, and premenstrual syndrome, although this has not been evaluated in a prospective, randomized, controlled trial.

The difference between Seasonale, a non-formulary (third) tier agent, and Seasonique is the substitution of seven low-dose estrogen (10 mcg EE) tablets in Seasonique for the seven placebo tablets in Seasonale. For this reason, Seasonique's regimen cannot be exactly duplicated by using conventional packages of Nordette or its equivalents and discarding unneeded placebo tablets, unlike Seasonale. With respect to efficacy in preventing pregnancy, there is no reason to believe that Seasonique would differ from other similar oral contraceptives.

Loestrin 24 FE: Loestrin 24 Fe is a monophasic oral contraceptive product with 20 mcg EE packaged as a 24-day regimen (24 days of 20 mcg EE /1 mg norethindrone followed by four days of placebo tablets).

The rationale for a 24- rather than a 21-day regimen is to decrease the number of bleeding days and reduce adverse events associated with estrogen withdrawal. It is also possible that a longer regimen would increase the safety margin for contraceptive effectiveness with low estrogen products; however, there is no supporting clinical evidence. An alternative using conventionally packaged Loestrin Fe 1/20 that may accomplish the same general goal would be to simply start a new package early.

Relative Clinical Effectiveness Conclusion: The Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that Seasonique and Loestrin 24 Fe do not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome, over the other oral contraceptives included on the UF.

Relative Cost Effectiveness Conclusion: Cost minimization analysis (CMA) showed that Seasonique is less cost-effective on a per cycle basis than all UF oral contraceptives containing 30 mcg EE and Loestrin 24 Fe is less cost-effective on a per cycle basis than all UF oral contraceptives containing 20 mcg EE. Based on the results of the CMAs and other clinical and cost considerations, the Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that Seasonique and Loestrin 24 Fe are substantially more costly than other oral contraceptives containing 30 mcg EE or 20 mcg EE included on the UF.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for Seasonique and Loestrin 24 Fe, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that Seasonique and Loestrin 24 Fe be classified as non-formulary under the UF. (See paragraphs 5B1, 5B2 and 5B3 on pages 14-16 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MEDICAL NECESSITY CRITERIA – Based on the clinical evaluation of Seasonique and Loestrin 24 Fe and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) medical necessity criteria for the contraceptive agents. (See paragraph 5B4 on page 17 of the P&T Committee minutes for the criteria).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 5B5 on page 17 of the P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows: *"Implement January 24, 2007"*

Topical antifungal agents – 0.25% miconazole, 15% zinc oxide, 81.35% white petrolatum ointment (Vusion)

Background: The topical antifungal agents were reviewed by the Committee in Aug 2005. A new ointment containing 0.25% miconazole, 15% zinc oxide, and 81.35% white petrolatum (Vusion) has been approved by the FDA. Vusion contains a much lower concentration of miconazole than other prescription and OTC miconazole products (0.25% vs. 2%) and is only available in an ointment formulation.

Vusion is specifically labeled for the adjunctive treatment of diaper dermatitis only when complicated by microscopically-documented candidiasis in immunocompetent pediatric patients four weeks and older.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that although Vusion is labeled for a specific type of diaper dermatitis in infants as young as four weeks of age, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome, over the other topical antifungals included on the UF.

Relative Cost Effectiveness Conclusion: CMA showed that Vusion is the least cost-effective of all comparators, including other antifungals commonly used for diaper rash, when analyzed on a cost per utilizer basis. Based on the results of the CMA and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that Vusion is substantially more costly than other antifungals commonly used for the treatment of the same condition.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determination for Vusion, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that Vusion be classified as non-formulary under the UF. (See paragraphs 5C1, 5C2 and 5C3 on pages 17-19 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MEDICAL NECESSITY CRITERIA – Based on the clinical evaluation of Vusion and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) medical necessity criteria for Vusion. (See paragraph 5C4 on page 19 of the P&T Committee minutes for the criteria).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 5C5 on page 19 of the P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows: *"Implement in 30 days."*

Antiemetic Agents - Nabilone (Cesamet)

Background: The Committee previously reviewed the antiemetic agents in May 2006. Nabilone is a synthetic cannabinoid antiemetic similar to dronabinol. Nabilone is indicated for treatment of chemotherapy-induced nausea and vomiting when conventional antiemetics have failed. There are no published clinical trials comparing nabilone with dronabinol, or with the 5-hydroxytryptamine-3 (5-HT3) antagonists.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that while nabilone offers a slight convenience of dosing frequency compared to dronabinol, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over the other antiemetics included on the UF.

Relative Cost Effectiveness Conclusion: CMA showed that nabilone has a cost-effectiveness profile that is similar to dronabinol. Based on the results of the CMA and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that nabilone is comparable in cost to dronabinol, a similar cannabinoid antiemetic included on the UF.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for nabilone, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that nabilone be classified as formulary on the UF.

(See paragraphs 5D1, 5D2 and 5D3 on pages 20-21 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

6. DRUG CLASS REVIEW – OLDER SEDATIVE HYPNOTICS (SED-2s)

The P&T Committee evaluated the relative clinical effectiveness of the Older Sedative/Hypnotic (SED-2) Medications. The SED-2 drug class is comprised of five hypnotic benzodiazepines: estazolam, flurazepam, quazepam, temazepam, and triazolam; two barbiturate hypnotics: butabarbital and secobarbital; and one nonbarbiturate hypnotic agent: chloral hydrate. All eight of these drugs have been marketed for a number of years, and all but quazepam, butabarbital, and two less commonly used strengths of temazepam are available in generic formulations. The SED-2 drug class accounted for $2.5 million in Military Health System (MHS) expenditures for the period Aug 2005 to July 2006 and is ranked #165 in terms of total expenditures during that time period.

Relative Clinical Effectiveness Conclusion: The Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) The five hypnotic benzodiazepines (estazolam, flurazepam, quazepam, temazepam, and triazolam) are widely considered interchangeable for the treatment of short-term insomnia when used in equipotent doses, despite differences in onset and duration of action.
2) Temazepam is the most desirable benzodiazepine in the SED-2 drug class, based on clinical factors (duration of action, tolerance to therapeutic effects, adverse effect profile).
3) The hypnotic barbiturates, secobarbital and butabarbital, have fallen out of favor compared to newer therapies, primarily due to safety concerns, and are infrequently utilized at any MHS point of service.
4) Chloral hydrate appears to have a unique niche in the setting of outpatient pediatric sedation.
5) There are no clinical reasons to justify designating any of the SED-2s as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: Based on the results of the CMA and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) Secobarbital, chloral hydrate, flurazepam, temazepam 15 and 30 mg, estazolam, and triazolam have similar relative cost-effectiveness.
2) Butabarbital, quazepam, and temazepam 7.5 and 22.5mg are more costly relative to the other agents in the class, but placing these agents in the non-formulary tier of the UF would achieve little savings due to current and projected low utilization.

A. COMMITTEE ACTION: UF RECOMMENDATION **-** Taking into consideration the conclusions from the relative clinical effectiveness and relative cost

effectiveness determinations for the SED-2s, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that estazolam, flurazepam, quazepam, temazepam, triazolam, butabarbital, secobarbital, and chloral hydrate be maintained as formulary on the UF, and that none of the SED-2s be classified as non-formulary under the UF. (See paragraphs 6A, 6B and 6C on pages 22-24 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: BASIC CORE FORMULARY (BCF) RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend retaining the generically available strengths of temazepam (15 mg and 30 mg) as the BCF selections in this class, excluding the 7.5 mg and 22.5 mg proprietary dosage strengths. (See paragraph 6F on page 25 of the P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

7. DRUG CLASS REVIEW – ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY AGENTS

The drugs in the Attention-Deficit / Hyperactivity Disorder (ADHD) and Narcolepsy Agents class are comprised of the following: for ADHD, there is one non-stimulant: atomoxetine (Strattera) and five stimulant compounds: methylphenidate, mixed amphetamine salts, dexmethylphenidate, dextroamphetamine, and methamphetamine; for narcolepsy, there are two drugs: modafinil (Provigil) and sodium oxybate (Xyrem). The ADHD and Narcolepsy Agents accounted for approximately $84.5 million dollars in MHS expenditures for Fiscal Year (FY) 2006 and are ranked #16 in terms of total expenditures during that time period.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the following:

1) For ADHD, interpretation of the data is limited due to the poor quality of studies, limited number of comparator trials, varying rating scales used, small number of patients enrolled, and short study duration.

2) There is no evidence to suggest a difference in efficacy between immediate release (IR) formulations of methylphenidate, dextroamphetamine, dexmethylphenidate, and mixed amphetamine salts.

3) The overall efficacy of the once daily methylphenidate formulations appears similar based on a few small studies, but differences exist in reported outcomes at specific times of the day, due to the individual release mechanisms of the

products. Methylphenidate 30% IR/70% extended release (ER) (Metadate CD) and methylphenidate SODAS (Ritalin LA) are eight- to nine-hour products, while methylphenidate OROS (Concerta), dexmethylphenidate SODAS (Focalin XR), and methylphenidate transdermal system (Daytrana) are 12-hour products.

4) Mixed amphetamine salts extended release (ER) (Adderall XR) appears to have similar efficacy to methylphenidate OROS (Concerta), based on one small study.

5) The efficacy of atomoxetine appears to be inferior to the stimulants, but it is the only non-stimulant available in the ADHD class.

6) Between 40% and 80% of patients who do not respond to one type of stimulant (methylphenidate products vs. amphetamine products) may respond to the other.

7) The adverse events and warnings of the stimulants are well-recognized and are similar between products.

8) The methylphenidate transdermal system can cause significant dermatological adverse events, which can lead to sensitization to oral products.

9) Atomoxetine remains the only alternative for patients who cannot tolerate stimulants, despite its association with an increased risk of hepatotoxicity and suicidal ideation.

10) Several products can be sprinkled on food for patients with swallowing difficulties.

11) Responders to a provider survey expressed a desire for availability of the following products to cover clinical needs: methylphenidate OROS, an IR methylphenidate product, mixed amphetamine salts ER, and atomoxetine.

12) The narcolepsy drug modafinil provides a unique niche in therapy as a wakefulness promoting agent.

13) The narcolepsy drug sodium oxybate has a high incidence of adverse events, but serves a unique niche in therapy for cataplexy. The manufacturer's restricted distribution program limits use to appropriate patients.

14) Based on clinical issues alone, there are no reasons to designate any of the ADHD drugs or narcolepsy drugs as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: Based on the results of the cost analysis (CMA) and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) Once daily ADHD agents: dexmethylphenidate SODAS (Focalin XR) and methylphenidate transdermal system (Daytrana) were not cost-effective relative to the other agents in the subclass.

2) Multiple daily use ADHD agents: dexmethylphenidate IR (Focalin) was not cost-effective relative to the other agents in the subclass.

3) Agents indicated in the treatment of narcolepsy: Although modafinil (Provigil) and sodium oxybate (Xyrem) were more costly relative to other agents indicated for the

treatment of narcolepsy, they possessed unique clinical advantages relative to other agents within the class.

A. COMMITTEE ACTION: UF RECOMMENDATION **-** Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ADHD and narcolepsy agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that mixed amphetamine salts IR (Adderall, generics), mixed amphetamine salts ER (Adderall XR), atomoxetine (Strattera), dexamphetamine IR (Dexedrine, Dextrostat, generics), methamphetamine IR (Desoxyn, generics), methylphenidate 30% IR/70% ER (Metadate CD), methylphenidate IR (Ritalin, generics), methylphenidate OROS (Concerta), methylphenidate SODAS (Ritalin LA), methylphenidate sustained-release (SR) (Ritalin SR), modafinil (Provigil), and sodium oxybate (Xyrem) be maintained as formulary on the UF and that dexmethylphenidate IR (Focalin), dexmethylphenidate SODAS (Focalin XR), and methylphenidate transdermal system (Daytrana) be classified as non-formulary under the UF. (See paragraphs 7A, 7B and 7C on pages 25-39 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MEDICAL NECESSITY CRITERIA **-** Based on the clinical evaluation for methylphenidate transdermal system (Daytrana), dexmethylphenidate IR (Focalin), and dexmethylphenidate SODAS (Focalin XR), and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) medical necessity criteria for methylphenidate transdermal system (Daytrana), dexmethylphenidate IR (Focalin) and dexmethylphenidate SODAS (Focalin XR). (See paragraph 7D on page 39-40 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD **-** The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 7E on page 40 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION - The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend retaining mixed amphetamine salts ER (Adderall XR), methylphenidate OROS (Concerta), and methylphenidate IR (Ritalin, generics) as the BCF selections in this class. (See paragraph 7F on page 40 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

8. PRIOR AUTHORIZATION REQUIREMENT (PA) FOR MODAFINIL (PROVIGIL)

The P&T Committee agreed that a PA was needed for modafinil, due to the potential for inappropriate use.

COMMITTEE ACTION – Based on its increasing use for off-label indications not well established by the medical literature, the P&T Committee recommended that a PA be required for modafinil (15 for, 0 against, 0 abstained, 2 absent). The Committee recommended that the PA should have an effective date of the first Wednesday following a 90-day implementation period, consistent with the recommended implementation period for non-formulary medications in the ADHD and narcolepsy agents class. The implementation period will begin immediately following approval by the Director, TMA. The Committee voted (15 for, 0 against, 0 abstained, 2 absent) to recommend PA criteria. (See paragraph 8 on pages 40-42 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

9. PA REQUIREMENT FOR FENTANYL PATCHES (DURAGESIC, GENERICS)

COMMITTEE ACTION – Based on safety concerns, the P&T Committee recommended that a PA be required for fentanyl patches (15 for, 0 against, 0 abstained, 2 absent). The criteria recommended by the P&T Committee are based on safety requirements in labeling and incorporate modifications to the Pharmacy Data Transaction Service (PDTS) that will allow automation of some PA criteria, reducing paperwork burden and cost. These modifications are scheduled for completion by December 2006. (See pages 41-43 of the P&T Committee minutes for rationale and summary of PA criteria.) The P&T Committee recommended that the PA should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible based on availability of the automated PA capability in PDTS. (See paragraph 9 on pages 42-43 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

Appendix A – Table 1. Implementation Status of UF Recommendations/Decisions

Appendix B – Table 2. Newly Approved Drugs

Appendix C – Table 3. Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____signed_____

William Winkenwerder, Jr., M.D.
Date: 17 January 2007