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 on 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.

S. Ward Casscells, M.D.

13 Feb '08

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.

Patricia Buss

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

28 January 2008

Executive Summary

UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL COMMENTS
January 2008

The Uniform Formulary (UF) Beneficiary Advisory Panel (BAP) commented on the recommendations from the DoD Pharmacy & Therapeutics (P&T) Committee November 2007 meeting.

Comment from the Chairman of the Panel. (The following comments pertained to the announcement made by Major Watson concerning the death of one of the panel members, Dr. Jeffrey Lenow.) On behalf of the Panel, Chairman Washington recognized with appreciation Dr. Lenow's many and valuable contributions to the BAP's deliberations since its establishment and noted how much they would be missed.

1. **Adrenergic Beta-Blocking (ABAs) Drug Class:** The P&T Committee recommended the following:

"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 to recommend that:

Atenolol (Tenormin, generics), atenolol-chlorthalidone (Tenoretic, generics), metoprolol (Lopressor, generics), metoprolol succinate (Toprol XL, generics), propranolol (Inderal, generics), propranolol-HCTZ (Inderide, generics), propranolol extended release (Inderal LA, generics), timolol (Blocadren, generics), timolol/HCTZ (Pimozide), bisoprolol (Zebeta, generics), bisoprolol/HCTZ (Ziac, generics), nadolol (Corgard, generics), nadolol/bendroflumethiazide (Corzide, generics), acebutolol (Sectral, generics), betaxolol (Kerlone, generics), penbutolol (Levatol, generics), carvedilol IR (Coreg IR, generics), and carvedilol extended release (Coreg CR) be designated formulary on the UF.

Because all agents in the ABA drug class were recommended for inclusion on the Uniform Formulary, no implementation recommendations were necessary.

Summary of Panel Vote/Comments:

- The Panel voted 9 Concur, 0 Non-Concur regarding the recommendations for formulary and non-formulary agents.

Director, TMA:

☑ These comments were taken under consideration prior to my final decision.

2. **BPH Alpha Blockers (BPH-ABs):** The P&T Committee recommended that:

1) Alfuzosin (Uroxatral) be maintained as the uroselective formulary AB, and that terazosin (Hytrin, generics) and doxazosin (Cardura, generics) be maintained as the non-uroselective fomulary ABs.

2) Tamsulosin (Flomax) be classified as non-formulary under the UF with a PA requiring a trial of alfuzosin (Uroxatral) for new patients.

The P&T Committee recommends 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 (TRRx), and at the Military Treatment Facilities (MTF) no later than a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

Summary of Panel Vote/Comments:

- The Panel voted 8 Concur, 0 Non-Concur and 1 Abstain regarding the recommendations for formulary and non-formulary agents.
- The Panel voted 7 Concur, 1 Non-Concur and 1 Abstain regarding the recommended implementation period of 60 days.

Director, TMA:

☑ These comments were taken under consideration prior to my final decision.

3. **Targeted Immunomodulatory Biologics (TIBs):** The P&T Committee recommended that Humira, Raptiva and Amevive be maintained as formulary on the UF and that Enbrel and Kineret be classified as non-formulary under the UF.

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.

Summary of Panel Vote/Comments:

- The Panel voted 5 Concur, 4 Non-Concur regarding the recommendations for formulary and non-formulary agents.
- The Panel was concerned about the number of people on Enbrel who would have to change, and the decision being based on pending approval of a new indication.
- The Panel voted 4 Concur, 5 Non-Concur regarding the recommended implementation period of 90 days.

- The Panel recommended an implementation date of 120 days versus the recommended 90 days.

***Director, TMA*:**

☑ These comments were taken under consideration prior to my final decision.

4. **Recently Approved Agents in Classes Reviewed for the Uniform Formulary:**

Exforge: The P&T Committee recommended that valsartin/amlodipine (Exforge) be classified as non-formulary on the UF.

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 at the Military Treatment Facilities (MTFs) no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

Vyvanse: The P&T Committee recommended that lisdexamfetamine (Vyvanse) be classified as non-formulary.

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 at the Military Treatment Facilities (MTFs) no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

Lybrel: The P&T Committee recommended that Ethinyl Estradiol 20/Levonorgestrel 0.09 (Lybrel) be classified as non-formulary.

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 at the Military Treatment Facilities (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 approval by the Director, TMA.

Summary of Panel Vote/Comments:

- **Exforge:** The Panel voted 9 Concur, 0 Non-Concur regarding the recommendation of non-formulary status for Exforge.

- The Panel voted 9 Concur, 0 Non-Concur regarding the recommended implementation period of 60 days.
- **Vyvanse:** The Panel voted 4 Concur, 5 Non-Concur regarding the recommendation of non-formulary status for Vyvanse.
- The Panel members commented that since there is no clinical advantage or disadvantage and not much difference in cost, this agent appears to be a good candidate for step therapy rather than third tier.
- The Panel voted 6 Concur, 3 Non-Concur regarding the recommended implementation period of 60 days.
- One Panel member stated they would prefer a 90-day implementation period.
- **Lybrel:** The Panel voted 9 Concur, 0 Non-Concur regarding the recommendation of non-formulary status for Lybrel.
- The Panel voted 9 Concur, 0 Non-Concur regarding the recommended implementation period of 60 days.

Director, TMA:

☑ These comments were taken under consideration prior to my final decision.

5. **Presentation on Status of amlodipine (Norvasc, generics) on the Uniform Formulary**

Amlodipine: The P&T Committee recommended that amlodipine (Norvasc, generics) be reclassified as formulary on the UF.

The P&T Committee recommends an effective date as the date the Director, TMA, signs the minutes.

Summary of Panel Vote/Comments:

- **Amlodipine:** The Panel voted 9 Concur, 0 Non-Concur regarding the recommendation of formulary status for amlodipine (Norvasc, generics).
- The Panel voted 9 Concur, 0 Non-Concur regarding the recommended implementation as of the date the Director, TMA, signs the minutes.

Director, TMA:

☑ These comments were taken under consideration prior to my final decision.

6. **Presentation on Re-Evaluation of Non-Formulary Agents**

The P&T Committee presented to the Panel a proposed new procedure for re-classifying drugs from non-formulary to formulary status. A list of the drugs to be reevaluated using this new procedure was presented.

Major Tiller explained that the Beneficiary Advisory Panel is being asked to comment on and approve the list of medications to be reevaluated. The process has already been approved; the concept now is to pre-approve the list so that once the drugs become available generically they can be added back on the Uniform Formulary with further action by the BAP. In future meetings, the changes will be presented as "information only" items.

Summary of Panel Vote/Comments:

- The Panel voted 9 Concur, 0 Non-Concur on the list of "Non-Formulary Agents for Re-Evaluation.

Director, TMA:

☑ These comments were taken under consideration prior to my final decision.