DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

November 2006

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

Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF): The P&T Committee was briefed on four new drugs approved by the Food and Drug Administration (FDA) that did not fall under drug classes previously reviewed for UF consideration. The committee discussed the need for quantity limits and prior authorization (PA) for two of the new drugs, human insulin inhalation powder (Exubera) and fentanyl buccal tablets (Fentora); there are existing quantity limits for other inhaled products and fentanyl lozenges. No recommendations were made for human insulin inhalation powder, as typical dosage requirements and utilization are unclear at this time. The Committee deferred a decision on quantity limits for fentanyl buccal tablets until the narcotic analgesic class is reviewed at an upcoming meeting.

Contraceptive Agents 30/10 mcg ethinyl estradiol (EE)/0.15 mg levonorgestrel for extended use, (Seasonique), and 20 mcg ethinyl estradiol (EE)/1 mg norethindrone acetate – 24 day regimen, (Loestrin 24 Fe).

Background: Two new contraceptive products, Seasonique and Loestrin 24 Fe, have been marketed since the contraceptive drug class was reviewed in May 2006.

Seasonique - Seasonique is a monophasic oral contraceptive with 30 mcg of EE specifically packaged and labeled for extended cycle use (84 days of 30 mcg EE/0.15 mg levonorgestrel, followed by seven days of low-dose estrogen [10 mcg EE]). The rationale for providing seven days of 10 mcg EE instead of placebo is to reduce symptoms associated with estrogen withdrawal, including dysmenorrhea, menstrual migraine, and premenstrual syndrome, although this has not been evaluated in a prospective, randomized, controlled trial.

The difference between Seasonale, a non-formulary (third) tier agent, and Seasonique is the substitution of seven low-dose estrogen (10 mcg EE) tablets in Seasonique for the seven placebo tablets in Seasonale. For this reason, Seasonique's regimen cannot be exactly duplicated by using conventional packages of Nordette or its equivalents and discarding unneeded placebo tablets, unlike Seasonale. With respect to efficacy in preventing pregnancy, there is no reason to believe that Seasonique would differ from other similar oral contraceptives.

Loestrin 24 FE: Loestrin 24 Fe is a monophasic oral contraceptive product with 20 mcg EE packaged as a 24-day regimen (24 days of 20 mcg EE /1 mg norethindrone followed by four days of placebo tablets).

The rationale for a 24- rather than a 21-day regimen is to decrease the number of bleeding days and reduce adverse events associated with estrogen withdrawal. It is also possible that a longer regimen would increase the safety margin for contraceptive effectiveness with low estrogen products; however, there is no supporting clinical evidence. An alternative using conventionally packaged Loestrin Fe 1/20 that may accomplish the same general goal would be to simply start a new package early.

Relative Clinical Effectiveness Conclusion: The Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that Seasonique and Loestrin 24 Fe do not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome, over the other oral contraceptives included on the UF.

Relative Cost Effectiveness Conclusion: Cost minimization analysis (CMA) showed that Seasonique is less cost-effective on a per cycle basis than all UF oral contraceptives containing 30 mcg EE and Loestrin 24 Fe is less cost-effective on a per cycle basis than all UF oral contraceptives containing 20 mcg EE. Based on the results of the CMAs and other clinical and cost considerations, the Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that Seasonique and Loestrin 24 Fe are substantially more costly than other oral contraceptives containing 30 mcg EE or 20 mcg EE included on the UF.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for Seasonique and Loestrin 24 Fe, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that Seasonique and Loestrin 24 Fe be classified as non-formulary under the UF. (See paragraphs 5B1, 5B2 and 5B3 on pages 14-16 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MEDICAL NECESSITY CRITERIA – Based on the clinical evaluation of Seasonique and Loestrin 24 Fe and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) medical necessity criteria for the contraceptive agents. (See paragraph 5B4 on page 17 of the P&T Committee minutes for the criteria).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 5B5 on page 17 of the P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows: *"Implement January 24, 2007"*

Topical antifungal agents – 0.25% miconazole, 15% zinc oxide, 81.35% white petrolatum ointment (Vusion)

Background: The topical antifungal agents were reviewed by the Committee in Aug 2005. A new ointment containing 0.25% miconazole, 15% zinc oxide, and 81.35% white petrolatum (Vusion) has been approved by the FDA. Vusion contains a much lower concentration of miconazole than other prescription and OTC miconazole products (0.25% vs. 2%) and is only available in an ointment formulation.

Vusion is specifically labeled for the adjunctive treatment of diaper dermatitis only when complicated by microscopically-documented candidiasis in immunocompetent pediatric patients four weeks and older.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that although Vusion is labeled for a specific type of diaper dermatitis in infants as young as four weeks of age, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome, over the other topical antifungals included on the UF.

Relative Cost Effectiveness Conclusion: CMA showed that Vusion is the least cost-effective of all comparators, including other antifungals commonly used for diaper rash, when analyzed on a cost per utilizer basis. Based on the results of the CMA and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that Vusion is substantially more costly than other antifungals commonly used for the treatment of the same condition.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determination for Vusion, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that Vusion be classified as non-formulary under the UF. (See paragraphs 5C1, 5C2 and 5C3 on pages 17-19 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MEDICAL NECESSITY CRITERIA – Based on the clinical evaluation of Vusion and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) medical necessity criteria for Vusion. (See paragraph 5C4 on page 19 of the P&T Committee minutes for the criteria).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 5C5 on page 19 of the P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows: *"Implement in 30 days."*

Antiemetic Agents - Nabilone (Cesamet)

Background: The Committee previously reviewed the antiemetic agents in May 2006. Nabilone is a synthetic cannabinoid antiemetic similar to dronabinol. Nabilone is indicated for treatment of chemotherapy-induced nausea and vomiting when conventional antiemetics have failed. There are no published clinical trials comparing nabilone with dronabinol, or with the 5-hydroxytryptamine-3 (5-HT3) antagonists.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that while nabilone offers a slight convenience of dosing frequency compared to dronabinol, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over the other antiemetics included on the UF.

Relative Cost Effectiveness Conclusion: CMA showed that nabilone has a cost-effectiveness profile that is similar to dronabinol. Based on the results of the CMA and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that nabilone is comparable in cost to dronabinol, a similar cannabinoid antiemetic included on the UF.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for nabilone, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that nabilone be classified as formulary on the UF.

(See paragraphs 5D1, 5D2 and 5D3 on pages 20-21 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

6. DRUG CLASS REVIEW – OLDER SEDATIVE HYPNOTICS (SED-2s)

The P&T Committee evaluated the relative clinical effectiveness of the Older Sedative/Hypnotic (SED-2) Medications. The SED-2 drug class is comprised of five hypnotic benzodiazepines: estazolam, flurazepam, quazepam, temazepam, and triazolam; two barbiturate hypnotics: butabarbital and secobarbital; and one nonbarbiturate hypnotic agent: chloral hydrate. All eight of these drugs have been marketed for a number of years, and all but quazepam, butabarbital, and two less commonly used strengths of temazepam are available in generic formulations. The SED-2 drug class accounted for $2.5 million in Military Health System (MHS) expenditures for the period Aug 2005 to July 2006 and is ranked #165 in terms of total expenditures during that time period.

Relative Clinical Effectiveness Conclusion: The Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) The five hypnotic benzodiazepines (estazolam, flurazepam, quazepam, temazepam, and triazolam) are widely considered interchangeable for the treatment of short-term insomnia when used in equipotent doses, despite differences in onset and duration of action.
2) Temazepam is the most desirable benzodiazepine in the SED-2 drug class, based on clinical factors (duration of action, tolerance to therapeutic effects, adverse effect profile).
3) The hypnotic barbiturates, secobarbital and butabarbital, have fallen out of favor compared to newer therapies, primarily due to safety concerns, and are infrequently utilized at any MHS point of service.
4) Chloral hydrate appears to have a unique niche in the setting of outpatient pediatric sedation.
5) There are no clinical reasons to justify designating any of the SED-2s as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: Based on the results of the CMA and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) Secobarbital, chloral hydrate, flurazepam, temazepam 15 and 30 mg, estazolam, and triazolam have similar relative cost-effectiveness.
2) Butabarbital, quazepam, and temazepam 7.5 and 22.5mg are more costly relative to the other agents in the class, but placing these agents in the non-formulary tier of the UF would achieve little savings due to current and projected low utilization.

A. COMMITTEE ACTION: UF RECOMMENDATION **-** Taking into consideration the conclusions from the relative clinical effectiveness and relative cost

effectiveness determinations for the SED-2s, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that estazolam, flurazepam, quazepam, temazepam, triazolam, butabarbital, secobarbital, and chloral hydrate be maintained as formulary on the UF, and that none of the SED-2s be classified as non-formulary under the UF. (See paragraphs 6A, 6B and 6C on pages 22-24 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: BASIC CORE FORMULARY (BCF) RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend retaining the generically available strengths of temazepam (15 mg and 30 mg) as the BCF selections in this class, excluding the 7.5 mg and 22.5 mg proprietary dosage strengths. (See paragraph 6F on page 25 of the P&T Committee minutes for rationale).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

7. DRUG CLASS REVIEW – ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY AGENTS

The drugs in the Attention-Deficit / Hyperactivity Disorder (ADHD) and Narcolepsy Agents class are comprised of the following: for ADHD, there is one non-stimulant: atomoxetine (Strattera) and five stimulant compounds: methylphenidate, mixed amphetamine salts, dexmethylphenidate, dextroamphetamine, and methamphetamine; for narcolepsy, there are two drugs: modafinil (Provigil) and sodium oxybate (Xyrem). The ADHD and Narcolepsy Agents accounted for approximately $84.5 million dollars in MHS expenditures for Fiscal Year (FY) 2006 and are ranked #16 in terms of total expenditures during that time period.

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

1) For ADHD, interpretation of the data is limited due to the poor quality of studies, limited number of comparator trials, varying rating scales used, small number of patients enrolled, and short study duration.

2) There is no evidence to suggest a difference in efficacy between immediate release (IR) formulations of methylphenidate, dextroamphetamine, dexmethylphenidate, and mixed amphetamine salts.

3) The overall efficacy of the once daily methylphenidate formulations appears similar based on a few small studies, but differences exist in reported outcomes at specific times of the day, due to the individual release mechanisms of the

products. Methylphenidate 30% IR/70% extended release (ER) (Metadate CD) and methylphenidate SODAS (Ritalin LA) are eight- to nine-hour products, while methylphenidate OROS (Concerta), dexmethylphenidate SODAS (Focalin XR), and methylphenidate transdermal system (Daytrana) are 12-hour products.

4) Mixed amphetamine salts extended release (ER) (Adderall XR) appears to have similar efficacy to methylphenidate OROS (Concerta), based on one small study.

5) The efficacy of atomoxetine appears to be inferior to the stimulants, but it is the only non-stimulant available in the ADHD class.

6) Between 40% and 80% of patients who do not respond to one type of stimulant (methylphenidate products vs. amphetamine products) may respond to the other.

7) The adverse events and warnings of the stimulants are well-recognized and are similar between products.

8) The methylphenidate transdermal system can cause significant dermatological adverse events, which can lead to sensitization to oral products.

9) Atomoxetine remains the only alternative for patients who cannot tolerate stimulants, despite its association with an increased risk of hepatotoxicity and suicidal ideation.

10) Several products can be sprinkled on food for patients with swallowing difficulties.

11) Responders to a provider survey expressed a desire for availability of the following products to cover clinical needs: methylphenidate OROS, an IR methylphenidate product, mixed amphetamine salts ER, and atomoxetine.

12) The narcolepsy drug modafinil provides a unique niche in therapy as a wakefulness promoting agent.

13) The narcolepsy drug sodium oxybate has a high incidence of adverse events, but serves a unique niche in therapy for cataplexy. The manufacturer's restricted distribution program limits use to appropriate patients.

14) Based on clinical issues alone, there are no reasons to designate any of the ADHD drugs or narcolepsy drugs as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: Based on the results of the cost analysis (CMA) and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) Once daily ADHD agents: dexmethylphenidate SODAS (Focalin XR) and methylphenidate transdermal system (Daytrana) were not cost-effective relative to the other agents in the subclass.

2) Multiple daily use ADHD agents: dexmethylphenidate IR (Focalin) was not cost-effective relative to the other agents in the subclass.

3) Agents indicated in the treatment of narcolepsy: Although modafinil (Provigil) and sodium oxybate (Xyrem) were more costly relative to other agents indicated for the

treatment of narcolepsy, they possessed unique clinical advantages relative to other agents within the class.

A. COMMITTEE ACTION: UF RECOMMENDATION **-** Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ADHD and narcolepsy agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that mixed amphetamine salts IR (Adderall, generics), mixed amphetamine salts ER (Adderall XR), atomoxetine (Strattera), dexamphetamine IR (Dexedrine, Dextrostat, generics), methamphetamine IR (Desoxyn, generics), methylphenidate 30% IR/70% ER (Metadate CD), methylphenidate IR (Ritalin, generics), methylphenidate OROS (Concerta), methylphenidate SODAS (Ritalin LA), methylphenidate sustained-release (SR) (Ritalin SR), modafinil (Provigil), and sodium oxybate (Xyrem) be maintained as formulary on the UF and that dexmethylphenidate IR (Focalin), dexmethylphenidate SODAS (Focalin XR), and methylphenidate transdermal system (Daytrana) be classified as non-formulary under the UF. (See paragraphs 7A, 7B and 7C on pages 25-39 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MEDICAL NECESSITY CRITERIA **-** Based on the clinical evaluation for methylphenidate transdermal system (Daytrana), dexmethylphenidate IR (Focalin), and dexmethylphenidate SODAS (Focalin XR), and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) medical necessity criteria for methylphenidate transdermal system (Daytrana), dexmethylphenidate IR (Focalin) and dexmethylphenidate SODAS (Focalin XR). (See paragraph 7D on page 39-40 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD **-** The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 7E on page 40 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION - The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend retaining mixed amphetamine salts ER (Adderall XR), methylphenidate OROS (Concerta), and methylphenidate IR (Ritalin, generics) as the BCF selections in this class. (See paragraph 7F on page 40 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

8. PRIOR AUTHORIZATION REQUIREMENT (PA) FOR MODAFINIL (PROVIGIL)

The P&T Committee agreed that a PA was needed for modafinil, due to the potential for inappropriate use.

COMMITTEE ACTION – Based on its increasing use for off-label indications not well established by the medical literature, the P&T Committee recommended that a PA be required for modafinil (15 for, 0 against, 0 abstained, 2 absent). The Committee recommended that the PA should have an effective date of the first Wednesday following a 90-day implementation period, consistent with the recommended implementation period for non-formulary medications in the ADHD and narcolepsy agents class. The implementation period will begin immediately following approval by the Director, TMA. The Committee voted (15 for, 0 against, 0 abstained, 2 absent) to recommend PA criteria. (See paragraph 8 on pages 40-42 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

9. PA REQUIREMENT FOR FENTANYL PATCHES (DURAGESIC, GENERICS)

COMMITTEE ACTION – Based on safety concerns, the P&T Committee recommended that a PA be required for fentanyl patches (15 for, 0 against, 0 abstained, 2 absent). The criteria recommended by the P&T Committee are based on safety requirements in labeling and incorporate modifications to the Pharmacy Data Transaction Service (PDTS) that will allow automation of some PA criteria, reducing paperwork burden and cost. These modifications are scheduled for completion by December 2006. (See pages 41-43 of the P&T Committee minutes for rationale and summary of PA criteria.) The P&T Committee recommended that the PA should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible based on availability of the automated PA capability in PDTS. (See paragraph 9 on pages 42-43 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

Appendix A – Table 1. Implementation Status of UF Recommendations/Decisions

Appendix B – Table 2. Newly Approved Drugs

Appendix C – Table 3. Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____signed_____

William Winkenwerder, Jr., M.D.
Date: 17 January 2007

Department of Defense
Pharmacy and Therapeutics Committee Minutes
15 November 2006

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 14 November 2006 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
CAPT Mark Richerson, MSC, USN	DoD P&T Committee Recorder
MAJ Travis Watson, MSC, USA *for* CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
No replacement *for* LtCol Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
LtCol Brian Crownover, MC	Air Force, Physician at Large
LtCol Charlene Reith *for* LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer
CDR Walter Downs, MC *for* LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatric Physician
CDR David Tanen, MC	Navy, Physician at Large
LT Tim Thompson *for* CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Ted Cieslak, MC	Army, Physician at Large
LTC Peter Bulatao, MSC for COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

COL Isiah Harper, MSC	Army, Pharmacy Officer
LtCol Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer (Pharmacy Consultant)
CAPT David Price, MSC	Navy, Pharmacy Officer (Pharmacy Consultant)

C. Non-Voting Members Present

Mr. Lynn T. Burleson	Assistant General Counsel, TMA
LT Thomas Jenkins, MSC, USN	TMOP/TRRx COR

D. Non-Voting Members Absent

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Ms Martha Taft	Health Plan Operations, TMA
Major Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

E. Others Present

Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
LCDR Joe Lawrence, MSC, USN	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Mr. Dan Remund	DoD Pharmacoeconomic Center
Ms. Shana Trice	DoD Pharmacoeconomic Center
Mr. David Bretzke	DoD Pharmacoeconomic Center
Ms. Angela Allerman	DoD Pharmacoeconomic Center
Mr. Eugene Moore	DoD Pharmacoeconomic Center
Ms. Julie Liss	DoD Pharmacoeconomic Center
Ms. Elizabeth Hearin	DoD Pharmacoeconomic Center
Mr. Dave Flowers	DoD Pharmacoeconomic Center
Mr. David Meade	DoD Pharmacoeconomic Center
Ms. Harsha Mistry	DoD Pharmacoeconomic Center
Col Nancy Misel	IMA DoD PEC
Janet Dailey	VAPBM
Charles R. Brown	TMA/CMB

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – August 2006 DoD P&T Committee meeting minutes were approved as written, with no corrections noted, however, there was a correction to the decision paper. The sentence on page 3, section B (Committee Action: Basic Core Formulary (BCF) Recommendation), line 3 was revised to "The Committee did not recommend addition of rosiglitazone/glimepiride to the BCF."

B. Approval of August Minutes - Dr. William Winkenwerder, Jr., M.D., approved the minutes of the August 2006 DoD P&T Committee meeting on 23 October 2006.

4. ITEMS FOR INFORMATION

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

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss and CAPT Richerson briefed the members of the P&T Committee regarding the August 2006 BAP meeting. The 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 August 2005. The Committee made the following observations:

1) **DuetAct (pioglitazone plus glimepiride) –** A new thiazolidinedione (TZD) combination agent has been marketed since the TZD class was reviewed in August 06. DuetAct is the combination of pioglitazone plus glimepiride. It is available in two strengths: 30mg pioglitazone/2mg glimepiride and 30mg pioglitazone/4mg glimepiride. The PEC informed the Committee that DuetAct was added to the UF as a line extension of the existing UF blanket purchase agreements (BPAs) and voluntary agreements for TRICARE retail pharmacy rebates (VARR) with the manufacturer.

2) **Implementation Status of UF Decisions –** The PEC briefed the members of the Committee on the progress of implementation for drug classes reviewed for UF status since February 2005. The Committee made the following observations:

a) Utilization in all UF classes continues to remain stable, suggesting continued access to drugs within the reviewed classes.

b) Collective utilization of UF agents across all reviewed drug classes and points of service (military treatment facility (MTF), TRICARE Mail Order Pharmacy Program (TMOP), and TRICARE Retail Network Pharmacy (TRRx)) continues to increase as a percentage of prescriptions dispensed, while utilization of non-formulary agents has decreased. Based on the UF decisions that have been fully implemented since the first UF DoD P&T meeting in February 2005, there has been an overall 30% reduction in the use of non-formulary agents (MTFs -89%, Mail +6%, Retail -11%), including those classes where implementation has only just begun. In classes with at least 6 months of implementation, there has been an overall 40% reduction in the use of non-formulary agents (MTFs -93%, Mail +1%, Retail -21%).

c) The cost per day of treatment across all reviewed drug classes has decreased, but magnitude varies by point of service. Based on the UF decisions that have been fully implemented since the first UF DoD P&T meeting in February 2005, there has been an overall 5% reduction in the cost per day of treatment (MTFs -23%, Mail -5%, Retail -2%), including those classes where implementation has only just begun. In classes with at least 6 months of implementation, there has been an overall 7% reduction in the cost per day of treatment (MTFs -30%, Mail -5%, Retail -4%).

d) Success in terms of generating increased market share for UF agents (while decreasing market share for non-formulary agents) varies by class and point of service.

e) Market shares by point of service continue to reflect the degree of utilization management applied to each point of service. The more highly managed points of service (i.e., MTFs) are generating higher market shares for UF agents than the unmanaged points of service (i.e., TMOP and TRRx).

f) It appears that more beneficiaries may be electing to receive non-formulary medications through TMOP.

5. REVIEW OF RECENTLY APPROVED AGENTS

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

The P&T Committee was briefed on four new drugs that were approved by the Food and Drug Administration (FDA) (see Appendix B). The P&T Committee determined that these four new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed.

The P&T Committee discussed the need for quantity limits or prior authorization (PA) requirements for two of these products: inhaled insulin (Exubera) and fentanyl buccal tablets (Fentora). Quantity limits are in place for other inhaled products (e.g., for asthma) and for fentanyl transmucosal lozenges or "lollipops" (Actiq). Some other health plans require PA for human insulin inhalation powder. The Committee agreed that more information was needed before making recommendations; the Narcotic Analgesic drug class is scheduled for UF review in February 2007.

B. Contraceptive Agents - 30/10 mcg ethinyl estradiol (EE)/0.15 mg levonorgestrel for extended use, (Seasonique), and 20 mcg ethinyl estradiol (EE)/1 mg norethindrone – 24 day regimen, (Loestrin 24 Fe)

1) *Relative Clinical Effectiveness* – Two new contraceptive products, Seasonique and Loestrin 24 Fe, have been marketed since the contraceptive drug class was reviewed in May 06.

Seasonique – Seasonique is a monophasic oral contraceptive with 30 mcg of EE specifically packaged and labeled for extended cycle use (84 days of 30 mcg EE/0.15 mg levonorgestrel, followed by seven days of low-dose estrogen [10 mcg EE]).

The UF contains multiple monophasic oral contraceptives containing 30 mcg of EE in combination with various progestogens. These products include Yasmin (3 mg

drospirenone) and generic equivalents to Desogen (0.15 mg desogestrel); Loestrin 1.5/30, Loestrin Fe 1.5/30 (1.5 mg norethindrone); Lo/Ovral (0.3 mg norgestrel); and Nordette (0.15 mg levonorgestrel). Two of these (Nordette equivalent products and Yasmin) are on the BCF. All of these products are available in conventional 28-day packaging (21 days of active tablets followed by 7 days of placebo tablets).

Another extended cycle product, Seasonale, was placed in the third (non-formulary) tier of the UF following the May 06 meeting, with an effective date of 24 Jan 2007. The difference between Seasonale and Seasonique is the substitution of the seven low-dose estrogen (10 mcg EE) tablets in Seasonique for the seven placebo tablets in Seasonale. For this reason, Seasonique's regimen cannot be exactly duplicated by using conventional packages of Nordette or its equivalents and discarding unneeded placebo tablets, unlike Seasonale.

The rationale for providing seven days of 10 mcg EE instead of placebo is to reduce symptoms associated with estrogen withdrawal, including dysmenorrhea, menstrual migraine, and premenstrual syndrome, although this has not been evaluated in a prospective, randomized, controlled trial. One other oral contraceptive product offering low-dose estrogen during the off period is available (Mircette, Kariva, and equivalents; 21 days of 20 mcg EE/0.15 mg desogestrel followed by 2 days of placebo and 5 days of 10 mcg EE). It is worth noting that utilization of this product, which is included on the UF, is relatively low compared to other 20 mcg EE products. Alternatives to Seasonique in women being treated on an extended cycle basis who are experiencing menstrual-related problems during the four annual off periods include addition of a low-dose conjugated estrogen product (e.g., 0.3 mg Premarin) during the off period, or decreasing the length or number of off periods.

With respect to efficacy in preventing pregnancy, there is no reason to believe that Seasonique would differ from other similar oral contraceptives. One non-controlled trial evaluating Seasonique in 1,000 women reported that it was >99% effective in preventing pregnancy; there are no head-to-head trials comparing Seasonique with other contraceptives.

Loestrin 24 Fe – Loestrin 24 Fe is a monophasic oral contraceptive product with 20 mcg EE packaged as a 24-day regimen (24 days of 20 mcg EE / 1 mg norethindrone followed by four days of placebo tablets).

The UF contains multiple monophasic oral contraceptives containing 20 mcg of EE in combination with various progestogens, including Yaz (3 mg drospirenone) and equivalents to Alesse (0.1 mg levonorgestrel) and Loestrin 1/20 / Loestrin Fe 1/20 (1.0 mg norethindrone). Alesse equivalent products and Yaz are on the BCF. Like Loestrin 24 Fe, Yaz is a 24-day regimen product; Alesse, Loestrin 1/20, and Loestrin Fe 1/20 are available in conventional 28-day packaging (21 days of active tablets followed by 7 days of placebo tablets). Loestrin 24 Fe offers the same daily estrogen and progestogen content as the existing Loestrin Fe 1/20 product (and its generic equivalents), differing only in the number of active and placebo tablets included.

The rationale for a 24- rather than a 21-day regimen is to decrease the number of bleeding days and reduce adverse events associated with estrogen withdrawal. It is also possible that a longer regimen would increase the safety margin for contraceptive

effectiveness with low estrogen products; however, there is no supporting clinical evidence. One trial in 938 women compared Loestrin 24 Fe with Loestrin Fe 1/20 and reported a Pearl Index (number of pregnancies per 100 women per year of use) of 1.85 (five pregnancies) with the 24-day regimen vs. 1.79 (two pregnancies) with the 21-day regimen (no statistics provided). There were no differences between the two products in terms of serious adverse events, treatment-related adverse events, and discontinuations due to adverse events.

An alternative using conventionally packaged Loestrin Fe 1/20 that may accomplish the same general goals as with the 24-day regimen would be to simply start a new package early.

Conclusion: The Committee concluded that Seasonique or Loestrin 24 Fe do not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome, over other oral contraceptives included on the UF.

2) *Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost-effectiveness of Seasonique and Loestrin 24 Fe in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the contraceptive drug class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

   Based on the information reported from the relative clinical effectiveness evaluation, there was insufficient evidence to suggest that Seasonique or Loestrin 24 Fe differed with regard to efficacy, safety, tolerability, or clinical outcomes compared to the existing drugs in the contraceptive class. As a result, two cost-minimization analyses (CMAs) were performed to determine the relative cost-effectiveness of Seasonique and Loestrin 24 Fe.

   The CMA for Seasonique compared the weighted average cost per cycle across all three points of service to the monophasic oral contraceptives with 30 mcg of EE, as listed above. The CMA for Loestrin 24 Fe compared the weighted average cost per cycle across all three points of service to the monophasic oral contraceptives with 20 mcg of EE, as listed above.

   Conclusion for Seasonique: The results of the CMA showed that Seasonique is less cost-effective on a per cycle basis than all UF oral contraceptives containing 30 mcg EE.

   Conclusion for Loestrin 24 Fe: The results of the CMA showed that Loestrin 24 Fe is less cost-effective on a per cycle basis than all UF oral contraceptives containing 20 mcg EE.

3) *UF Recommendations* – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical and cost effectiveness conclusions stated above.

   COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that Seasonique and Loestrin 24 Fe be classified as non-formulary under the UF.

4) *Medical Necessity Criteria* – Based on the clinical evaluation of Seasonique, 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 medical necessity criteria for Seasonique:

   a) Use of formulary alternatives is contraindicated.

   b) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.

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

   Based on the clinical evaluation of Loestrin 24 Fe, 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 medical necessity criteria for Loestrin 24 Fe:

   a) Use of formulary alternatives is contraindicated.

   The P&T Committee did not agree that other general medical necessity criteria would apply to Loestrin 24 Fe given the UF status of Loestrin Fe 1/20, which contains the same combination of the same active ingredients and which can be used on the same shortened off-period basis by discarding unneeded placebo tablets.

   COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to approve the medical necessity criteria outlined above.

5) *UF Implementation Period* – The P&T Committee discussed the advantages and disadvantages of a longer versus a shorter implementation period for Seasonique and Loestrin 24 Fe. The fact that Seasonique is packaged as a three-month supply supported a longer implementation period, while a shorter implementation period would avoid patient disruption as utilization of new products increases. As of Oct 2006, there have been 161 unique utilizers of Seasonique and 2,227 of Loestrin 24 Fe, at all three points of service. The P&T Committee also discussed the prospect for coordinating implementation of non-formulary status for Seasonique and Loestrin 24 Fe with the already established effective date for Seasonale non-formulary status (24 Jan 07), but it was unclear if this was possible given timelines for the BAP meeting and subsequent review of P&T minutes and BAP comments by the Director, TMA. Ultimately, the Committee recommended a shorter implementation period because it would avoid patient disruption as utilization of new products increases.

   COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

C. Topical Antifungal Agents - 0.25% miconazole, 15% zinc oxide, 81.35% white petrolatum ointment (Vusion)

1) *Relative Clinical Effectiveness:* The topical antifungal agents were reviewed by the P&T Committee in Aug 05. Topical antifungal agents included on the UF include clotrimazole (Lotrimin, generics), nystatin (Mycostatin, generics), miconazole (Monistat, generics), ketoconazole (Nizoral, generics), butenafine (Mentax, generics),

and naftifine (Naftin). Clotrimazole (Lotrimin, generics) and nystatin (Mycostatin, generics) are classified as BCF agents. Topical antifungal agents classified as non-formulary under the UF are econazole (Spectazole, generics), sertaconazole (Ertaczo), sulconazole (Exelderm), ciclopirox (Loprox, generics), and oxiconazole (Oxistat).

Vusion contains 0.25% miconazole along with 15% zinc oxide and 81.35% white petrolatum, and is only available as an ointment. Over-the-counter (OTC) and prescription miconazole products contain a 2% concentration of miconazole, and are available in several formulations (e.g., cream, ointment, spray, spray liquid, powder, and solution). The zinc oxide and petrolatum components of Vusion are skin protectants; numerous OTC products (e.g., Balmex, Happy Hiney) contain varying amounts of these two ingredients, which form a physical barrier on the skin.

Vusion is specifically labeled for the adjunctive treatment of diaper dermatitis only when complicated by microscopically-documented candidiasis in immunocompetent pediatric patients four weeks and older. Vusion is the first product with a labeled indication for diaper rash in infants as young as four weeks, and the first one to include candidiasis in the label. Vusion is not approved for use in adults, immunocompromised patients, or infants with diaper rash that is not confirmed to have candidiasis as the causative factor. The Committee agreed that Vusion is likely to be used for non FDA-approved indications, particularly for diaper rash without documented candidiasis. The existing BCF and UF topical antifungal products have much broader indications than Vusion and treat several types of infections (e.g., tinea pedis, tinea corporis, tinea cruris, or tinea capitis).

The rationale for Vusion incorporating a low concentration of 0.25% miconazole is to provide efficacy and safety in young infants without achieving measurable plasma concentrations. It is not clear, however, that Vusion is the only topical antifungal that may be used for this purpose. Nystatin (Mycostatin, generics) can be used in infants as young as neonates, and the package insert states that it is well tolerated, even in debilitated infants, even with prolonged administration. Both miconazole (Monistat, generics) 2% and clotrimazole (Lotrimin, generics) 1% can be used in children as young as two years of age.

There are no published clinical trials comparing Vusion with other miconazole formulations, clotrimazole (Lotrimin, generics) or nystatin (Mycostatin, generics). One published, 330-patient trial compared Vusion with a zinc oxide/petrolatum vehicle and reported a complete cure rate after seven days of 7% with Vusion versus 0.8% with vehicle; adverse event rates with Vusion were similar to vehicle.

Conclusion: The P&T Committee concluded that, although Vusion is labeled for a specific type of diaper dermatitis in infants as young as four weeks of age, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over other topical antifungals included on the UF.

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

Based on the information reported from the relative clinical effectiveness evaluation, there was insufficient evidence to suggest that Vusion differed significantly with regard to efficacy, safety, tolerability, or clinical outcomes compared to the existing drugs in the topical antifungal class. As a result, a CMA was performed to determine the relative cost-effectiveness of Vusion within the topical antifungal drug class.

The CMA for Vusion compared the weighted cost per treated utilizer across all three points of service to other antifungal agents previously analyzed during the DoD P&T Committee's August 2005 review of topical antifungals. Comparative antifungals used specifically for diaper rash included clotrimazole (Lotrimin, generics), miconazole (Monistat, generics), and nystatin (Mycostatin, generics). Other topical antifungals compared included cyclopirox (Loprox, generics), sertaconazole (Ertaczo), oxiconazole (Oxistat), naftifine (Naftin), butenafine (Mentax), sulconazole (Exelderm), econazole (Spectazole, generics), and ketoconazole (Nizoral, generics).

Conclusion: The results of the CMA showed that Vusion is the least cost-effective of all comparators, when analyzed on a cost per utilizer basis.

3) *UF Recommendation:* The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical and cost effectiveness conclusions stated above.

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that Vusion be classified as non-formulary under the UF.

4) *Medical Necessity Criteria:* Based on the clinical evaluation of Vusion, 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 medical necessity criteria for Vusion:

   a) Use of formulary agents is contraindicated.

   b) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.

   COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to approve the medical necessity criteria outlined above.

5) *UF Implementation Period:* The P&T Committee recommended an implementation period of 60 days, due to existing low utilization in the MHS. As of October 2006, a total of 581 Vusion prescriptions have been dispensed at all three points of service. For the six month period between Apr 2006 and Oct 2006, there have been 426 unique utilizers of Vusion in the MHS.

   COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

D. Antiemetic Agents (Cesamet)

1) *Relative Clinical Effectiveness:* The Committee previously reviewed the antiemetic agents at the May 06 P&T meeting. The antiemetic class includes the following agents, which may be sub-classified based on typical use and mechanism of action. All of these agents are on the UF with the exception of dolasetron (Anzemet).

   - *The newer antiemetics*
     - 5-hydroxytryptamine-3 [5-HT3] antagonists: ondansetron (Zofran), granisetron (Kytril), dolasetron (Anzemet)
     - Neurokinin-1 (NK-1) antagonist: aprepitant (Emend)
   - *The older antiemetics*
     - Cannabinoids: dronabinol (Marinol)
     - Antihistamines: meclizine (Antivert, generics) and promethazine (Phenergan, generics). Promethazine is on the BCF.
     - Phenothiazines: prochlorperazine (Compazine, generics), thiethylperazine (Torecan)
     - Anticholinergics: trimethobenzamide (Tigan, generics), transdermal scopolamine (Transderm Scop)

   Nabilone (Cesamet) is a synthetic cannabinoid antiemetic similar to dronabinol. It was previously approved for marketing in 1985, but withdrawn by the manufacturer in 1989 due to commercial reasons not related to efficacy or safety. It is indicated for treatment of chemotherapy-induced nausea and vomiting (CINV) when conventional antiemetics have failed. The other available cannabinoid antiemetic, dronabinol, is also indicated for CINV, but has an additional indication for treating anorexia in patients with AIDS. The duration of action of nabilone is longer than dronabinol: 8-12 hours vs. 4-6 hours. This allows for a dosing regimen of BID-TID (2 to 3 times a day) with nabilone, compared to TID-QID (3 to 4 times a day) for dronabinol.

   There are no published clinical trials comparing nabilone with dronabinol (Marinol). Additionally, there are no trials comparing nabilone with any of the 5-HT3 antagonists—ondansetron, granisetron, or dolasetron – which have replaced older antiemetics as the standard of care for CINV. Nabilone was approved by the FDA based on clinical trial data submitted in the early 1980s. In published trials, nabilone showed superior efficacy to prochlorperazine, but with an increased incidence of adverse effects; another trial found the combination of nabilone plus prochlorperazine inferior to a combination of dexamethasone plus metoclopramide.

   The psychoactive adverse effects of nabilone relegate it to use as a second-line agent. Nabilone is a DEA (Drug Enforcement Administration) Schedule II drug, compared to dronabinol, a Schedule III drug.

   Conclusion: The P&T Committee concluded that, while nabilone offers a slight convenience of dosing frequency compared to the other cannabinoid antiemetics, dronabinol, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other antiemetics included on the UF.

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

   Based on the information reported from the relative clinical effectiveness evaluation, there was insufficient evidence to suggest that nabilone differed with regards to efficacy, safety, tolerability, or clinical outcomes compared to the other antiemetics. As a result, a CMA was performed to determine the relative cost-effectiveness of the nabilone within the antiemetic drug class.

   The CMA compared the ranges of cost per day of treatment at all three points of service (at recommended starting doses) for nabilone versus the other cannabinoid antiemetic dronabinol, which is currently included on the UF.

   Conclusion: The results of the CMA showed that nabilone has a cost-effectiveness profile that is similar to dronabinol.

3) *UF Recommendations:* The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical and cost effectiveness conclusions stated above.

   COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that nabilone be maintained as formulary on the UF.

4) *Medical Necessity Criteria:* Since nabilone was not recommended for non-formulary status under the UF, establishment of medical necessity criteria is not applicable.

5) *UF Implementation Period:* Since nabilone was not recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

6. DRUG CLASS REVIEW – OLDER SEDATIVE HYPNOTICS (SED-2s)

The P&T Committee evaluated the relative clinical effectiveness of the Older Sedative/Hypnotic Medications (SED-2s). The SED-2 drug class is comprised of five hypnotic benzodiazepines: estazolam (Prosom, generics), flurazepam (Dalmane, generics), quazepam (Doral), temazepam (Restoril, generics), and triazolam (Halcion, generics); two barbiturate hypnotics: butabarbital (Butisol) and secobarbital (Seconal, generics); and one nonbarbiturate hypnotic agent: chloral hydrate (generics). All eight of these drugs have been marketed for a number of years, and all but quazepam (Doral), and the 7.5 mg and 22.5 mg strengths of temazepam (Restoril) are available in generic formulations. The SED-2 drug class accounted for $2.5 million in MHS expenditures for the period August 2005 to July 2006 and is ranked #165 in terms of total expenditures during that time period. In terms of numbers of prescriptions dispensed for all sedative hypnotics in the MHS, the SED-2 agents account for 20% of the overall market, with the newer non-benzodiazepine sedative

hypnotics – eszopiclone (Lunesta), zolpidem (Ambien), ramelteon (Rozerem) and zaleplon (Sonata) – accounting for the remaining 80%.

A. SED-2s – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the SED-2s 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.

1) Efficacy

Hypnotic benzodiazepines – The hypnotic benzodiazepines [estazolam (Prosom, generics), flurazepam (Dalmane, generics), quazepam (Doral), temazepam (Restoril, generics), and triazolam (Halcion, generics)] are indicated for the short-term (two weeks or less) treatment of insomnia. When given before bedtime, all five hypnotic benzodiazepines have been shown in numerous clinical trials to improve total sleep time, sleep latency, and number of awakenings, and they are effective in reducing early morning awakening. When used in equipotent doses, all the hypnotic benzodiazepines are effective and considered therapeutically interchangeable for short-term treatment of insomnia. Like other benzodiazepines, the hypnotic benzodiazepines are also effective in treating anxiety disorders.

Temazepam (Restoril, generics) is frequently preferred over flurazepam (Dalmane, generics), as the latter has a long half-life (47-160 hours compared to 3.5-18.4 hours for temazepam) that increases the occurrence of residual sedative effects. Triazolam (Halcion, generics) is commonly considered by providers to have an unacceptable adverse effect profile. Quazepam (Doral) and estazolam (Prosom, generics) are infrequently used; they were late entrants to the market, have longer half-lives, and offer no real clinical advantage compared to temazepam.

The agents are selected for clinical use according to their pharmacokinetic profiles (onset of action, duration of action), which vary among the agents. Although much of their usage has been supplanted by the newer sedative hypnotic drug class, the hypnotic benzodiazepines are still utilized for the short-term treatment of insomnia.

Hypnotic barbiturates – The hypnotic barbiturates include butabarbital (Butisol), and secobarbital (Seconal, generics). Secobarbital has been used in the short-term treatment of insomnia, and also in the pre-operative setting and in alcohol withdrawal. Butabarbital (Butisol) has a half-life of 34 to 42 hours, and is also effective as a sedative.

The hypnotic barbiturates have no safety or efficacy advantage compared to the benzodiazepines or newer sedative hypnotics, and their use has largely fallen out of favor for the treatment of insomnia. They may have a niche in therapy when the

benzodiazepines or newer hypnotics are contraindicated in an individual patient, or in the setting of pre-operative sedation.

Chloral hydrate - Chloral hydrate is no longer routinely used as a primary treatment for insomnia, as it is not as effective as the benzodiazepines. Chloral hydrate is more commonly used preoperatively or prior to procedures to ally anxiety or induce sedation. It has a unique niche for use in the setting of outpatient pediatric sedation, due to the perception that chloral hydrate produces less paradoxical excitement than the barbiturates. Chloral hydrate is included in the 1992 update to the American Academy of Pediatric (AAP) guidelines for pediatric sedation.

2) Safety / Tolerability

Benzodiazepines – There are no major differences between the five hypnotic benzodiazepines with respect to safety and tolerability. Adverse events that include daytime sedation, memory problems, and falls may limit utility, especially in the elderly. There are also concerns that benzodiazepines may limit deep sleep. The class is deemed relatively safe based on more than 30 years of clinical use. The agents have differing safety profiles with respect to drug interactions, anterograde amnesia, and daytime sedation. All benzodiazepines are contraindicated in pregnancy.

Hypnotic barbiturates – The hypnotic barbiturates have multiple safety and abuse/addiction concerns and a self-limiting mechanism of action; overdoses can be lethal. They also induce the action of hepatic microsomal drug-metabolizing enzymes, leading to increased metabolism of many drugs and endogenous substrates, such as steroid hormones, cholesterol, bile salts, and several others. Secobarbital (Seconal, generics) and butabarbital (Butisol) have been associated with withdrawal symptoms, such as multiple seizures or psychosis similar to alcohol delirium; disorientation, hallucinations, and even death have been reported. They are classified as pregnancy category D. These products were largely replaced by the benzodiazepines.

Chloral hydrate – Chloral hydrate has been associated with cardiac dysrhythmias in both adults and children. Chloral hydrate has numerous safety concerns when it is administered to children for pre-operative sedation prior to the child's arrival at the clinic; however, when properly administered it is both safe and effective. The drug has not been studied in pregnancy; a limited number of reports indicate use with no fetal harm. The AAP recommends that, while chloral hydrate can be safely administered to lactating women, infants should be observed for symptoms of drowsiness as drug and metabolites are excreted into breast milk.

Clinical Effectiveness Conclusion – The older sedative hypnotic drugs still play a role in the treatment of insomnia and pre-operative sedation, although they have been largely replaced by newer agents in clinical practice. It is widely accepted that the five hypnotic benzodiazepines are therapeutically interchangeable, although temazepam (Restoril, generics) has the most favorable half-life and safety profile. The barbiturates and chloral hydrate are used infrequently and primarily for special patient populations. There are no clinical reasons to justify designating any of these eight drugs as non-formulary under the UF.

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

B. SED-2s – Relative Cost Effectiveness

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

A cost-minimization analysis was employed to assess the relative cost-effectiveness of the agents within the SED-2 therapeutic class. The agents were evaluated on their weighted average cost per day of therapy. The results of the analysis showed all of the agents to have similar relative cost-effectiveness, with the exception of the brand-only agents: quazepam (Doral), butabarbital (Butisol), and temazepam (Restoril) 7.5 and 22.5mg. Although these agents were less cost-effective relative to the other agents in the class, the Committee agreed that little savings would be achieved by placing any of these agents in the non-formulary tier due primarily to their low current and projected MHS utilization/expenditures. Butabarbital and quazepam account for less than 0.25% of SED-2 prescriptions across the MHS and approximately 2% of annual SED-2 MHS expenditures. Temazepam (Restoril) 7.5 and 22.5 mg account for less than 5% of all MHS prescriptions for temazepam.

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

3) Secobarbital (Seconal, generics), chloral hydrate (generics), temazepam (Restoril, generics) 15 and 30 mg, estazolam (Prosom, generics), and triazolam (Halcion, generics) have similar relative cost-effectiveness.

4) Butabarbital (Butisol), quazepam (Doral), and temazepam (Restoril) 7.5 and 22.5mg are more costly relative to the other agents in the class, but placing these agents in the non-formulary tier of the UF would achieve little savings due to current and projected low utilization.

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

C. SED-2s – UF Recommendations

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the SED-2 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that butabarbital (Butisol), secobarbital (Seconal, generics), chloral hydrate (generics), quazepam (Doral), temazepam (Restoril), estazolam (Prosom, generics), and triazolam (Halcion, generics) be maintained as formulary on the UF and that no agents be classified as non-formulary under the UF.

D. SED-2s – Medical Necessity Criteria – Since no agents were recommended for non-formulary status under the UF, establishment of medical necessity criteria is not applicable.

E. SED-2s – UF Implementation Period – Since no agents were recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

F. SED-2s – Basic Core Formulary (BCF) Review and Recommendations – The P&T Committee had previously determined that at least one SED-2 agent should be added to the BCF based on the clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that temazepam (Restoril, generics) 15 and 30 mg be added to the BCF. These strengths of temazepam are generically available and represent more than 95% of temazepam prescriptions. Temazepam is the most commonly used, clinically preferred, and cost-effective SED-2 agent at all points of service.

COMMITTEE ACTION – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend adding temazepam 15 and 30 mg as the BCF selection in this class.

7. DRUG CLASS REVIEW – ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY AGENTS

The drugs in the Attention-Deficit / Hyperactivity Disorder (ADHD) and Narcolepsy Agents class are comprised of the following: for ADHD, there is one non-stimulant: atomoxetine (Strattera) and five stimulant compounds: methylphenidate, mixed amphetamine salts, dexmethylphenidate, dextroamphetamine, and methamphetamine; for narcolepsy, there are two drugs: modafinil (Provigil) and sodium oxybate (Xyrem). The ADHD and Narcolepsy Agents accounted for approximately $84.5 million dollars in MHS expenditures for Fiscal Year (FY) 2006 and are ranked #16 in terms of total expenditures during that time period.

The ADHD stimulant drugs are further divided into once daily products and multiple daily use products, based on differences in drug delivery mechanism. There are four once daily methylphenidate formulations: 1) an osmotically controlled-release delivery system [OROS)] tablet (Concerta); 2) a 30% immediate release (IR) and 70% extended release (ER) beads in a capsule (Metadate CD); 3) a mixture of 50% IR and 50% ER beads in a capsule using a spheroidal oral drug absorption system [SODAS] (Ritalin LA); and 4) a transdermal system (Daytrana patch). The other stimulant once daily products include mixed amphetamine salts ER (Adderall XR) and dexmethylphenidate SODAS (Focalin XR).

Multiple daily use products include five methylphenidate products: Ritalin, Ritalin sustained release (SR) (generics), Metadate ER (generics), Methylin ER (generics), and Methylin (generics). Other multiple daily use products include mixed amphetamine salts IR (Adderall, generics), dexmethylphenidate IR (Focalin), dextroamphetamine IR (Dexedrine, Dextrostat, generics), and methamphetamine IR (Desoxyn, generics).

A. ADHD and Narcolepsy Agents – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the ADHD and narcolepsy agents 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.

1) Efficacy

a) ADHD Drugs

i) Standard Therapy – Stimulants have remained the mainstay of therapy for treating children with ADHD. A systematic review completed by the state of Oregon Health and Science University Drug Effectiveness Review Program (DERP) concluded that the overall response rate with the stimulants ranges from 60-80%, but varying definitions of response were reported in the clinical trials.

ii) Clinical Trials – Interpretation of the efficacy literature is difficult due to the poor study design of published trials, use of different outcome rating scales, the limited number of comparator trials available, small number of patients enrolled in the studies, and overall short duration of evaluation. Direct comparisons of the trials are difficult, due to wide heterogeneity among trials and use of different ADHD rating scales.

IR versus IR stimulant products – The DERP systematic review compared the clinical efficacy of dextroamphetamine IR (Dexedrine, Dextrostat, generics) to methylphenidate IR (Ritalin, generics); reviewers concluded that none of the studies showed an efficacy difference between the two IR stimulants.

Two studies [Pelham 1999, Pliska 2000] that compared methylphenidate IR (Ritalin, generics) vs. mixed amphetamine salts IR (Adderall, generics) did not show a difference in efficacy. A study [Wigal 2004] comparing dexmethylphenidate IR (Focalin) with Adderall also found no difference in efficacy between the two drugs. The Committee concluded that the current body of evidence does not indicate a difference in the efficacy between methylphenidate IR, dextroamphetamine IR, dexmethylphenidate IR, and mixed amphetamine salts IR.

IR versus once daily stimulant products – The DERP systematic review identified only three studies comparing IR with once daily stimulants that were of sufficient study design quality to evaluate; all three trials compared methylphenidate IR (Ritalin, generics) with methylphenidate OROS (Concerta). One trial [Pelham 2001] enrolling 70 patients found no difference in the teacher rating scale, but reported a statistically significant difference in the parent rating scale that favored Concerta over methylphenidate IR. In a small study assessing driving skills in six adolescents [Cox 2004], there was no difference between the drugs at four to six hours after dosing. However, at 9 to 12 hours after administration, there was a statistically significant difference favoring Concerta. Another study enrolling 282 patients [Wolraich 2001] reported no difference in efficacy. The Oregon systematic review reported that in short-term studies, once daily

Concerta was preferred over methylphenidate IR products. However in trials with a longer duration of evaluation, there was no efficacy difference reported.

Once daily stimulants vs. once daily stimulants – When comparing the once daily products, the different drug release mechanisms influence the timing of effect. Methylphenidate OROS (Concerta) releases 22% of the drug dose immediately followed by release of 78% of the drug over 12 hours. Methylphenidate SODAS (Ritalin LA) releases 50% of the dose immediately and the remaining 50% over an 8- to 9-hour period. The methylphenidate formulation of 30% IR/70% ER beads (Metadate CD) releases 30% of the dose immediately, followed by the remaining 70% over an 8 to 9 hour period.

The drug delivery system appeared to have direct bearing on the results of two studies comparing sustained release products. A trial in 184 patients comparing methylphenidate 30% IR/70% ER (Metadate CD) with methylphenidate OROS (Concerta) [Swanson 2004] used a classroom rating scale as the outcome measure. Metadate CD was superior to Concerta in the morning, and there was no difference between the two drugs in the afternoon. However, in the evening, Concerta was superior to Metadate CD, reflecting the long duration of Concerta via the OROS system.

Methylphenidate OROS (Concerta) was compared to methylphenidate SODAS (Ritalin LA) in a randomized crossover trial enrolling 36 patients [Lopez 2003] using the classroom rating scale. At the four hour assessment time, Ritalin LA 20 mg was superior to 18 mg and 36 mg doses of Concerta. At the eight hour assessment, there was no difference between the Ritalin LA 20 mg and Concerta 36 mg. This study did not include a 12-hour assessment.

Once daily mixed amphetamine salts ER (Adderall XR) was compared to methylphenidate OROS (Concerta) and placebo in a driving assessment test conducted in 35 adolescents [Cox 2006*]*. Concerta compared more favorably to placebo than did mixed amphetamine salts ER (Adderall XR).

Dexmethylphenidate SODAS (Focalin XR) and methylphenidate transdermal system (Daytrana): There are no published trials comparing the efficacy of dexmethylphenidate SODAS (Focalin XR) or methylphenidate transdermal system (Daytrana) with other once daily stimulants; only placebo control trials are available for both products. The pharmacokinetic profiles of both drugs reflect a 12-hour duration of action.

Atomoxetine (Strattera): The DERP systematic review evaluated four studies comparing the non-stimulant atomoxetine (Strattera) and placebo, and reported that atomoxetine was superior to placebo. One trial reported superior efficacy with that atomoxetine compared to methylphenidate IR (Ritalin, generics) [Kratochvil 2002], while another other trial [Sangal 2004] reported no difference in efficacy. Three trials comparing atomoxetine with

either Concerta [Kremmer 2004; Michelson 2004] or Adderall XR [Wigal 2004] showed superior efficacy of the stimulants over atomoxetine.

iii) Treating non-responders – One study evaluating treatment response compared methylphenidate IR (Ritalin, generics) with dextroamphetamine IR (Dexedrine, Dextrostat, generics) [Efron 1997], and concluded that 40% to 80% of patients who did not respond to the initial stimulant would respond to the second stimulant. Clinically, patients who do not respond to a methylphenidate formulation often receive a trial of mixed amphetamine salts IR or ER (Adderall, Adderall XR).

iv) Clinical efficacy conclusion – All stimulant and non-stimulant formulations reviewed, no matter the delivery mechanism, have superior efficacy to placebo. Based on the limited data available, there does not appear to be a difference in efficacy between methylphenidate IR (Ritalin, generics), dextroamphetamine IR (Dexedrine, Dextrostat, generics), dexmethylphenidate IR (Focalin) and mixed amphetamine salts IR (Adderall, generics). Studies comparing IR to once daily methylphenidate products overall yielded no apparent difference in efficacy. The efficacy outcomes of studies comparing once daily methylphenidate products are dependent on the individual release mechanisms of the drugs. Methylphenidate 30% IR/70% ER (Metadate CD) and methylphenidate SODAS (Ritalin LA) showed superior efficacy to methylphenidate OROS (Concerta) at four and eight hour timeframes respectively. Concerta has an efficacy advantage over the other once daily products at the 9-12 hour timeframe. The only products with a sustained 12-hour effect are Concerta, dexmethylphenidate ER (Focalin XR), and methylphenidate transdermal system (Daytrana). The stimulants Concerta and mixed amphetamine salts ER (Adderall XR) appear to have superior efficacy compared to atomoxetine (Strattera).

b) Narcolepsy Drugs

i) Pharmacology

Modafinil (Provigil) – The exact mechanism of action by which modafinil promotes wakefulness is unknown. In contrast to drugs with high addiction potential (e.g., cocaine, amphetamine), modafinil only weakly stimulates receptors in the brain that play a role in reward, pleasure and addiction. This may explain the decreased addiction potential of modafinil compared to other stimulants.

Sodium oxybate (Xyrem) – The exact mechanism of action of sodium oxybate (Xyrem) is unknown. This medication, known chemically as the sodium salt of gamma-hydroxybutyrate (GHB), is similar to gamma-aminobutyric acid (GABA). However, there are distinct GHB receptors in the CNS, where GHB is believed to function as a neurotransmitter and cause marked CNS depression.

ii) FDA-approved indications – Both modafinil (Provigil) and sodium oxybate (Xyrem) are indicated for the treatment of excessive sleepiness associated with narcolepsy. Modafinil (Provigil) is also indicated for the treatment of excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome (OSAHS) when used as an adjunct to continuous positive airway pressure (CPAP) treatment, and shift-worker sleep disorder (SWSD). Sodium oxybate (Xyrem) is also indicated for the treatment of cataplexy in narcolepsy.

Sodium oxybate (Xyrem) under the moniker of GHB attained notoriety in the 1980s as an illicit drug abused for drug-assisted sexual assault. In 2002, action by the U.S. Congress reclassified the drug as a schedule III product for treatment of narcolepsy. The FDA required a restricted distribution system, the Xyrem Success Program, as a condition for the 2002 approval to reduce the likelihood of diversion for illicit purposes. This program consists of exclusive distribution through a centralized pharmacy, a physician and patient registry, compulsory educational materials for both the physician and the patient, and a tracked method of shipping.

iii) Non-FDA approved indications – Modafinil (Provigil) is used for several conditions that are not approved by the FDA, including ADHD; fatigue associated with chronic diseases (cancer, Parkinson's disease, chronic fatigue syndrome, multiple sclerosis, fibromyalgia); fatigue associated with myotonic dystrophy, idiopathic hypersomnia, or due to antipsychotic or narcotic mediations; augmentation therapy for depression; cocaine dependence; schizophrenia; fatigue related to polio; and several others.

iv) Efficacy

Modafinil (Provigil)

- *Narcolepsy (FDA approved indication):* Four randomized double-blinded placebo controlled trials [US Modafinil in Narcolepsy Multicenter Study Group 1998, 2000; Broughton 1997; Billiard 1994] reported statistically significant improvements in objective and subjective daytime sleepiness. The American Academy of Sleep Medicine rates modafinil as the "standard" of treatment for narcolepsy.
- *Excessive daytime sleepiness associated with OSAHS (FDA approved indication):* Three randomized double-blinded placebo controlled trials evaluated the efficacy of modafinil administered as an adjunct to CPAP treatment [Black 2005, Pack 2005, Kingshott 2001]. In the majority of the patients studied, there were statistically significant improvements (rated both objectively by providers and subjectively by the subjects) in daytime sleepiness.
- *Excessive daytime sleepiness associated with SWSD (FDA approved indication):* Two randomized double-blinded placebo controlled trials [Czeisler 2005, Rosenberg 2003] both showed statistically significant

improvement in objective and subjective measures of fatigue in patients during work-time shifts.

- *Depression (non-FDA approved indication)*: Two randomized double-blinded placebo controlled trials [Fava 2005, Frye 2005] reported statistically significant improvement in objective measures of global improvement. There were improvements in some (but not all) depression-specific rating scales. There was no evidence of increased manic emergence in patients with bipolar depression.
- *Multiple Sclerosis (MS) (non-FDA approved indication)*: One randomized double-blinded placebo controlled trial and one single blinded trial [Stankoff 2005, Rammohan 2002] evaluated efficacy of modafinil for fatigue associated with multiple sclerosis (MS). Stankoff et al showed no statistically significant difference in subjective measures of fatigue and daytime sleepiness. However, Rammohan et al showed a statistically significant improvement in objective measures of fatigue and daytime sleepiness. The National MS Society's expert opinion guideline on management of multiple sclerosis fatigue recommends 200 mg of modafinil daily as a primary treatment of MS fatigue, once secondary causes of fatigue have been addressed.
- *Cocaine dependence (non-FDA approved indication)*: There are two randomized double-blinded placebo controlled trials evaluating use of modafinil to treat cocaine dependency [Dackis 2003, 2005]. One trial showed a statistically significant decrease in self-rated euphoria in treated patients versus placebo. The other trial reported a statistically significant increase in the number of patients who remained abstinent from cocaine abuse for greater than three weeks versus placebo.
- *Myotonic dystrophy (non-FDA approved indication):* Two randomized double-blinded placebo controlled trials [MacDonald 2002, Talbot 2003] showed statistically significant improvements in subjective measures of daytime sleepiness, fatigue, and improvements in subjective quality of life measures.

Sodium oxybate (Xyrem)

- *Excessive daytime sleepiness:* Three randomized, double-blinded placebo controlled trials [Black et al 2006, US Xyrem Multicenter Study Group 2002, 2003] supported the FDA new drug application of sodium oxybate (Xyrem) for excessive daytime sleepiness. All three trials statistically significant improvements in subjective measures of daytime sleepiness with sodium oxybate compared to placebo; in some cases improvements approached normal values. Improvements in sleep quality, alertness, and concentration were also noted.
- *Narcolepsy associated with cataplexy:* Four randomized, double-blinded placebo controlled trials [US Xyrem Multicenter Study Group

2002, 2003, 2005, Scrima 1989] support the use of the drug for narcolepsy associated with cataplexy. All four trials reported statistically significant reductions in the number of cataplexy attacks ranging from 50% to 90%, compared to placebo.

- *Idiopathic hypersomnia:* Two open-label trials [Bastuji 1988, Laffont 1994] showed statistically significant reductions in the number of sleep attacks and daytime drowsiness in most patients treated. This disorder is clinically very similar to narcolepsy, and is diagnosed only through a sleep study by a sleep specialist.

2) Safety and Tolerability

a) ADHD Drugs

i) Black box warning

Stimulants: All the stimulants carry a black box warning of dependence, tolerance and abuse potential. The amphetamines carry a black box warning for sudden cardiac death. An FDA review of the adverse event reporting system concluded that the risk of sudden deaths was not greater than expected, given the large number of people taking the drug. Since the majority of the deaths occurred in children who had structural cardiovascular abnormalities, a warning against using any stimulant in such patients was added to labeling.

Non-stimulant: Atomoxetine (Strattera), which is mechanistically similar to some antidepressants, has a similar black box warning for suicidal ideation.

ii) Contraindications – The stimulants are contraindicated for use in patients with tics, a history of Tourette's syndrome, psychosis, or mania. Stimulants are also contraindicated in patients with significant cardiovascular disease and in patients who experience agitation. Stimulants and atomoxetine (Strattera) are contraindicated in patients who have ingested monoamine oxidase inhibitors (MAOIs) within the last 14 days, and in patients with glaucoma.

iv) Cardiovascular warnings – All the drugs in the ADHD class (both stimulant and non-stimulant) can raise blood pressure (on average by 2-4 mm Hg) and heart rate (on average by 3-6 beats per minute). All the products in the class carry a general warning for patients with underlying cardiac conditions.

v) Hepatotoxicity – Atomoxetine (Strattera) carries a bolded warning for liver injury in the package literature. In over two million treated patients, there have been two cases of significant liver injury. There is currently no recommendation by the manufacturer to monitor liver function in patients treated with atomoxetine.

vi) Decreased growth velocity – Early studies conducted with the stimulants showed a relationship between drug treatment and decreased growth velocity. Decreases in height can range from 0.7 to 1.9 cm in treated patients versus control patients. Long-term studies show trends for treated

patients to catch up with non-treated peers. Labeling for all stimulant products contains strong warnings for continual evaluation of growth velocity in treated patients.

vii) Dermatological reactions – Methylphenidate transdermal system (Daytrana patch) can cause contact sensitization, which is characterized by erythema with an intense local reaction. Rechallenge with the transdermal system may cause skin eruptions, headache, fever and malaise. Data provided by the manufacturer of the transdermal system shows that up to 13% of patients treated with methylphenidate transdermal system may become sensitized to orally administered methylphenidate.

viii) Drug interactions

Stimulants: The stimulants have clinically relevant drug interactions with MAOIs, anticonvulsants, and antidepressants. The body's ability to eliminate the mixed amphetamine salts IR and ER (Adderall, generics; Adderall XR) can be significantly affected by drugs or foods that alkalinize or acidify the urine.

Non-stimulants: Atomoxetine (Strattera) can interact with drugs that inhibit CYP2D6, including paroxetine (Paxil, generics), fluoxetine (Prozac, generics), and quinidine (generics).

ix) Minor adverse events

Stimulants: General adverse events frequently reported during use with any stimulant include delayed sleep onset, headache, decreased appetite, and weight loss. Mixed amphetamine salts IR and ER (Adderall, generics; Adderall XR) have a high percentage of patients who experience irritability and insomnia.

Non-stimulants: Atomoxetine (Strattera) is associated with somnolence, nausea, and vomiting, particularly when dosages are titrated to maximum doses over a few days. Decreased appetite is less of a concern with the atomoxetine than with the stimulants. Patients unable to tolerate adverse effects of the stimulants are often started on therapy with atomoxetine. Atomoxetine is not a controlled drug and is not associated with the same potential for abuse and tolerance as the stimulants.

x) Tolerability

Discontinuation due to adverse effects: Approximately 1%-7% of patients will discontinue ADHD drugs due to adverse events. The most frequently noted adverse events causing discontinuation are irritability, headache, anorexia, nervousness, and agitation.

Persistence: One report [Kenner 2003] comparing the once daily stimulant formulations showed that patients taking methylphenidate OROS (Concerta) and mixed amphetamine salts ER (Adderall XR) took their medication more consistently than patients receiving methylphenidate 30% IR/70% ER (Metadate CD). Another report [Marcus

2005] showed that patients were more persistent with Concerta for longer time periods than methylphenidate IR (Ritalin, generics).

xi) Safety and tolerability conclusion – Major concerns with the stimulants include potential for abuse and tolerance, as well as the potential for sudden cardiac death in patients with underlying structural heart defects. Slowed growth velocity remains an issue with all stimulants. The methylphenidate transdermal system (Daytrana) can cause significant dermatological adverse events and sensitization that can preclude subsequent use of any methylphenidate product. Patients receiving a once daily stimulant may be more persistent with therapy than with IR stimulants.

b) Narcolepsy Drugs

i) Modafinil (Provigil)

Serious adverse events: Three cases of clinically important rashes, including Stevens-Johnson Syndrome (SJS), occurred with modafinil (Provigil) in clinical trials investigating use of the drug for ADHD in children. The FDA adverse event reporting system has received five reports of SJS or erythema multiforme in adults. The new drug application for modafinil (submitted under the trade name Sparlon) for ADHD was denied by the FDA due to these reports.

Addiction potential: Modafinil (Provigil) is a Schedule IV controlled drug. It has not been associated with producing withdrawal symptoms or tolerance.

Drug Interactions: Modafinil (Provigil) undergoes primarily hepatic metabolism; however, there are few clinically significant drug-drug interactions. Absorption of methylphenidate and dextroamphetamine may be delayed by approximately one hour when co-administered with modafinil. Concurrent administration with oral contraceptives containing ethinyl estradiol may result in an 18% reduction in peak concentrations of ethinyl estradiol, thus alternate forms of contraception should be considered in females of child-bearing age.

General adverse events: In the six randomized double-blinded placebo controlled trials performed to obtain FDA approval, the most commonly reported treatment emergent adverse events included headache (34% with modafinil vs. 23% with placebo), nausea (11% with modafinil vs. 3% with placebo), nervousness (7% with modafinil vs. 3% with placebo), and insomnia or anxiety (5% with modafinil vs. 1% with placebo). The percentage of patients discontinuing therapy due to an adverse event was 8% with modafinil-treated patients vs. 3% with placebo-treated patients. Modafinil does not cause clinically significant increases in blood pressure or heart rate, and does not affect sleep architecture.

ii) Sodium oxybate (Xyrem)

Serious adverse events: Sodium oxybate (Xyrem) is a CNS depressant with a high potential for abuse. It carries a black box warning against concomitant use with alcohol or other CNS depressants. In the clinical trials used to gain FDA approval, two deaths were reported due to drug overdoses from ingestion of multiple drugs. Multiple deaths have been reported in association with GHB use, mostly in the setting of intentional abuse with other substances, where it is difficult to determine the exact doses used.

Addiction potential: The drug has demonstrated abuse potential given its properties as a psychoactive drug. A wide range of psychoactive effects have been reported, including dose-dependent sedation/hypnosis.

Drug interactions: Concomitant use of sodium oxybate (Xyrem) with barbiturates, benzodiazepines, and centrally acting muscle relaxants results in additive CNS and respiratory depression. One case report of sodium oxybate taken with methamphetamine resulted in seizure. Use with opioid analgesics and ethanol may result in respiratory depression.

General adverse events: In clinical trials enrolling over 700 patients with narcolepsy, the most commonly reported adverse events were headache (22%), nausea (21%), dizziness (17%), somnolence (8%), vomiting (8%), and enuresis (7%). In these trials, 10% of patients discontinued sodium oxybate (Xyrem) therapy due to adverse events (compared to 1% with placebo), most commonly due to nausea, dizziness, or vomiting (each occurring with a 2% incidence).

3) Other Factors

a) ADHD Drugs

i) Pregnancy/Lactation – All of the ADHD drugs are rated as pregnancy category C. The amphetamines and atomoxetine (Strattera) are excreted in breast milk. It is not known whether methylphenidate products are excreted in breast milk.

ii) Pediatrics – The FDA has approved the use of the ADHD drugs in patients down to the age of six years. Dextroamphetamine (Dexedrine, Dextrostat, generics) is labeled for use in patients as young as three years of age.

iii) Renal and hepatic dysfunction – Dosage adjustments are not required for any of the ADHD drugs in patients with renal failure. In patients with hepatic impairment, only atomoxetine (Strattera) requires dosage adjustment.

iv) Dosage formulations – The methylphenidate transdermal system (Daytrana) is the only non-oral formulation in this class. Methylphenidate 30% IR/70% ER (Metadate CD), mixed amphetamine salts ER (Adderall XR), dexmethylphenidate SODAS (Focalin XR) and methylphenidate SODAS (Ritalin LA) are capsule formulations that can be opened and sprinkled on

food for patients with swallowing difficulties. Methylphenidate IR (Methylin) is available in an oral solution and chewable tablets.

v) One survey [Wilens 2004] of students taking stimulant medications for ADHD treatment reported that 22% of patients escalated doses, with 10% escalating doses specifically for euphoric effects. Also of note, 11% of the students sold their medication to peers. Another survey [Teter 2006] of college students taking stimulant medication found that mixed amphetamine salts IR and ER (Adderall, generics; Adderall XR) were the most frequently abused products. A concerning finding was that the stimulants were crushed and snorted for their euphoric effects. Respondents also used the stimulants for weight loss and to increase concentration for studying.

vi) MTF provider opinion and clinical coverage: A total of 214 MTF providers responded to an opinion survey. All responders desired the availability of a long-acting methylphenidate product; providers specifically preferred methylphenidate OROS (Concerta). Providers prescribed Concerta more frequently than mixed amphetamine salts ER (Adderall XR) or atomoxetine (Strattera) when initiating therapy. However, providers requested availability of both Adderall XR and atomoxetine as therapeutic options for patients intolerant of or not responding to methylphenidate products. A methylphenidate IR product was also requested. Providers were not familiar with and did not prescribe the methylphenidate transdermal system (Daytrana), dexmethylphenidate IR and SODAS (Focalin, Focalin XR), and methamphetamine IR (Desoxyn, generics).

Survey responders stated that in addition to the current BCF agents, most pharmacies stocked methylphenidate SR (Ritalin SR) and about half the pharmacies stocked atomoxetine (Strattera). The most requested non-formulary agent was atomoxetine, followed by long-acting methylphenidate 30% IR/70% ER (Metadate CD.)

vii) Other Factors Conclusion: All the products in the ADHD class are rated pregnancy category C. All the products are indicated for use in pediatric patients. The dose of atomoxetine (Strattera) must be adjusted in patients with hepatic insufficiency. There are multiple products available for patients who have difficulty swallowing a tablet or capsule. The stimulants have significant abuse potential. MTF providers desired availability of a long-acting methylphenidate product, preferably methylphenidate OROS (Concerta); an IR methylphenidate product; mixed amphetamine salts ER (Adderall XR); and atomoxetine.

b) Narcolepsy agents

i) Modafinil (Provigil): Modafinil (Provigil) has not been evaluated in patients older than 65 years of age or younger than 16 years of age. The dosage should be decreased in patients with severe hepatic impairment.

ii) Sodium oxybate (Xyrem): Sodium oxybate is primarily metabolized in the liver; patients with hepatic insufficiency require dosage reduction by 50%. No dosage adjustment is necessary in patients with renal insufficiency. There is no clinical trial experience with patients over the age of 65 or under 16 years of age.

ADHD and Narcolepsy Overall Clinical Effectiveness Conclusion – The P&T Committee concluded that:

1) For ADHD, interpretation of the data is limited due to the poor quality of studies, limited number of comparator trials, varying rating scales used, small number of patients enrolled, and short study duration.

2) There is no evidence to suggest a difference in efficacy between IR formulations of methylphenidate (Ritalin, generics), dextroamphetamine (Dexedrine, Dextrostat, generics), dexmethylphenidate (Focalin), and mixed amphetamine salts (Adderall, generics).

3) The overall efficacy of the once daily methylphenidate formulations appears similar based on a few small studies, but differences exist in reported outcomes at specific times of the day, due to the individual release mechanisms of the products. Methylphenidate 30% IR/70% ER (Metadate CD) and methylphenidate SODAS (Ritalin LA) are eight- to nine-hour products, while methylphenidate OROS (Concerta), dexmethylphenidate SODAS (Focalin XR), and methylphenidate transdermal system (Daytrana) are 12-hour products.

4) Mixed amphetamine salts ER (Adderall XR) appears to have similar efficacy to methylphenidate OROS (Concerta), based on one small study.

5) The efficacy of atomoxetine (Strattera) appears to be inferior to the stimulants, but it is the only non-stimulant available in the ADHD class.

6) Between 40% and 80% of patients who do not respond to one type of stimulant (methylphenidate products vs. amphetamine products) may respond to the other.

7) The adverse events and warnings of the stimulants are well-recognized and are similar between products.

8) The methylphenidate transdermal system (Daytrana) can cause significant dermatological adverse events, which can lead to sensitization to oral products.

9) Atomoxetine (Strattera) remains the only alternative for patients who cannot tolerate stimulants, despite its association with an increased risk of hepatotoxicity and suicidal ideation.

10) Several products can be sprinkled on food for patients with swallowing difficulties.

11) Responders to a provider survey expressed a desire for availability of the following products to cover clinical needs: methylphenidate OROS, an IR methylphenidate product, mixed amphetamine salts ER, and atomoxetine.

12) The narcolepsy drug modafinil (Provigil) fills a unique niche in therapy as a wakefulness promoting agent.

13) The narcolepsy drug sodium oxybate (Xyrem) has a high incidence of adverse events, but fills a unique niche in therapy for cataplexy. The manufacturer's restricted distribution program limits use to appropriate patients.

14) Based on clinical issues alone, there are no reasons to designate any of the ADHD drugs or narcolepsy drugs as non-formulary under the UF.

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

B. ADHD and Narcolepsy Agents – Relative Cost Effectiveness

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

The cost-effectiveness review was conducted on subclasses based on each agent's indication for treatment (ADHD or narcolepsy). Drugs evaluated in the ADHD subclass were further grouped by duration of action. This process of categorization left three subclasses:

1) A once daily use subclass of ADHD products including mixed amphetamine salts ER (Adderall XR), atomoxetine (Strattera), dexmethylphenidate SODAS (Focalin XR), methylphenidate OROS (Concerta), methylphenidate 30% IR/70% ER (Metadate CD), methylphenidate SODAS (Ritalin LA), and methylphenidate transdermal system (Daytrana).

2) A multiple daily use subclass of ADHD products including mixed amphetamine salts IR (Adderall, generics), dexamphetamine IR (Dexedrine, Dextrostat, generics), dexmethylphenidate IR (Focalin), methamphetamine IR (Desoxyn, generics), methylphenidate IR (Ritalin, generics), and methylphenidate sustained-release (Ritalin SR).

3) A subclass of drug products indicated for narcolepsy including mixed amphetamine salts IR (Adderall, generics), dexamphetamine IR (Dexedrine, Dextrostat, generics), methylphenidate IR (Ritalin, generics), modafinil (Provigil), and sodium oxybate (Xyrem).

The choice of cost-effectiveness analysis for each subclass was based on the findings from the clinical effectiveness review. The results of the clinical review showed evidence of differences among the drugs in the once daily use subclass in regards to efficacy. However, there was insufficient evidence to conclude that the multiple daily use and narcolepsy subclasses differed based on efficacy, safety, tolerability, or clinical outcomes. In light of these conclusions, the cost-effectiveness analyses were conducted as follows: (1) cost-utility analysis of the once daily use subclass; (2) cost-minimization analysis of the multiple daily use subclass; and (3) cost-minimization analysis of the drugs indicated for the treatment of narcolepsy.

1) The cost-utility analysis compared the costs per quality-adjusted life year (QALY) among the once daily use products. The results showed methylphenidate OROS (Concerta) to be the most cost-effective agent in this subclass. The mixed

amphetamine salts ER (Adderall XR) and methylphenidate 30% IR/70% ER (Metadate CD) also performed well with similar cost-effectiveness ratios. Atomoxetine (Strattera) was cost-effective under a scenario assuming greater patient preference for a non-stimulant once daily use product. Dexmethylphenidate SODAS (Focalin XR) and methylphenidate transdermal system (Daytrana) were not cost-effective relative to the other agents in the subclass.

2) The cost-minimization analysis of the multiple daily use products compared the weighted average cost per day of treatment across all three points of service for each drug product. The results revealed that most products were cost-effective, with methylphenidate IR (Ritalin, generics) being the most cost-effective agent in this subclass. Dexmethylphenidate IR (Focalin) was less cost-effective than other agents in this subclass. Furthermore, the absence of a compelling clinical rationale for inclusion on the UF suggested dexmethylphenidate IR should be evaluated for non-formulary status.

3) The cost-minimization analysis for the drug products indicated in the treatment of narcolepsy compared the weighted average cost per day of treatment across all three points of service for mixed amphetamine salts IR (Adderall, generics), dexamphetamine IR (Dexedrine, Dextrostat, generics), methylphenidate IR (Ritalin, generics), and modafinil (Provigil). Sodium oxybate (Xyrem) also was included and evaluated at its cost per day of treatment in the retail point of service only, since it is not available at the other points of service due to its controlled distribution system. The results showed that methylphenidate IR was the most cost-effective agent in the treatment of narcolepsy, followed closely by dexamphetamine IR and mixed amphetamine salts IR. Sodium oxybate and modafinil, although more costly per day of treatment relative to the other drugs in this subclass, possessed unique clinical advantages justifying their inclusion on the Uniform Formulary. Modafinil has a unique niche for wakefulness promotion in a variety of disorders (as described in the clinical review) and sodium oxybate has proven efficacy for narcolepsy complicated by cataplexy.

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

Cost Effectiveness Conclusion

1) Once daily ADHD agents: dexmethylphenidate SODAS (Focalin XR) and methylphenidate transdermal system (Daytrana) were not cost-effective relative to the other agents in the subclass.

2) Multiple daily use ADHD agents: dexmethylphenidate IR (Focalin) was not cost-effective relative to the other agents in the subclass.

Agents indicated in the treatment of narcolepsy:

1) Although modafinil (Provigil) and sodium oxybate (Xyrem) were more costly relative to the other agents in the subclass, they possessed unique clinical advantages relative to other agents indicated for the treatment of narcolepsy.

2) The UF scenario that included dexmethylphenidate IR (Focalin), dexmethylphenidate SODAS (Focalin XR), and methylphenidate transdermal system (Daytrana) as non-formulary under the UF best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS and was the most cost-effective UF scenario.

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

C. ADHD and Narcolepsy Agents – UF Recommendations

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ADHD and Narcolepsy agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that mixed amphetamine salts IR (Adderall, generics), mixed amphetamine salts ER (Adderall XR), atomoxetine (Strattera), dexamphetamine IR (Dexedrine, Dextrostat, generics), methamphetamine IR (Desoxyn, generics), methylphenidate 30% IR/70% ER (Metadate CD), methylphenidate IR (Ritalin, generics), methylphenidate OROS (Concerta), methylphenidate SODAS (Ritalin LA), methylphenidate SR (Ritalin SR), modafinil (Provigil), and sodium oxybate (Xyrem) be maintained as formulary on the UF and that dexmethylphenidate IR (Focalin), dexmethylphenidate SODAS (Focalin XR), methylphenidate transdermal system (Daytrana) be classified as non-formulary under the UF.

D. ADHD and Narcolepsy Agents – Medical Necessity Criteria

Based on the clinical evaluation for methylphenidate transdermal system (Daytrana), dexmethylphenidate IR (Focalin) and dexmethylphenidate SODAS (Focalin XR), and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general medical necessity criteria for methylphenidate transdermal system (Daytrana), dexmethylphenidate IR (Focalin), and dexmethylphenidate SODAS (Focalin XR):

1) Use of formulary alternatives is contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.

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

4) No formulary alternative is available.

The P&T Committee noted that criterion #4 would apply only to the use of methylphenidate transdermal system (Daytrana) by patients who require treatment with a once daily methylphenidate product, but who are unable to take oral medication.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to approve the medical necessity criteria outlined above.

E. ADHD and Narcolepsy Agents – UF Implementation Period

Because of the small number of unique utilizers affected (approximately 3,000 patients out of approximately 175,000 unique utilizers at all three POS), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have methylphenidate transdermal system (Daytrana), dexmethylphenidate IR (Focalin), or dexmethylphenidate SODAS (Focalin XR) on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) medical necessity is established. MTFs may (but are not required to) fill a prescription for a non-formulary ADHD agent written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. ADHD and Narcolepsy Agents – Basic Core Formulary (BCF) Review and Recommendations – The P&T Committee had previously determined that two once daily use products and one or more multiple daily use products should be added to the BCF based on the clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that the BCF remain unchanged with mixed amphetamine salts ER (Adderall XR), methylphenidate OROS (Concerta), and methylphenidate IR (Ritalin, generics) on the BCF. Concerta has high utilization due to current BCF status, is a methylphenidate product with a 12-hour duration, and was determined to be the most cost-effective once daily methylphenidate product. Similarly, Adderall XR has high utilization at the MTFs; is an amphetamine product with a 12-hour duration, and was cost-effective relative to the other agents in the subclass. Methylphenidate IR is extremely cost-effective, is available in a generic formulation, and allows for dose titration.

COMMITTEE ACTION – The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend retaining mixed amphetamine salts ER (Adderall XR), methylphenidate OROS (Concerta), and methylphenidate IR (Ritalin) as the BCF selections in this class.

8. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR MODAFINIL (PROVIGIL)

Modafinil (Provigil) is approved by the FDA for treatment of excessive daytime sleepiness associated with narcolepsy, excessive daytime sleepiness associated with obstructive sleep apnea/hypopnea syndrome (OSAHS) when used as an adjunct to continuous positive airway pressure (CPAP) treatment, and excessive daytime sleepiness associated with shift-worker sleep disorder (SWSD). There are numerous off-label uses for the drug.

Modafinil (Provigil) accounted for approximately $24 million in DoD expenditures in FY 06. Given the rapid increase in use and expenditures, a DoD-specific analysis of modafinil utilization was performed. Among unique utilizers of modafinil, as many as 44% of the total prescriptions appeared to be written for indications not supported by well-controlled studies with clinically meaningful endpoints that are published in refereed medical literature. Given the increasing use of modafinil for off-label indications not well established by the medical literature, the Committee agreed that a PA should be required for modafinil.

Taking into consideration the clinical review recommendation that modafinil (Provigil) require a PA, a threshold analysis was conducted to estimate the relationship between the administrative costs of conducting a PA policy and the cost-offset from reduced utilization of modafinil secondary to the policy. The results suggested that the administrative costs of a PA requirement for modafinil would not be cost-prohibitive.

The P&T Committee identified five off-label indications, in addition to the three FDA-approved indications, as supportable based on published clinical evidence or recommendations from nationally recognized expert organizations, based on guidelines from the TRICARE Policy Manual 6010.54 (August 2002) chapter 1 section 2.1 regarding coverage of unproven drugs, devices, medical treatments and procedures. With respect to the off-label uses, clinical evidence supports use of modafinil (Provigil) for augmentation of treatment for major depression, fatigue associated with multiple sclerosis (MS), augmentation of primary cognitive-behavioral therapy in acute rehabilitation of cocaine dependence, fatigue associated with myotonic dystrophy, and fatigue associated with idiopathic hypersomnia. Other off-label uses (e.g., in chronic fatigue syndrome, stroke rehabilitation, appetite suppression, Parkinson's disease and others) are supported only by case reports, uncontrolled trials, single-blinded trials, or chart reviews, which constitute insufficient evidence to establish efficacy and safety per TRICARE regulations. The PEC will continue to monitor the clinical literature on an ongoing basis for evidence that may justify revision of these criteria.

COMMITTEE ACTION – Based on its increasing use for off-label indications not well established by the medical literature, the P&T Committee recommended that a PA be required for modafinil (Provigil) (15 for, 0 against, 0 abstained, 2 absent). The Committee recommended that the PA should have an effective date of the first Wednesday following a 90-day implementation period, consistent with the recommended implementation period for non-formulary medications in the ADHD and narcolepsy agents class. The implementation period will begin immediately following the approval by the Director, TMA.

The Committee agreed that the following PA criteria should apply (15 for, 0 against, 0 abstained, 2 absent). PA approval would be good for one year. The P&T Committee noted that the PA is not intended to apply to modafinil (Provigil) use in Active duty operational/readiness situations based on established protocols; MTFs should make necessary allowances for such use.

1) Narcolepsy
2) OSAHS, only after adequate titration of CPAP treatment
3) SWSD, only in patients who work night shifts
4) MS, only after secondary causes of fatigue have been addressed

5) Myotonic dystrophy

6) Depression, only after primary therapy has failed and if the use of other stimulant augmentation is contraindicated

7) Idiopathic hypersomnia diagnosed by a sleep specialist

8) Cocaine dependence when approved by a DoD substance abuse program

9. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR FENTANYL PATCHES (DURAGESIC, GENERICS)

Based on the following considerations, the P&T Committee agreed that a PA should be required for fentanyl patches (Duragesic, generics).

- Fentanyl, a strong opioid narcotic, can cause severe respiratory depression in patients who are not tolerant to opioids. Product labeling for fentanyl patches was strengthened in July 2005 following reports of serious adverse events and fatalities. Fentanyl patches are indicated for management of persistent, moderate to severe chronic pain requiring continuous, around-the-clock administration for an extended period of time, that cannot be managed by other means, and ONLY in patients who are already receiving opioids, have demonstrated opioid tolerance, and require a total daily dose at least equivalent to fentanyl 25 mcg/hr. They should not be used for management of acute pain or short periods of opioid analgesia; post-op pain, including outpatient/day surgeries; mild pain; or intermittent pain.
- Warnings concerning safe use of fentanyl patches have been issued by various organizations, including the DoD Patient Safety Center, the FDA, and the Institute of Safe Medication Practices. On 31 July 2006, in response to reports of improper use of fentanyl patches, the Air Force established a policy restricting the prescription of fentanyl patches to pain specialists and other authorized providers and requiring drug utilization review by each facility. Pharmacists are required to review all fentanyl patch prescriptions to verify that:
  - Fentanyl is being prescribed for management of chronic pain.
  - The patient has already received opioid therapy, and requires a total daily dose at least equivalent to fentanyl 25mcg/h.
  - Fentanyl is NOT being prescribed for intermittent (prn) pain.
  - The patient is 2 years of age or older.
  - The patient is NOT receiving both fentanyl and potent CYP3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, or nefazodone).

- Modifications to the Pharmacy Data Transaction Service (PDTS) scheduled for completion by December 2006 will add the capability of "looking back" at a given patient's profile for the presence or absence of prescription fills for specific medications within a defined time period. This will allow the fentanyl PA to be targeted only to patients who may not be opioid-tolerant based on prior patterns of opioid use and limit the administrative impact of the PA on patients receiving fentanyl patches on a chronic basis.

COMMITTEE ACTION – Based on safety concerns, the P&T Committee recommended that a PA be required for fentanyl patches (15 for, 0 against, 0 abstained, 2 absent). The Committee recommended that the PA should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible based on availability of the automated PA capability in PDTS. The implementation period will begin immediately following approval by the Director, TMA.

The P&T Committee agreed that the following general PA criteria should apply (15 for, 0 against, 0 abstained, 2 absent), based on requirements in product labeling. Patients meeting the automated PA criteria would not be required to have their providers submit any additional information. PA requirements will apply to each prescription (note, however, that a patient receiving fentanyl patches on a chronic basis would meet automated PA criteria for each prescription).

1) Automated PA criteria:

- Patient is likely to be opioid-tolerant based on the pattern of opioid use in the patient's profile during a defined "look-back" period

2) PA criteria if automated criteria are not met:

- Patient is likely to be opioid-tolerant based on prior opioid use not captured by PDTS (e.g., medications started on an inpatient basis or prescriptions filled outside the DoD pharmacy benefit) AND
- Patient requires a fentanyl patch for treatment of persistent, moderate to severe chronic pain requiring continuous, around-the-clock administration for an extended period of time that cannot be managed by other means and NOT for management of acute pain or short periods of opioid analgesia, post-op pain (including outpatient/day surgeries), mild pain, or intermittent pain.

10. CLASS OVERVIEWS

Portions of the clinical reviews for each of the following classes were presented to the Committee: Topical Glaucoma Agents, Narcotic Analgesics, Angiotensin Receptor Blockers (ARBs), Growth Stimulant Agents, MAOI Antidepressants, 5-Alpha Reductase Inhibitors, 5-HT Receptor Agonists ("Triptans"), Antilipidemics II (LIP-2s), and (Proton Pump Inhibitors (PPIs).

The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed during the February 2007 or May 2007 meetings; no action is necessary.

11. ADJOURNMENT

The second day of the meeting adjourned at 1430 hours on 15 November 2006. The dates of the next meeting are 13-15 February 2007.

_____signed_____

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

List of Appendices

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	Pending approval	NA
Nov 06	ADHD	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	Pending approval	Pending approval
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06 (updated for new drugs Nov 06)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospironone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			Pending approval	Pending approval
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated for new drugs Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
		Recommended Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			Pending approval	Pending approval
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	**-**
Feb 05	ARBs	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary

ER = extended release; IR = immediate release; SR = sustained release

ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs = thiazolidinediones

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs. November 2006 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Insulin Human (rDNA origin) Inhalation Powder (Exubera; Pfizer/Nektar Therapeutics) inhaled insulin	Jan 06 ▪ For control of hyperglycemia in adults with type 1 diabetes in conjunction with long-acting ▪ For control of hyperglycemia in adults with type 2 diabetes either as monotherapy, or in combination with oral agents or long-acting insulin	No UF recommendation at this meeting. Consideration of UF status deferred until insulins are reviewed.
Fentanyl buccal tablet (Fentora; Cephalon) narcotic analgesic	Sep 06 ▪ Management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. ▪ Patients considered opioid tolerant are those who are taking at least 60 mg of morphine/day, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of hydromorphone daily, or an equianalgesic dose or another opioid for a week or longer.	No UF recommendation at this meeting. Consideration of UF status deferred until narcotic analgesics are reviewed; scheduled for Feb 07.
Posaconazole oral suspension (Noxafil; Schering-Plough) oral antifungal agent	Sep 06 ▪ Prophylaxis of invasive Aspergillus and Candida infections in patients 13 years of age and older who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant recipients with graft-versus-hose disease, or those with hematologic malignancies with prolonged neutropenia from chemotherapy ▪ Treatment of oropharngeal candidiasis, including infections refractory to itraconazole and /or fluconazole	No UF recommendation at this meeting. Consideration of UF status deferred until oral antifungal medications are reviewed.
Drosperinone / estradiol 0.5 mg/1 mg (Angeliq; Berlex) hormonal replacement therapy	Sep 05 (launched Oct 06) Indicated in women who have a uterus for the: ▪ Treatment of moderate to severe vasomotor symptoms associated with the menopause. ▪ Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.	No UF recommendation at this meeting. Consideration of UF status deferred until hormonal replacement therapies are reviewed

Appendix C – Table 3. Table of Abbreviations

5-HT3	5-hydroxytryptamine-3
AAP	American Academy of Pediatrics
ADHD	Attention Deficit Hyperactivity Disorder
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BPA	blanket purchase agreement
CD	controlled delivery
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CINV	chemotherapy-induced nausea and vomiting
CMA	cost minimization analysis
CNS	central nervous system
CPAP	continuous positive airway pressure
DERP	Drug Effectiveness Review Project (state of Oregon)
DoD	Department of Defense
EE	ethinyl estradiol
ER	extended release
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FY	fiscal year
GABA	gamma-aminobutyric acid
GHB	gamma-hydroxybutyrate
IV	intravenous
IR	immediate release
LA	long acting
MAOI	monoamine oxidase inhibitor
MHS	Military Health System
MTF	military treatment facility
MS	multiple sclerosis
OTC	over-the-counter
OROS	osmotically controlled-release oral delivery system
OSAHS	obstructive sleep apnea/hypopnea syndrome
PA	prior authorization
PPI	proton pump inhibitor
P&T	Pharmacy and Therapeutics
PDTS	Pharmacy Data Transaction Service
PEC	Pharmacoeconomic Center
QD	once daily
QID	four times daily
SED-2s	older sedative hypnotics
SJS	Stevens-Johnson Syndrome
SODAS	spheroidal oral drug absorption system
SR	sustained release
SWSD	shift worker shift disorder
TID	three times daily
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
UF	Uniform Formulary
VARR	voluntary agreements for TRICARE retail pharmacy rebates
XR	extended release

DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

August 2006

1. CONVENING

2. ATTENDANCE

3. REVIEW MINUTES OF LAST MEETING

4. ITEMS FOR INFORMATION

5. REVIEW OF RECENTLY APPROVED AGENTS

The P&T Committee was briefed on five new drugs that were approved by the Food and Drug Administration. None of the medications fall into drug classes already reviewed by the P&T Committee, therefore Uniform Formulary (UF) consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits, dasatinib (Sprycel), which is an oral multi-kinase inhibitor approved for treatment of patients with chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia. The Committee agreed that quantity limits were needed for dasatinib, based on the risk of discontinuation of therapy, the probability that dosage adjustments requiring changes in tablet strength will be needed, potential for drug interactions, and variable patient response to therapy and drug-related adverse effects. Other oral chemotherapy drugs also have quantity limits.

COMMITTEE ACTION: The DoD Pharmacy and Therapeutics (P&T) Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend quantity limits for dasatinib in the TRICARE Mail Order Pharmacy (TMOP) Program of 90 tablets for the 70 mg strength, 180 tablets for the 50 mg strength, and 180 tablets for the 20 mg strength per 45 days, with a days supply limit of 45 days (not collective across strengths). In the TRICARE Retail Pharmacy Network (TRRx), the recommended quantity limits were 60 tablets for the 70 mg strength, 120 tablets for the 50 mg strength, and 120 tablets for the 20 mg strength per 30 days, with a days supply limit of 30 days (not collective across strengths). (See page 14 of the P&T Committee minutes.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

6. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR EXENATIDE (BYETTA)

The Committee agreed that a PA was needed for exenatide subcutaneous injection due to the potential for inappropriate use.

COMMITTEE ACTION: Based on exenatide's potential use for indications not covered by TRICARE (i.e., weight loss) and/or not supported by clinical evidence, the P&T Committee recommended (14 for, 1 against, 0 abstained, 2 absent) that PA be required for exenatide. The criteria recommended by the P&T Committee incorporate modifications to the Pharmacy Data Transaction Service (PDTS) that will allow automation of some PA criteria, reducing paperwork burden and cost. These modifications are scheduled for completion by December 2006. (See pages 14-16 of the P&T Committee minutes for rationale and summary of PA criteria.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

COMMITTEE ACTION: The Committee recommended (14 for, 1 against, 0 abstained, 2 absent) that the PA for exenatide should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible based on availability of the automated PA capability in PDTS. The implementation period will begin immediately following the approval by the Director, TRICARE Management Activity (TMA). (See pages 14-16 of the P&T Committee minutes.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

7. THIAZOLIDINEDIONE (TZD) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost-effectiveness of the TZD drugs marketed in the United States. The drugs in this class include the parent compounds rosiglitazone (Avandia) and pioglitazone (Actos); their respective combinations with metformin, rosiglitazone/metformin (Avandamet) and pioglitazone/metformin (Actoplus Met); and one combination of a TZD with a sulfonylurea, rosiglitazone/ glimepiride (Avandaryl). The TZDs accounted for approximately $110 million dollars in Fiscal Year (FY) 2005 and are ranked 12th in Military Health System (MHS) drug class expenditures.

The Committee voted (16 for, 0 opposed, 1 abstained, 0 absent) that:

1) Neither rosiglitazone nor pioglitazone appears less effective in reducing elevated hemoglobin A1c or fasting plasma glucose values.

2) There is insufficient evidence to determine if there are significant differences between the two parent compounds in the prevention of microvascular or macrovascular complications of diabetes.

3) Neither rosiglitazone nor pioglitazone appears less likely to cause hepatotoxicity, congestive heart failure, weight gain, edema, decreased blood pressure, hypoglycemia, or reduced hemoglobin and hematocrit.

4) Safety and tolerability differences appear to be limited to the potential for more drug interactions with pioglitazone.

5) Rosiglitazone appears to have a less favorable effect on lipid parameters than pioglitazone, however the clinical significance of this is unknown.

6) There are only minor differences between the two TZDs based on dosing frequency and receptor binding – provider opinion was split between preferring pioglitazone and no preference.

7) Neither rosiglitazone nor pioglitazone – or their respective combination products – appears sufficiently less clinically effective than the other to warrant classification as non-formulary under the UF based on clinical issues alone.

Based on the results of the cost-effectiveness analysis (CEA) and other clinical and cost considerations, the Committee concluded (16 for, 0 opposed, 1 abstained, 0 absent) that the UF scenario that maintained rosiglitazone, pioglitazone, rosiglitazone/metformin, pioglitazone/metformin, and rosiglitazone/glimepiride on the UF formulary was the most cost effective UF scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the TZD drugs, and other relevant factors, the P&T Committee voted (13 for, 1 opposed, 2 abstained, 1 absent) to recommend that rosiglitazone, pioglitazone, rosiglitazone/metformin, pioglitazone/metformin, and rosiglitazone/glimepiride be maintained as formulary on the UF and that no agents from this class be classified as non-formulary under the UF. (See paragraphs 7A and 7B on pages 16-23 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: BASIC CORE FORMULARY (BCF) RECOMMENDATION – Based on the relative clinical and cost-effectiveness analysis, the P & T Committee voted (13 for, 1 opposed, 3 abstained, 0 absent) to recommend retaining rosiglitazone and rosiglitazone/metformin as the BCF selections in this class. The Committee did not recommend addition of rosiglitazone/metformin to the BCF. (See paragraph 7E on page 23 of the P&T Committee minutes for rationale.

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

8. HISTAMINE-2 (H2) ANTAGONISTS AND OTHER GASTROINTESTINAL (GI) PROTECTANT AGENTS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the H2 antagonists and other GI protectant agents. The drug class comprises: the four H2 antagonists, ranitidine (Zantac, generics), cimetidine (Tagamet, generics), famotidine (Pepcid, generics), and nizatidine (Axid, generics); the prostaglandin analog misoprostol (Cytotec, generics); and the mucosal protectant sucralfate (Carafate, generics). These six drugs have been marketed for several years, and all are available in generic formulations. This drug class accounted for $10.9 million in FY 2005, and is ranked 75th in MHS drug class expenditures.

The Committee voted (16 for, 0 opposed, 1 abstained, 0 absent) that:

1) The four H2 antagonists ranitidine, cimetidine, famotidine, and nizatidine are widely considered interchangeable for treatment of gastroesophageal reflux disease, peptic ulcer disease, and *H. pylori* infections, despite differences in potency, duration of action, and onset of action.
2) Compared to the other three H2 antagonists, cimetidine has evidence for use in non-gastrointestinal conditions.
3) Ranitidine is the most widely used H2 antagonist across the MHS, is dosed once or twice daily, has a low potential for drug interactions, and is available in an oral syrup for pediatric patients.
4) Famotidine and nizatidine have similar dosing intervals, drug interaction profiles and formulations as ranitidine, but are less frequently prescribed in the MHS.
5) Cimetidine is more difficult to use clinically compared to the other three H2 antagonists due to its need for multiple daily dosing (BID-QID) and drug interaction profile.
6) Misoprostol serves a unique niche for use in high risk patients for non-steroidal anti-inflammatory drug (NSAID)-induced ulcers, despite its adverse effect profile and warnings in women of child bearing age.
7) Sucralfate has a unique mechanism of action (physical barrier formation) and offers an alternative to proton pump inhibitors and H2 antagonists for stress ulcer prophylaxis.

Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) that: (1) ranitidine was the most cost effective H2 antagonist; (2) two other H2 antagonists, famotidine and cimetidine, were shown to have similar relative cost-effectiveness compared to ranitidine; (3) nizatidine was found to be slightly more costly compared to the other generic H2 antagonists, due to recent

availability of the generic version; and (4) misoprostol and sucralfate are available in generic versions and have an established niche in therapy for select patients.

A. 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 voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend that the H2 antagonists ranitidine, cimetidine, famotidine and nizatidine; the prostaglandin analog misoprostol; and the mucosal protective agent sucralfate should be maintained as formulary on the UF, and that no agents from this class be classified as non-formulary under the UF. (See paragraphs 8A and 8B on pages 23-27 of the P&T Committee minutes).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend retaining ranitidine as the BCF selection in this class, excluding the effervescent tablet and gel-filled capsule formulations. (See paragraph 8E on page 27 of the P&T Committee minutes for rationale.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

9. ANTILIPIDEMIC I (LIP-I) AGENTS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the agents in the LIP-1 drug class. This class is currently ranked number one in the MHS with drug class expenditures exceeding $595 million annually. The individual drugs included in the LIP-1 class are listed below:

- *Statins*: atorvastatin (Lipitor), fluvastatin (Lescol), fluvastatin extended release (Lescol XL), lovastatin (Mevacor, generics), lovastatin extended release (Altoprev), pravastatin (Pravachol, generics), rosuvastatin (Crestor), and simvastatin (Zocor, generics)
- *Statin combination products*: atorvastatin/amlodipine (Caduet), lovastatin/niacin extended release (Advicor), and ezetimibe/simvastatin (Vytorin)
- *Add-on therapies:* niacin immediate release (Niacor), niacin extended release (Niaspan), and ezetimibe (Zetia)

The Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) that the following conclusions apply:

1) Across equipotent doses, the statins achieve similar % low density lipoprotein (LDL) lowering, with rosuvastatin 40 mg and ezetimibe/simvastatin 10/80 mg as the only statins capable of achieving LDL lowering >55%.
2) Across equipotent doses, the statins achieve similar % high density lipoprotein (HDL) raising ability, but all statins show a plateau and drop-off of HDL raising effect at increasing doses.
3) There are no head-to-head trials comparing equivalent doses of statins that evaluate clinical outcomes for reducing mortality or other clinical outcomes (e.g., myocardial infarction, stroke, need for revascularization).
4) In low to moderate doses, the effects of atorvastatin, pravastatin and simvastatin appear similar for long-term cardiovascular protection, based on one meta-analysis [Zhou 2006].
5) In trials assessing the primary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin 10 mg, lovastatin 20 to 40 mg, pravastatin 40 mg, and simvastatin 40 mg.
6) In trials assessing the secondary prevention of CHD, beneficial effects on clinical outcomes have been noted with atorvastatin 10 to 80 mg, lovastatin 40 to 80 mg, pravastatin 40 mg, simvastatin 20-40 mg, and fluvastatin 40 mg (administered BID).
7) In one trial assessing acute coronary syndrome patients, beneficial effects on clinical outcomes were noted with atorvastatin 80 mg when it was compared to pravastatin 40 mg [PROVE-IT 2004].
8) There are no published trials assessing the benefits of rosuvastatin on clinical outcomes.
9) There is no evidence that increases in liver function tests or minor adverse events (gastrointestinal disturbances, headaches, rash, itching) are less likely to occur with one statin vs. another, and these adverse effects are dose-related.
10) Concerns of proteinuria and myotoxicity remain with rosuvastatin; the overall incidence of rhabdomyolysis occurs rarely with statins.
11) Fluvastatin, pravastatin, and rosuvastatin have the most favorable drug-drug interaction profiles.
12) There is insufficient evidence to determine whether one statin is less tolerable than another.
13) In terms of other factors, the statins can be initiated at maximum doses, with the exception of rosuvastatin 40 mg.
14) There is insufficient evidence to determine the clinical applicability of differences between the statins in terms of pleiotropic effects or effects on markers of atherosclerotic progression (intravascular ultrasound or carotid intima media thickness).

15) Ezetimibe offers an additional 15-20% LDL lowering by a mechanism distinct from that of the statins, but has not yet been evaluated for clinical outcomes.

16) Ezetimibe/simvastatin provides added efficacy in terms of LDL lowering and has a safety and efficacy profile reflecting that of its two individual components.

17) Niacin extended release is required in the MHS as its primary benefit is to raise HDL by 25%.

18) Lovastatin/niacin extended release, atorvastatin/amlodipine, lovastatin extended release, and fluvastatin extended release do not offer additional clinical benefits over the other LIP- I agents and have low utilization in the MHS (<5,000 Rxs/month dispensed).

19) A survey of MTF providers, including cardiologists, was overwhelmingly in support of simvastatin for treating the 80-85% of MHS patients requiring LDL lowering ≤45%, and also supported use of ezetimibe.

20) Based on clinical issues alone, none of the LIP-1 agents are sufficiently less effective than the others agents within the class to be classified as non-formulary.

Based on the results of the CEA and other clinical and cost considerations, the P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) that (1) simvastatin could meet the vast majority of the needs of patients requiring low to moderate % LDL lowering agents (≤ 45%); (2) ezetimibe/simvastatin was the most cost-effective intensive % LDL lowering agent; (3) some low to moderate % LDL lowering agents were considered to be clinically necessary (pravastatin, ezetimibe, and niacin); (4) of the remaining low to moderate % LDL lowering agents, nothing would be gained clinically or economically by making them non-formulary, especially considering their low market share; (5) atorvastatin/amlodipine was considerably more costly compared to the combination of atorvastatin and a UF dihydropyridine calcium channel blocker, regardless of point of service; and (6) the UF scenario that included the intensive % LDL lowering agents atorvastatin and ezetimibe/simvastatin on the UF was the most cost-effective UF scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the LIP-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 1 opposed, 1 abstained, and 0 absent) to recommend that atorvastatin, fluvastatin immediate and extended release, pravastatin, simvastatin, lovastatin immediate and extended release, lovastatin/niacin, ezetimibe/simvastatin, niacin extended & immediate release, and ezetimibe be maintained as formulary on the UF, and that rosuvastatin and the combination product atorvastatin/amlodipine be classified as non-formulary under the UF. (See paragraphs 9A and 9B on pages 28-38 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:
"Our efforts to sustain the TRICARE benefit, and the TRICARE Rx benefit, require that MTF prescribers continue using simvastatin when that drug is clinically appropriate. I strongly encourage MTF commanders, doctors and pharmacists to maximize the use of simvastatin."

B. COMMITTEE ACTION: MEDICAL NECESSITY CRITERIA – Based on the clinical evaluation of rosuvastatin and atorvastatin/amlodipine, and the conditions for establishing medical necessity for a non-formulary medication provided in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) medical necessity criteria for the LIP-1 agents. (See paragraph 9C on pages 38-39 of the P&T Committee minutes for criteria

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (15 for, 0 opposed, 2 abstained, 0 absent) to recommend an effective date no sooner than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 9D on page 39 of the P&T Committee minutes for rationale.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost-effectiveness analysis, the P&T Committee voted (15 for, 1 opposed, 1 abstained, 0 absent) to recommend simvastatin, pravastatin, ezetimibe/ simvastatin, and niacin extended release as the BCF selections in this drug class. (See paragraph 9E on page 40 of the P&T Committee minutes.)

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

10. CLASS OVERVIEWS. ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY MEDICATIONS; SEDATIVE HYPNOTICS I (NON-BENZO-DIAZEPINE SEDATIVE HYPNOTICS); SEDATIVE HYPNOTICS II

Portions of the clinical reviews for each class were presented to the Committee. The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review, and for developing the appropriate cost effectiveness models. Both the clinical and economic analyses of these three classes will be completed during the November 2006 meeting; no action necessary.

Appendix A – Table 1. Implementation Status of UF Decisions

Appendix B – Table 2. Newly Approved Drugs

Appendix C – Table 3. Abbreviations

Appendix D – Figure 1. Estimated Percent of Population Expected to Reach ATP-III LDL Goals with Increasing LDL Reduction

Appendix E – Table 4. Expected Mean LDL Reductions, by Statin and Dose

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____signed_____

William Winkenwerder, Jr., M.D.
Date: 23 October 2006

Department of Defense
Pharmacy and Therapeutics Committee Minutes
16 August 2006

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 15 August 2006 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
CAPT Mark Richerson, MSC, USN	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
LtCol Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
LtCol Brian Crownover, MC	Air Force, Physician at Large
LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer (Pharmacy Consultant)
LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatric Physician
Not Appointed	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer (Pharmacy Consultant)
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Ted Cieslak, MC	Army, Physician at Large
LTC Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
LT Thomas Jenkins, MSC, USN	TMOP/TRRx COR
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

COL Isiah Harper, MSC	Army, Pharmacy Officer

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Mr. Lynn T. Burleson	Assistant General Counsel, TMA
Mr. John Felicio *for* Ms Martha Taft	Health Plan Operations, TMA
Major Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

None	

E. Others Present

CAPT Don Nichols, MC, USN	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Mr. Dan Remund	DoD Pharmacoeconomic Center
Ms. Shana Trice	DoD Pharmacoeconomic Center
Mr. David Bretzke	DoD Pharmacoeconomic Center
Ms Angela Allerman	DoD Pharmacoeconomic Center
Mr. Eugene Moore	DoD Pharmacoeconomic Center
Ms. Julie Liss	DoD Pharmacoeconomic Center
Ms. Elizabeth Hearin	DoD Pharmacoeconomic Center
Mr. Dave Flowers	DoD Pharmacoeconomic Center
Mr. David Meade	DoD Pharmacoeconomic Center
Ms. Harsha Mistry	DoD Pharmacoeconomic Center
LCDR Joe Lawrence, MSC, USN	DoD Pharmacoeconomic Center
LTC Bret Kelly, MSC, USA	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
Mr. Charles R. Brown	TMA/CMB
Mr. Vincent Calabrese	Department of Veterans Affairs

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – May 2006 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. May Minutes Approval – Dr. William Winkenwerder, Jr., M.D., approved the minutes of the May 2006 DoD P&T Committee meeting on July 26, 2006.

4. ITEMS FOR INFORMATION

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

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss and CAPT Richerson briefed the members of the DoD P&T Committee regarding the June 29, 2006 BAP meeting. The Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Administrative Action: Quantity Limits for Tramadol Extended Release (Ultram ER) – Quantity limits apply to all tramadol-containing products, including new formulations, based on DoD P&T Committee recommendations made at the February 2005 meeting and subsequently approved by the Director, TMA, on 18 April 2005. The major potential concern with tramadol is safety (risk of seizure at higher than recommended doses); the potential for overuse or diversion may also exist. The Committee concurred with the specific quantity limits established for a new extended release formulation of tramadol (Ultram ER): 30 tablets per 30 days or 90 tablets per 90 days for all strengths, with quantity limits for the 200- and 300-mg tablets applied collectively. These limits were based on available strengths, dosing, titration, and maximum dose recommendations in product labeling (100-, 200-, and 300-mg extended release tablets initiated at 100 mg once daily and titrated up as necessary by 100-mg increments every five days to a maximum of 300 mg per day). The quantity limit is not collective with the immediate release formulations (tramadol 50 mg tablets and tramadol/acetaminophen 37.5/325 mg tablets) because of differences in strengths, Food and Drug Administration (FDA)-approved indications, and dosing recommendations. The Committee noted that Express Scripts, Inc. (ESI), the contractor for the TRICARE Mail Order Pharmacy (TMOP), and TRICARE Retail Pharmacy Network (TRRx) programs, has established procedures to deal with circumstances that may require temporary overrides of quantity limits (e.g., increases in dose).

C. Administrative Action: Removal of Carbinoxamine/Pseudoephedrine Drops from the Basic Core Formulary (BCF) – Like a number of older products, carbinoxamine combination products have been widely used, but were never approved by the FDA as safe and effective. On 8 June 2006, the FDA announced enforcement actions to stop manufacture of unapproved carbinoxamine-containing products due to safety concerns in children $\leq$ 2 years of age, and as part of ongoing FDA efforts to bring all unapproved products in line with provisions of the Food, Drug, and Cosmetic Act. Manufacturers of unapproved products containing carbinoxamine have been directed to cease manufacture over the next 30 to 90 days. One FDA-approved carbinoxamine 4 mg tablet and one 4 mg/5 mL oral solution will remain on the market, but no combination products. The Committee concurred with an administrative action removing carbinoxamine 1 mg / pseudoephedrine 15 mg per mL oral drops from the BCF. They did not feel that addition of another antihistamine/ decongestant combination to the BCF was warranted at the present time, pending future UF review of these medications.

D. UF Change Request Process – The P&T Committee discussed the process by which MTF healthcare providers could request that the DoD P&T Committee consider potential changes to the BCF, Extended Core Formulary (ECF), or UF, including changes to

medical necessity criteria for non-formulary medications, prior authorization criteria, or quantity limits. The P&T Committee agreed on three general process goals:

1) Requests should contain adequate supporting evidence, including a fair, balanced, and thorough discussion of the relevant clinical literature, and present a rational argument supporting suggested changes.

2) The process should address potential conflicts of interest and discourage pharmaceutical industry representatives from putting pressure on providers to submit requests.

3) The process should require review and concurrence by the local military treatment facility (MTF) P&T Committee.

A request form and supporting materials are currently under development.

E. Fentanyl Patch (Duragesic, generics) – The P&T Committee discussed various issues related to the use of fentanyl patches, including safety warnings from the DoD Patient Safety Center, the FDA, and the Institute of Safe Medication Practices; and the July 2006 Air Force policy on the use of fentanyl patches. Fentanyl, a strong opioid narcotic, can cause severe respiratory depression in patients who are not tolerant to opioids. Other safety issues include failing to remove old patches, unsafe disposal of old patches, application of heat to the patch site (e.g., heating pads, water beds), concurrent use of potent CYP3A4 inhibitors, conditions that affect respiratory function or affect metabolism of fentanyl, abuse, and diversion.

Product labeling for fentanyl patches was strengthened in July 2005 following reports of serious adverse events and fatalities. Fentanyl patches are indicated for management of *persistent*, moderate to severe chronic pain requiring continuous, around-the-clock administration for an extended period of time, that cannot be managed by other means, and ONLY in patients who are already receiving opioids, have demonstrated opioid tolerance, and require a total daily dose at least equivalent to fentanyl 25 mcg/hr. They should not be used for management of acute pain or short periods of opioid analgesia; postop pain, including outpatient/day surgeries; mild pain; or intermittent pain.

F. Implementation Status of UF Decisions – The PEC briefed the members of the Committee on the progress of implementation for drug classes reviewed for UF status since August 2005. The Committee made the following observations:

1) Utilization in all UF classes continues to remain stable, suggesting continued access to drugs within the reviewed classes.

2) Collective utilization of UF agents across all reviewed drug classes and points of service (MTF, TMOP, and TRRx) continues to increase as a percentage of prescriptions dispensed, while utilization of non-formulary agents has decreased. Based on the UF decisions that have been fully implemented since the first UF DoD P&T meeting in February 2005, there has been a 26% reduction in the use of non-formulary agents, including those classes where implementation has only just begun (July 2006).

3) Success in terms of generating increased market share for UF agents (while decreasing market share for non-formulary agents) varies by class and by point of service.

4) Market shares by point of service continue to reflect the degree of utilization management applied to each point of service. The more highly managed points of service (i.e., MTFs) are generating higher market shares of UF agents than the unmanaged points of service (i.e., TMOP and TRRx).

5) For drug classes fully implemented, MTFs have reduced the use of non-formulary drugs by 84% as projected, but the change in the use of non-formulary medications at mail (+1%) and retail (-14%) is significantly less.

6) It appears that more beneficiaries are electing to receive non-formulary medications through TMOP.

5. REVIEW OF RECENTLY-APPROVED AGENTS

The P&T Committee was briefed on five new drugs that were approved by the FDA. None of the medications fall into drug classes already reviewed by the P&T Committee; therefore, UF consideration was deferred until the corresponding drug class reviews are completed.

The P&T Committee reviewed one new drug for quantity limits. Dasatinib (Sprycel) is an oral multi-kinase inhibitor approved for treatment of patients with chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia, with resistance or intolerance to prior therapy including imatinib (Gleevec). Dasatinib is available in 20-, 50- and 70-mg tablets which should not be crushed or cut. It is administered at a target dosage of 70 mg twice daily, but dosing can vary from 20 mg once daily to 100 mg twice daily, based on potential drug interactions, patient response, or drug-related adverse effects. Quantity limits were recommended for dasatinib due to the risk of discontinuation of therapy and the probability that dosage adjustments requiring changes in tablet strength will be needed, based on potential drug interactions, patient response to therapy, or drug-related adverse effects. Quantity limits also apply to other oral chemotherapy drugs, including imatinib, erlotinib (Tarceva), sorafenib (Nexavar), and sunitinib (Sutent), based on previous DoD P&T Committee recommendations and subsequent approval by the Director, TMA.

COMMITTEE ACTION – The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend quantity limits for dasatinib in TMOP of 90 tablets for the 70 mg strength, 180 tablets for the 50 mg strength, and 180 tablets for the 20 mg strength per 45 days, with a days supply limit of 45 days. In TRRx, the recommended quantity limits were 60 tablets for the 70 mg strength, 120 tablets for the 50 mg strength, and 120 tablets for the 20 mg strength per 30 days, with a days supply limit of 30 days.

6. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR EXENATIDE (BYETTA)

Exenatide is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus (DM) who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, but have not achieved adequate glycemic control. Pharmacologically, exenatide is an incretin mimetic agent that stimulates insulin production in the pancreatic islet cells when glucose levels are elevated, slows gastric emptying, and helps produce a feeling of satiety. Exenatide also reduces the secretion of glucagon, thus lowering elevated post-prandial blood glucose levels. It is given twice daily by subcutaneous injection, prior to the morning and evening meals. Exenatide should not be used as a

substitute for insulin in patients who need insulin, has not been studied in patients also using insulin, and is not indicated for use in patients with type 1 DM.

In clinical trials, exenatide decreased glycosylated hemoglobin A1c (HbA1c) by 0.7 to 1.1% (insulin typically decreases HbA1c by 1-2%). Also noted during clinical trials were reduced sulfonylurea requirements and reductions in weight (1.9 to 4.5 kg). From a safety standpoint, use of exenatide with a sulfonylurea may increase the risk of hypoglycemia, and the sulfonylurea dose may need to be reduced. Concurrent use of exenatide and metformin is relatively unlikely to cause hypoglycemia. Because it slows gastric emptying, exenatide may alter the rate and extent of absorption of oral drugs; drugs dependent on threshold concentrations for efficacy (e.g., antibiotics, contraceptives) should be taken at least one hour prior to exenatide. Exenatide is not recommended in patients with severe gastrointestinal (GI) disease, including gastroparesis, or in patients with severe/end stage renal disease. It is associated with GI adverse effects, including nausea, vomiting, and diarrhea; patients receiving exenatide in clinical trials also complained of significantly more jitteriness, dizziness, and headache than those receiving placebo.

Exenatide has achieved some notoriety as a weight loss medication (even in non-diabetic patients), an off-label use that is both not supported by clinical evidence and not covered by TRICARE. In addition, it appears likely that exenatide may be used in some patients with metabolic syndrome or "pre-diabetes," another off-label use not supported by clinical evidence. Based on results of a utilization study performed by the PEC, about 90% of Military Health System (MHS) patients who received a first prescription for exenatide from June 2005 to May 2006 had also filled a prescription for an oral antidiabetic drugs, blood glucose test strips, or both during the 180 days prior to starting exenatide (8,681 out of a total of 9,634 patients). In other words, about 10% of MHS patients starting exenatide appear unlikely to be diabetic, based on absence of prescription fills for either diabetic medications or blood glucose testing supplies during the six months prior to starting exenatide. While there may be alternative explanations for some of these cases, it appears that some of these patients are receiving exenatide as a weight-loss medication and/or in a setting of "pre-diabetes." Many health plans have PA requirements for exenatide, primarily based on its FDA indication.

The cost of exenatide ranges from $1250 to $2500 per year, depending on dose and pharmacy point of service. Exenatide prescription fills are increasing rapidly at retail network pharmacies, where most exenatide fills are dispensed; relatively few fills and a slower rate of increase are seen at TMOP or MTFs.

Based on the following considerations, the P&T Committee agreed that a PA should be required for exenatide:

- In the MHS, up to 10% of exenatide usage appears likely to be used for indications not covered by TRICARE and/or not supported by clinical evidence. The use of exenatide for weight loss may increase based on continued coverage in the lay press increasing familiarity with the medication. Overall, utilization of exenatide is increasing.
- Modifications to the Pharmacy Data Transaction Service (PDTS) scheduled for completion by December 2006 will add the capability of "looking back" at a given patient's profile for the presence or absence of prescription fills for specific medications within a defined time period. This will allow automation of some PA criteria, reducing

paperwork burden and cost (PA fees), and limiting the scope of the PA to those patients most likely to fail to meet the established criteria.

COMMITTEE ACTION – Based on its potential use for indications not covered by TRICARE and/or not supported by clinical evidence, the P&T Committee recommended that a PA be required for exenatide (14 for, 1 against, 0 abstained, 2 absent). The Committee recommended that the PA should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible based on availability of the automated PA capability in PDTS. The implementation period will begin immediately following the approval by the Director, TMA.

The Committee agreed that the following PA criteria should apply (14 for, 1 against, 0 abstained, 2 absent). Patients meeting the automated PA criteria would not be required to have their providers submit any additional information and in all likelihood would not even be aware of the existence of the PA. PA approvals would be valid indefinitely.

1) Automated PA criteria:
   - Patient has received any oral antidiabetic agent in the last 120 days
2) PA criteria if automated criteria are not met:
   - Coverage is approved if the patients meets both of the following criteria:
     - Diagnosis of type 2 DM
     - Patient has not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea

7. THIAZOLIDINEDIONE DRUG CLASS REVIEW

The drugs in the thiazolidinedione (TZD) class include the parent compounds rosiglitazone (Avandia) and pioglitazone (Actos); their respective combinations with metformin, rosiglitazone/metformin (Avandamet) and pioglitazone/metformin (Actoplus Met); and one combination of a TZD with a sulfonylurea, rosiglitazone/glimepiride (Avandaryl). The TZDs accounted for approximately $110 million dollars in Fiscal Year (FY) 2005 and are ranked 12th in MHS drug class expenditures.

A. TZD Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the TZD products 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.

1) Efficacy for Glycemic Control

Rosiglitazone and pioglitazone and their fixed-dose combinations with metformin or

glimepiride are FDA-approved for treating patients with type 2 DM. The primary efficacy measures evaluated included HbA1c and fasting plasma glucose (FPG).

- *Monotherapy* – TZDs may be given as monotherapy, but are usually administered with other antidiabetic drugs, including metformin, sulfonylureas, or insulin. Placebo-controlled trials show that rosiglitazone monotherapy reduces HbA1c by 0.6% to 1.5% and FPG by 33 mg/dL to 55 mg/dL, while pioglitazone monotherapy reduces HbA1c by 0.7% to 1.2% and FPG by 36 mg/dL to 56 mg/dL.
    - *Head-to-Head Monotherapy Trials* – The only rigorously designed head-to-head clinical trial comparing rosiglitazone and pioglitazone monotherapy included 802 patients. The trial showed similar reductions in HbA1c after 24 weeks of therapy (0.6% with rosiglitazone vs. 0.7% with pioglitazone, p=0.129) and FPG (36 mg/dL with rosiglitazone vs. 33 mg/dL with pioglitazone, p=0.233). [Goldberg 2005]
    - *Meta-Analyses* – A meta-analysis of 23 placebo-controlled TZD monotherapy trials concluded that, when relatively equivalent doses of the TZD were compared, similar mean changes from baseline in HbA1c were reported: -0.90% (95% Confidence Interval [CI] -1.42% to -0.38%) with rosiglitazone 4 mg once daily (QD); -0.99% (95% CI -1.32% to -0.66%) with pioglitazone 30 mg QD. Similar point estimates and overlapping confidence intervals were reported for rosiglitazone 8 mg QD and pioglitazone 45 mg QD for reductions in both HbA1c and FPG. [Chiquette 2004]
- *Combination Therapy* – When a TZD is added on to another antidiabetic drug, greater reductions in HbA1c and FPG are seen than if the TZD is administered as monotherapy.
    - *Head-to-Head Combination Therapy Trials* – There is one head-to-head trial comparing the TZDs used in combination with the sulfonylurea glimepiride, which enrolled 91 patients. Similar changes in glycemic parameters from baseline were reported in both treatment groups. HbA1c decreased by 1.3% with rosiglitazone plus glimepiride vs. 1.4% with pioglitazone plus glimepiride; FPG decreased by 31 mg/dL in both groups. [Derosa 2004]
    - *Meta-analyses* – A meta-analysis of 15 clinical trials evaluating metformin, sulfonylurea or insulin plus a TZD compared to metformin, sulfonylurea, or insulin plus placebo concluded that when relatively equivalent doses of the TZDs were compared, similar mean changes from baseline in HbA1c were reported: [-1.05 (95% CI-1.2 to -0.9) with rosiglitazone 4 mg QD plus other antidiabetic drugs vs. -1.16 (95% CI -1.4 to -0.0) with pioglitazone 30 mg QD plus other antidiabetic drugs]. Similar reductions in HbA1c and FPG, with overlapping confidence intervals, were reported for rosiglitazone 8 mg QD plus other antidiabetic drugs vs. pioglitazone 45 mg QD plus other antidiabetic drugs. [Chiquette 2004]
- *Monotherapy and Combination Therapy* – A systematic review evaluating placebo-controlled trials with the TZDs used as either monotherapy or added on to other antidiabetic drugs reported an adjusted indirect comparison between

rosiglitazone and pioglitazone. Overall, there was no significant difference between the two drugs (adjusted mean difference, pioglitazone minus rosiglitazone, of -0.12% (95% CI -0.50 to 0.26)). [State of Oregon 2006]

Conclusion: Efficacy for Glycemic Control – The available evidence suggests that neither rosiglitazone nor pioglitazone is superior to the other in reducing HbA1c or FPG.

2) *Effectiveness for Prevention of Microvascular and Macrovascular Events*

For clinical outcomes, endpoints evaluated included microvascular (e.g., nephropathy, retinopathy, neuropathy) and macrovascular (e.g., cardiovascular disease, cerebral vascular disease, peripheral vascular disease) complications of type 2 DM, when available.

- *Microvascular Complications* – There are no clinical trials with either rosiglitazone or pioglitazone that evaluate the effects of long-term TZD therapy on prevention of microvascular complications. However, both TZDs reduce HbA1c, and reductions in HbA1c are correlated with a reduced risk of microvascular events, as previously shown in the United Kingdom Prospective Diabetes Study.
- *Macrovascular Complications* – Coronary heart disease is the major cause of mortality in diabetic patients, thus clinical trials evaluating cardiovascular outcomes are of importance when comparing the TZDs. There is one published trial, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE), that evaluated the effects of pioglitazone on clinical outcomes in over 5,000 patients. After three years, there was no significant difference with pioglitazone added to other antidiabetic medications compared to placebo plus other antidiabetic medications in the primary composite outcome, which included both disease and procedure-related endpoints (i.e., myocardial infarction (MI), stroke, need for coronary artery bypass grafting, percutaneous coronary intervention or leg amputation). Overall, 21% of patient reached the primary endpoint with pioglitazone vs. 23% with placebo; p=0.095). However, a significant difference in favor of pioglitazone was reported in a secondary composite endpoint that only included disease-related endpoints (all-cause death, non-fatal MI and stroke); 11.6% with pioglitazone vs. 13.6% with placebo, p=0.027. The design of this trial has been debated, and the clinical applicability of these results is limited. There are no completed trials with rosiglitazone evaluating clinical outcomes, although two trials (ADOPT and RECORD) are underway.

Conclusion: Effectiveness for Prevention of Microvascular and Macrovascular Events – Due to the absence of published trials with rosiglitazone and design limitations of the one published trial with pioglitazone PROACTIVE, there is insufficient evidence to determine whether one TZD is superior to the other in preventing the clinical complications of diabetes.

3) *Safety and Tolerability*

- *Hypoglycemia* – One meta-analysis compared the differences in the incidence of hypoglycemia between rosiglitazone and pioglitazone. The pooled risk

differences were compared with each drug vs. placebo, and the results were similar for each TZD; rosiglitazone risk difference vs. placebo 3% (95% CI 0% to 5%) and pioglitazone risk difference vs. placebo 2% (95% CI -1% to 4). [State of Oregon 2006]

- *Edema* – Mild to moderate edema has been reported with the TZDs and appears to be dose-related. One meta-analysis reported the pooled risk difference for the incidence of edema with the TZDs in placebo-controlled trials. The pooled risk difference compared to placebo was similar between the two TZDs: rosiglitazone 4% (95% CI 2% to 5%), pioglitazone 4% (95% CI 2% to 7%). [State of Oregon 2006]
- *Heart Failure* – Both rosiglitazone and pioglitazone have been linked to development of heart failure; neither are recommended for use in patients with New York Heart Association Class III or IV heart failure Product labeling for both rosiglitazone and pioglitazone are similar regarding warnings for fluid retention, which may lead to or worsen heart failure. The highest risk occurs when a TZD is used in combination with insulin. A retrospective review using a large health plan database found no difference between the two TZDs in the development of heart failure in a cohort of over 28,000 patients: rosiglitazone 2.39% vs. pioglitazone 1.63%; p=0.091. [Delea 2003]
- *Weight Gain* – Both TZDs cause statistically significant increases in body weight from baseline. The effect on body weight appears similar between TZDs, as evidenced by the results from head-to-head clinical trials – mean weight gain of 1.6 kg with rosiglitazone vs. 2.0 kg with pioglitazone – and published meta-analyses showing similar weight gain (about 3 kg with each TZD, with overlapping confidence intervals).
- *Hepatotoxicity* – Clinical trials for both TZDs report an incidence <1% for elevations in ALT three times the upper limit of normal. Both TZDs carry similar labeling regarding monitoring of liver enzymes.
- *Blood Pressure* – An association between TZD use and small but statistically significant reductions in blood pressure has been reported. There is insufficient information at this time to determine whether the blood pressure effects are different between rosiglitazone and pioglitazone.
- *Hematologic Effects* – Reductions in hemoglobin and hematocrit have been reported with both TZDs. This may be due to an increase in plasma volume rather than a decrease in red cell mass. The clinical significance of these hematologic effects is unknown.
- *Macular Edema* – An association between TZD use and macular edema has been reported in the literature. GlaxoSmithKline issued a “Dear Doctor Letter” on January 5, 2006 regarding the association of rosiglitazone with new onset and worsening macular edema. Takeda, the manufacturer of pioglitazone, disputes the occurrence of this adverse effect and has not issued a similar warning.
- *Drug-Drug Interactions* – The potential for drug-drug interactions may be greater with pioglitazone than rosiglitazone, due to metabolism of the former by CYP3A4

enzymes. However, the clinical significance of the drug-drug interactions with pioglitazone may be counterbalanced by the availability of multiple metabolic pathways. Of note, use of pioglitazone with oral contraceptives containing ethinyl estradiol and norethindrone has resulted in reduced plasma concentrations of both hormones by 30%, which could result in decreased contraceptive efficacy. The clinical significance of this interaction is unknown, and no dosage adjustments are required in the package labeling for pioglitazone.

- *Withdrawal Due to Adverse Effects* – Drug discontinuations due to adverse effects were similar for rosiglitazone and pioglitazone in one head-to-head monotherapy trial: 2.7% for both TZDs [Goldberg 2005]. A systematic review reported withdrawal rates due to adverse effects of 4.9% with rosiglitazone vs. 4.8% with pioglitazone. [State of Oregon 2006]

Conclusion: Safety and Tolerability – The risk of heart failure, hypoglycemia, weight gain and edema do not appear to differ between rosiglitazone and pioglitazone. Hepatotoxicity has not been a concern with either TZD. There is insufficient evidence to determine whether the TZDs differ in respect to macular edema, changes in blood pressure, hemoglobin or hematocrit; only small changes from baseline in these parameters have been noted. The potential for drug-drug interactions may be greater with pioglitazone than rosiglitazone, but this does not appear to have translated into a clinically significant difference between the two TZDs. The tolerability profiles of both TZDs appear similar, based on drug withdrawals due to adverse effects during clinical trials.

4) Effects on Lipid Parameters

The TZDs exhibit other actions that can have unintended consequences in type 2 DM patients. Treatment with rosiglitazone and pioglitazone can affect serum lipid parameters, including total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG). Diabetes is a coronary heart disease (CHD) risk equivalent, and most type 2 DM patients require treatment with lipid lowering therapy. CHD is the number one cause of death in type 2 DM patients.

- Two head-to-head trials (one as monotherapy, the other as add-on therapy with other diabetic medications) reported that rosiglitazone adversely affected the lipid panel, as reflected by increases in TC (by 15-16%), LDL (by 17-23%), and TG (by 15-18%). In contrast, pioglitazone showed a favorable effect on the lipid profile, as reflected by to increases in HDL (by 15%), and decreases in TG (by 12 to 22%). However, these two head-to-head trials differed in the reported results for the effect of pioglitazone on TC and LDL. Goldberg et al (2005) showed an increase in TC (6%) and LDL (16%), while Derosa et al (2003) showed a reduction in TC (by 6%) and LDL (by 12%).
- Two meta-analyses [Chiqeutte 2004 and Canada 2002] concluded that rosiglitazone therapy resulted in increases in TC (10-21%), LDL (7-15%), and HDL (2-3%), but did not affect TGs. Pioglitazone increased HDL (2-5%) and reduced LDL (0.4 to 0.5%). Reductions in TG were more pronounced with pioglitazone, but a statistically significant difference was noted only for

pioglitazone in the Canadian analysis. Both TZDs were associated with modest increases in HDL (by 2-5%); the marked difference between rosiglitazone and pioglitazone seen in the two head-to-head trials is not as noticeable in the two meta-analyses.

Conclusion: Effects on Lipid Parameters – Results from two head-to-head clinical trials and two meta-analyses that assessed the lipid effects with TZDs vary, but are mostly consistent with the results of the head-to-head monotherapy trial. [Goldberg 2005] Pioglitazone appears to have a more favorable effect on lipid parameters than rosiglitazone. The clinical significance of this difference has yet to be determined.

5) *Other Factors*

- Rosiglitazone is dosed either once or twice daily, while pioglitazone is dosed once daily.
- Rosiglitazone binds primarily to peroxisome proliferator-activated receptors (PPARs) gamma receptors, while pioglitazone binds to both PPAR gamma and alpha receptors; differences in receptor binding are theorized to account for differences in the effects on lipid parameters.
- There are no differences in the product labeling for the two TZDs for FDA-approved indications, contraindications, and use in special populations.
- Neither rosiglitazone nor pioglitazone are indicated for use in the pediatric population, in pregnancy, or while breast feeding.
- A survey of MTF providers revealed a split opinion as to whether the TZDs were therapeutically interchangeable, with half of the respondents favoring pioglitazone due to once-daily dosing and lack of detrimental effect on lipids, and the other half voicing no preference.

Conclusion: Other factors – There are only minor differences in terms of other factors for the TZDs. MTF provider opinion is split between preferring pioglitazone and no preference between the two.

Overall Clinical Effectiveness Conclusion – The Committee concluded that:

1) Neither rosiglitazone nor pioglitazone appears less effective in reducing elevated hemoglobin A1c or fasting plasma glucose values.
2) There is insufficient evidence to determine if there are significant differences between the two parent compounds in the prevention of microvascular or macrovascular complications of diabetes.
3) Neither rosiglitazone nor pioglitazone appears less likely to cause hepatotoxicity, congestive heart failure, weight gain, edema, decreased blood pressure, hypoglycemia, or reduced hemoglobin and hematocrit.
4) Safety and tolerability differences appear to be limited to a possibly greater potential for drug interactions with pioglitazone.
5) Rosiglitazone appears to have a less favorable effect on lipid parameters than pioglitazone, however the clinical significance of this is unknown.

6) There are only minor differences between the two TZDs based on dosing frequency and receptor binding; provider opinion was split between preferring pioglitazone and no preference.

7) Neither rosiglitazone nor pioglitazone – or their respective combination products – appears sufficiently less clinically effective than the other to warrant classification as non-formulary under the UF based on clinical issues alone.

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

B. TZD Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the TZDs 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).

Given the evidence-based relative clinical effectiveness evaluation conclusion that there was insufficient evidence to suggest that the TZDs differed in regards to efficacy, safety, tolerability, or clinical outcomes in the treatment of type 2 DM, two cost-minimization analyses (CMAs) were performed to determine the relative cost-effectiveness of the agents within the TZD class.

1) The first CMA evaluated the agents based on their total weighted average cost per day of treatment, which was derived from their submitted prices for UF condition sets (1 of 1 TZD agent on the UF or 1 of 2 TZD agents on the UF) and their utilization history. The results of this analysis revealed that pioglitazone was more cost-effective compared to rosiglitazone for a 1 of 1 position on the UF, whereas rosiglitazone was more cost-effective compared to pioglitazone for a 1 of 2 position on the UF.

2) The second CMA evaluated the agents under various UF scenarios which placed one or more agents on the UF. In this analysis, all viable UF scenarios were considered. The various UF scenarios were evaluated on their projected post-decision total weighted average cost per day of treatment. The results of this analysis showed that the UF scenario that included both agents on the UF to be the most cost-effective.

To account for other factors and costs associated with a UF decision (market share migration, switch costs, non-formulary cost shares, and medical necessity processing fees), a budget impact analysis was performed. The goal of the budget impact analysis (BIA) was to assist the Committee in determining which group of TZDs best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS.

Cost Effectiveness Conclusion – Based on the BIA results and other clinical and cost considerations, the Committee agreed that the UF scenario that included both of the TZD agents and their associated combination products on the UF best achieved this goal when compared to other more restrictive alternative UF scenarios, and thus was determined to be more cost-effective relative to other UF scenarios. The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 1 abstention, 0 absent) to accept the TZD cost analysis presented by the PEC. The P&T Committee concluded that the UF scenario that maintained rosiglitazone, pioglitazone, rosiglitazone/metformin,

pioglitazone/metformin, and rosiglitazone/glimepiride on the UF was the most cost effective UF scenario considered.

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the TZD agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 1 abstention, 1 absent) to recommend that rosiglitazone, pioglitazone, rosiglitazone/metformin, pioglitazone/metformin, and rosiglitazone/glimepiride be maintained as formulary on the UF and that no agents from this class be classified as non-formulary under the UF.

C. TZD Medical Necessity Criteria – Since no agents were recommended for non-formulary status under the UF, establishment of medical necessity criteria is not applicable.

D. TZD UF Implementation Period – Since no agents were recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

E. TZD Basic Core Formulary (BCF) Review and Recommendations – The P&T Committee had previously determined that no more than one parent TZD, with or without its associated combinations, should be added to the BCF based on the clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that rosiglitazone and rosiglitazone/metformin be maintained on the BCF. The Committee did not recommend addition of rosiglitazone/glimepiride to the BCF.

COMMITTEE ACTION – The P&T Committee voted (13 for, 1 opposed, 3 abstention, 0 absent) to recommend retaining rosiglitazone and rosiglitazone/metformin as the BCF selections in this class. The Committee did not recommend addition of rosiglitazone/ glimepiride to the BCF.

8. HISTAMINE-2 (H2) ANTAGONISTS AND OTHER GASTROINTESTINAL (GI) PROTECTANTS

This drug class is comprised of the four H2 receptor antagonists (H2 antagonists), ranitidine (Zantac, generics), cimetidine (Tagamet, generics), famotidine (Pepcid, generics), and nizatidine (Axid, generics); the prostaglandin analog misoprostol (Cytotec, generics); and the mucosal protectant sucralfate (Carafate, generics). These six drugs have been marketed for several years, and all are available in generic formulations. This drug class accounted for $10.9 million dollars in FY 2005, and is ranked approximately 75th in MHS drug class expenditures. More than 440,000 prescriptions for these medications are filled annually in the MHS, based on prescription data from July 2005 to June 2006.

A. H2 Antagonists & Other GI Protectants Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the H2 antagonists and other GI protectant agents. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR, 199.21 (e)(1).

1) Efficacy

- *H2 Antagonists and GI Indications* – All four of the H2 antagonists have been

shown in numerous clinical trials to reduce gastric acid pH, particularly after a meal. They are all effective when used before meals to reduce reflux symptoms associated with food or exercise. Although largely replaced by proton pump inhibitors (PPIs) in clinical practice, H2 antagonists may still play a role in the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease, and *H. pylori* infections. A 1997 drug class review conducted by the Department of Veterans Affairs, as well as the 1999 American College of Gastroenterology guidelines for the treatment of GERD, concluded that, although there are differences in the potency, duration of action and onset of action, H2 antagonists may be used interchangeably at equivalent doses. A search of the literature since 1999 yields little additional clinical literature concerning the H2 antagonists and does not change this conclusion.

- *H2 Antagonists and Non-GI Indications* – Cimetidine is distinct from the other H2 antagonists in that it has evidence to support use in non-GI conditions based both on its histamine-blocking characteristics and its apparent immunomodulating effects. Non-GI uses for cimetidine are numerous, and include treatment of chronic idiopathic urticaria, adjunctive treatment of cancer or herpes virus infections, and intermittent porphyria.
- *Sucralfate* – Sucralfate does not affect gastric acid pH, but is thought to act by forming a non-absorbable physical barrier over mucosal ulcerations. At least ten clinical trials addressing the treatment of both gastric and duodenal ulcers (all conducted in the 1980s) reported similar healing rates with sucralfate compared to cimetidine or ranitidine. Overall, sucralfate appears to be as effective and safe as the H2 antagonists for treating duodenal and gastric peptic ulcers, but it is only approved for treating duodenal ulcers. One landmark clinical trial comparing intravenous (IV) ranitidine with nasogastric sucralfate reported benefits for use in stress ulcer prophylaxis in the intensive care setting, where it may offer an advantage over IV use of the H2 antagonists, due to a reduced potential for development of aspiration pneumonia. Sucralfate should be reserved for mild cases of esophagitis only. As with the H2 antagonists, the popularity of sucralfate has diminished due to availability of PPIs.
- *Misoprostol* – Misoprostol is a synthetic prostaglandin analog that inhibits gastric acid secretion by directly stimulating parietal cells. It also appears to function as a mucosal protective agent. The drug is effective as an adjunctive medication to reduce GI events associated with non-steroidal anti-inflammatory drug (NSAID) use, and has been shown to significantly reduce the risk of NSAID-associated serious GI complications and symptomatic ulcers by about 40-60%. Non-GI (off-label) uses of misoprostol are primarily gynecological in nature. A review of MHS utilization patterns, based on quantities dispensed and the age and gender of patients receiving misoprostol, confirms that the overwhelming majority of misoprostol usage in DoD is for treatment of GI conditions.

2) Safety and Tolerability

- *H2 Antagonists* – There are no major differences between the four H2 antagonists with respect to safety and tolerability, with the exception of a greater potential for

drug interactions with cimetidine. Cimetidine inhibits cytochrome P450 enzymes, and is associated with several clinically significant drug interactions when administered concomitantly with other drugs metabolized via the CYP450 pathway, including theophylline, phenytoin, quinidine, nifedipine, amitriptyline, and warfarin. Labeling for all four H2 antagonists contains warnings concerning an association of H2 antagonist use with necrotizing enterocolitis in the fetus or neonate. All four are associated with minor complaints of nausea, vomiting, diarrhea or constipation.

- *Sucralfate* – The major safety concern with sucralfate is the risk of seizures due to aluminum absorption in patients with impaired renal function. There are reports of bezoar development in patients with gastroparesis. Constipation develops in about 3% of patients receiving sucralfate, and complaints of metallic taste and diarrhea are frequent. The aluminum component of sucralfate may interact with antacids.
- *Misoprostol* – A Cochrane review addressing adverse events found that significantly more patients receiving misoprostol vs. placebo withdrew from therapy due to adverse effects, primarily diarrhea, abdominal pain, and nausea [Rostom 2004]. Diarrhea occurs in 13% to 40% of patients. It is dose-related, occurs early in treatment, usually resolves with continued treatment, and can be minimized with administration with meals and at bedtime and avoidance of magnesium-containing antacids. Abdominal pain is reported in 7% to 20% of patients. Misoprostol is rated pregnancy category X, and is contraindicated in women of child-bearing age unless the benefits exceed the risks.

3) Other Factors

- *Dosing* – The four H2 antagonists exhibit minor differences in potency, duration of action, onset of action, and frequency of dosing. Cimetidine requires twice daily to four times daily dosing, while the remaining three H2 antagonists can be dosed once to twice daily.
- *Available formulations* – All four H2 antagonists are available in tablet and liquid dosage formulations. The available dosage formulations for sucralfate include a tablet and oral suspension, while misoprostol is only available in a tablet. Ranitidine is also available in a gel-filled capsule, granule, and effervescent tablet.
- *Utilization* – Of the six drugs included in the class, the H2 antagonists account for over 90% of the prescriptions written in the MHS for this drug class. Ranitidine is the most widely prescribed H2 antagonist in the MHS, accounting for 67% of all H2 antagonist prescriptions, followed by famotidine (22%), cimetidine (8%) and nizatidine (3%).
- *Pediatrics* – Ranitidine and famotidine are indicated for use in children as young as two years of age; nizatidine is indicated in children older than 11 years, and cimetidine is indicated for use in children older than 15 years of age.
- *Pregnancy* – The four H2 antagonists and sucralfate are rated as pregnancy category B. Misoprostol is rated as pregnancy category X.

Overall Clinical Effectiveness Conclusion - The Committee concluded that:

1) The four H2 antagonists ranitidine, cimetidine, famotidine, and nizatidine are widely considered interchangeable for treatment of GERD, peptic ulcer disease and *H. pylori* infections, despite differences in potency, duration of action, and onset of action.
2) Compared to the other three H2 antagonists, cimetidine has evidence for use in non-gastrointestinal conditions.
3) Ranitidine is the most widely used H2 antagonist across the MHS, is dosed once or twice daily, has a low potential for drug interactions, and is available in an oral syrup for pediatric patients.
4) Famotidine and nizatidine have similar dosing intervals, drug interaction profiles and formulations as ranitidine, but are less frequently prescribed in the MHS.
5) Cimetidine is more difficult to use clinically compared to the other three H2 antagonists due to its need for multiple daily dosing (BID-QID) and drug interaction profile.
6) Misoprostol serves a unique niche for use in high risk patients for NSAID-induced ulcers, despite its adverse effect profile and warnings in women of child bearing age.
7) Sucralfate has a unique mechanism of action (physical barrier formation) and offers an alternative to PPIs and H2 antagonists for stress ulcer prophylaxis.

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

B. H2 Antagonists & Other GI Protectants Relative Cost Effectiveness

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

A simple cost analysis was employed to assess the relative cost-effectiveness of the agents within the H2 antagonist/GI protective therapeutic class. The agents within this class were evaluated on their weighted average cost per unit. The results of the cost analysis showed ranitidine to be the most cost effective H2 antagonist. A sole source joint DoD/VA contract is currently in place for ranitidine. The other generic H2 antagonists were shown to have similar relative cost-effectiveness compared to ranitidine, with the exception of nizatidine. Not surprisingly, nizatidine was found to be slightly more costly compared to the other generic H2 antagonists, since a generic version has only recently become available. In regards to misoprostol and sucralfate, both of these agents are available in generic versions and have a niche place in therapy for select patients.

Conclusion – The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 1 abstention, 0 absent) to accept the H2 antagonists and other

GI protectants cost analysis presented by the PEC. The P&T Committee concluded that the H2 antagonists ranitidine, cimetidine, famotidine and nizatidine; the prostaglandin analog misoprostol; and the mucosal protective agent sucralfate should be maintained on the UF.

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the H2 antagonists and other GI protectants, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend that the H2 antagonists ranitidine, cimetidine, famotidine and nizatidine; the prostaglandin analog misoprostol; and the mucosal protective agent sucralfate should be maintained on the UF and that no agents from this class be classified as non-formulary under the UF.

C. H2 Antagonists & Other GI Protectants Medical Necessity Criteria – Since no agents were recommended for non-formulary status under the UF, establishment of medical necessity criteria is not applicable.

D. H2 Antagonists & Other GI Protectants UF Implementation Period – Since no agents were recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

E. H2 Antagonists & Other GI Protectants BCF Review and Recommendations – The P&T Committee had previously determined that one or more agents in this class should be considered for addition to the BCF. Currently, ranitidine (Zantac, generics) is on the BCF, with the effervescent tablet and gel-filled capsule formulations specifically excluded. The committee agreed that ranitidine should remain on the BCF. Since the gel-filled capsule and effervescent tablet dosage formulations were shown to be 19 to 64 times more costly per unit than generic ranitidine without offering any substantial increase in clinical effectiveness, the P&T Committee agreed that the gel-filled capsule and effervescent tablet formulations should continue to be excluded from the BCF.

COMMITTEE ACTION – The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend retaining ranitidine as the BCF selection in this class, excluding the effervescent tablet and gel-filled capsule formulations.

9. ANTILIPIDEMIC AGENTS 1 DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the Antilipidemic Agents I (LIP-1) agents. This class is currently ranked number one in the MHS with drug class expenditures exceeding $595 million annually. On average, during a twelve month period from July 2005 and ending June 2006, there were approximately 975,000 unique utilizers per quarter. Individual drugs in the LIP-1 class are listed below:

- *Statins*. atorvastatin (Lipitor), fluvastatin (Lescol), fluvastatin extended release (Lescol XL), lovastatin (Mevacor, generics), lovastatin extended release(Altoprev), pravastatin (Pravachol, generics), rosuvastatin (Crestor, generics), and simvastatin (Zocor, generics)
- *Statin combination products*. atorvastatin/amlodipine (Caduet), lovastatin/niacin extended release (Advicor), and ezetimibe/simvastatin (Vytorin)

- *Add-on therapies:* niacin immediate release (Niacor), niacin extended release (Niaspan), and ezetimibe (Zetia)

A. LIP-1 Relative Clinical Effectiveness Review:

Information regarding the safety, effectiveness, and clinical outcomes of the LIP-1 agents was considered. The Committee's review focused primarily on the agents' ability to lower LDL concentrations, to raise HDL concentrations, and to reduce clinical outcomes including all-cause mortality, cardiovascular mortality, myocardial infarction (MI), stroke, and need for revascularization. Differences in the agents' effect on triglyceride concentrations, and benefits in treating non-cardiovascular conditions were not assessed in detail. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1).

1) Efficacy for %LDL lowering and %HDL raising

Endpoints: The differences between the statins in terms of %LDL lowering and %HDL raising were assessed. Elevated LDL concentrations and low HDL concentrations are both strong independent risk factors of CHD.

%LDL Lowering:

- The primary action of the statins is to reduce elevated LDL concentrations, which is the main target of cholesterol-lowering therapy recommended by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines. LDL reduction occurs in a dose-dependant fashion with the statins. However, increasing a statin dose provides only an additional 5 to 6% LDL lowering.
- Data obtained from the individual statin product labeling and clinical trials was used to compare differences in the agents' ability to lower LDL. The statins were divided into two groups: the low to moderate group can achieve ≤45% LDL lowering, and the intensive group can achieve >45% LDL lowering. (See Appendix E)
- The following statins are considered low to moderate %LDL lowering statins: all doses of fluvastatin, fluvastatin extended release, pravastatin, lovastatin, lovastatin extended release, atorvastatin 10 and 20 mg (as well as corresponding Caduet doses which include atorvastatin 10 or 20 mg), simvastatin 10, 20, and 40 mg, ezetimibe/simvastatin 10/10 mg, and rosuvastatin 5 mg.
- The following statins are considered intensive %LDL lowering statins: atorvastatin 40 and 80mg (as well as corresponding Caduet doses which include atorvastatin 40 and 80 mg), rosuvastatin 10, 20, and 40 mg, simvastatin 80 mg, and ezetimibe/simvastatin 10/20, 10/40, and 10/80 mg.
- When equipotent doses are used, the statins achieve similar %LDL lowering (e.g., atorvastatin 20 mg, simvastatin 40 mg and ezetimibe/simvastatin 10/10 mg all attain 41 to 45% LDL lowering). Rosuvastatin 40 mg and ezetimibe/simvastatin 10/80 mg are the only statins capable of attaining >55% LDL lowering.
- Based on a previous model constructed by the PEC that evaluated National Health and Nutrition Examination Survey data, 80 to 85% of the DoD population

requiring a statin is expected to attain their LDL goal on simvastatin doses ≤40mg. Simvastatin is the highest utilized statin in the DoD. (See Figure 1).

%HDL Raising:

- The primary clinical use of the statins is to reduce elevated LDL concentrations; however beneficial effects on HDL are also seen.
- Evidence from published trials and product labeling support the conclusion that HDL generally rises in a dose-dependent fashion, however all statins show a plateau and drop-off of HDL raising effect as the highest doses are approached. For example, atorvastatin 20 mg, simvastatin 40 mg and ezetimibe/simvastatin 10/10 mg can achieve an 8 to 9% increase in HDL concentrations, but at doses of atorvastatin 80 mg and ezetimibe/simvastatin 10/40 mg, only achieve a 5-6% increase in HDL.
- The Committee commented that other drugs that primarily target HDL are available (e.g., niacin, fibrates, bile acid resins), and that providers should choose a drug other than a statin if the primary goal is to raise HDL concentrations. Currently the most potent option for raising HDL is niacin.

2) *Efficacy for clinical outcomes:*

Endpoints: The main clinical endpoints used to evaluate differences in statin efficacy include all-cause mortality, cardiovascular mortality, MI, stroke, and need for revascularization. Numerous clinical trials have shown the benefits of statin therapy on reducing cardiovascular events. However, differences in clinical outcomes between the statins are difficult to compare, due to widely varying patient populations evaluated, vaguely defined endpoints, and comparison of non-equipotent statin doses.

Meta-analyses:

- There are no head-to-head trials comparing equivalent doses of statins that evaluate differences in mortality or other clinical outcomes. One meta-analysis (Zhou 2006) evaluated the differences between low to moderate doses of atorvastatin, simvastatin, and pravastatin in reducing mortality or cardiovascular events. Eight clinical trials (comprising both primary and secondary prevention trials) met the criteria for inclusion in the analysis. An adjusted indirect comparison was calculated.
- For all comparisons between the three statins (e.g., atorvastatin vs. pravastatin, atorvastatin vs. simvastatin, and simvastatin vs. pravastatin), there was no significant difference between the drugs in all-cause mortality, major coronary events (fatal CHD and nonfatal MI), cardiovascular death (coronary and cerebrovascular death), and major cardiovascular events (stroke); ($p>0.05$ for all comparisons).

Efficacy for primary prevention of CHD: Primary prevention trials consist of patients without clinically evident CHD. Beneficial effects on clinical outcomes for primary prevention of CHD have been noted with atorvastatin 10 mg (ASCOT-LLA and CARDS trials), lovastatin 20 to 40 mg (AFCAPS, TexCAPS trials), pravastatin 40 mg (WOSCOPS), and simvastatin 40 mg (HPS).

Efficacy for secondary prevention of CHD: Secondary prevention trials include patients with pre-existing cardiovascular disease, such as prior MI, or prior revascularization procedures. In trials assessing the secondary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin 10 to 80 mg (GREACE, TNT), lovastatin 40 to 80 mg (CABG), pravastatin 40 mg (LIPID, CARE), simvastatin 20 to 40 mg (4S), and fluvastatin 40 mg (administered bid) (LIPS).

- TNT: In the Treat to Target (TNT) trial, low dose atorvastatin 10 mg was compared to intensive dose atorvastatin 80 mg for 5 years in 10,000 patients with stable CHD. Intensive dose atorvastatin 80 mg was associated with significantly fewer patients reaching the primary composite outcome (which included non-fatal MI) vs. atorvastatin 10 mg (28.1% vs. 33.5%, $p<0.001$). There was no benefit of intensive dose atorvastatin when mortality was assessed as a single endpoint. The main conclusion was that reducing LDL to <100 mg/dL yielded incremental clinical benefits.
- IDEAL: In the Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) trial, intensive dose atorvastatin 80 mg was compared to low to moderate dose simvastatin 20 to 40 mg. In contrast to TNT, intensive dose atorvastatin did not show a benefit in the primary composite endpoint (CHD death, hospitalized non-fatal MI, resuscitated cardiac arrest); (9.3% of atorvastatin patients reached the primary endpoint, vs. 10.4% of simvastatin patients; $p=0.07$).

Efficacy for ACS: A subgroup of secondary prevention trials focuses on ACS patients who can experience unstable angina and myocardial ischemia due to severe atherosclerotic plaque progression.

- PROVE-IT:
  - In the Pravastatin or Atorvastatin Evaluation and Intensive Therapy (PROVE-IT) trial, moderate dose pravastatin 40 mg was compared to intensive dose atorvastatin 80 mg for two years in over 4,000 recently hospitalized (< 10 days) patients with ACS. Significantly fewer patients receiving intensive dose atorvastatin 80 mg reached the primary composite endpoint (all cause death, MI, unstable angina requiring hospitalization, stroke) than moderate dose pravastatin 40 mg (22.4% vs. 26.3%, $p=0.005$).
  - The PROVE-IT trial provides evidence for immediate use of intensive dose statin in ACS patients. Additionally, a goal LDL <70 mg/dL should be considered in this population, as the ending mean atorvastatin LDL was 62 mg/dL vs. 95 mg/dL with pravastatin 40 mg.
  - It is unknown whether the beneficial results seen in the PROVE-IT trial would be duplicated if an intensive dose statin other than atorvastatin were evaluated, as no such studies have been published.
- PACT: In the Pravastatin in Acute Treatment (PACT) trial, pravastatin 20 to 40 mg did not show a reduction in coronary events vs. placebo, however statin administration was delayed for 24 hours and the trial duration was only 4 weeks.

- A to Z: In the Aggrastat to Zocor (A to Z) trial, no statistically significant reduction in coronary events was shown after 2 years in 4,000 ACS patients receiving early initiation (after one month) intensive dose simvastatin 40 to 80 mg vs. delayed initiation (after four months) of low dose simvastatin 20 mg. The long delay in statin administration, and not the individual statin evaluated, likely contributed to the negative results.

Rosuvastatin and ezetimibe/simvastatin: There are no published trials assessing the benefits of rosuvastatin on clinical outcomes; one large trial (JUPITER) is in progress. While there are no clinical trials specifically assessing the ezetimibe/ simvastatin formulation, there is evidence for clinical benefits of the simvastatin component from the Scandinavian Simvastatin Survival Study (4S) and Heart Protection Study (HPS) trials. There is no evidence to suggest that addition of ezetimibe to simvastatin would negate the clinical benefits of the simvastatin component.

3) *Safety and Tolerability*

Minor Adverse Events: The statins show similar common adverse event profiles. Data from the package insert suggests that the there is no evidence that minor adverse events (GI disturbances, headaches, rash, itching) are less likely to occur with one statin vs. another. These adverse effects appear dose-related.

Serious Adverse Events: The P&T Committee specifically focused on three main areas, elevated liver transaminases, proteinuria, and myotoxicity.

- Elevations in liver transaminases
  - Transient elevations of aspartate aminotransferase and alanine amino-transferase (AST/ALT) to greater than three times the upper limit of normal (ULN) can occur with all the statins. The incidence of elevations in transaminases with all the statins ranges from 0.3 to 3%, according to data from statin package inserts.
  - Increases in liver transaminases are more likely to occur with intensive dose statins vs. low to moderate dose statins. No evidence suggests that one statin is less likely than another to cause increased liver transaminases. There is no data to date that suggest elevations in ALT or AST are predictive of liver injury or long term hepatotoxicity.
- Proteinuria:
  - A retrospective analysis conducted by the FDA using preclinical NDA submissions reported that rosuvastatin 40 mg was associated with a 4 to 5% incidence of proteinuria. This was higher than the incidence reported with rosuvastatin doses $\leq$20 mg (1 to 4%), atorvastatin 10 to 80 mg (0.4% to 2%), simvastatin 20 to 80 mg (0.6% to 4%), or pravastatin 20 to 40 mg (0 to 1%). Limitations to this analysis include the use of spot urine dipstick testing rather than 24-hour urine collections, and the inclusion of data from both open label and placebo-controlled trials.

- Currently there are no requirements for monitoring of renal function with any of the statins. Due to the insufficient and poor quality evidence available at this time, it cannot be determined whether the incidence of proteinuria differs between the statins.

- Myotoxicity:
  - Varying definitions of the terms myotoxicity, myopathy, myalgia, myositis, and rhabdomyolysis make interpretation of the literature difficult. Rhabdomyolysis (symptoms of muscle pain accompanied by increased creatine kinase >10 times ULN, increased serum creatine and brown colored urine) occurs rarely with all the statins. Muscle symptoms with the statins appear to be dose related, and the intensive dose statins should be used with caution in patients at increased risk of myotoxicity.
  - One meta-analysis [CTTC 2004] reported an overall low incidence of rhabdomyolysis with simvastatin, pravastatin, lovastatin and fluvastatin that did not differ from placebo (0.023% with the statins vs. 0.015% with placebo).
  - Rosuvastatin was associated with an incidence rate of rhabdomyolysis two times higher than that of the other marketed statins after the first six months of therapy (hazard ratio 1.98; [95% CI 0.18 to 21.90] in one retrospective cohort study of health claims. [McAfee 2006]. This result was not statistically significant. The analysis excluded cerivastatin (Baycol), as it was removed from the market in 2001 due to a high risk of rhabdomyolysis.
  - Spontaneous adverse event reporting data from the FDA uses a reporting rate (number of spontaneous case reports for rhabdomyolysis per 1 million US prescriptions) instead of an incidence rate to determine differences in myotoxicity between the statins.
    - Cerivastatin had the highest reporting rate of rhabdomyolysis (72.88 per 1 million US prescriptions) based on data from the years 1988 to 2000 were analyzed, while it was still marketed.
    - Data from 2002 to 2004 show that the reporting rate of rhabdomyolysis is higher with rosuvastatin at 13.54 reports per 1 million prescriptions, compared to simvastatin (8.71), fluvastatin (3.44), lovastatin (2.76), atorvastatin (1.67) and pravastatin (1.63).
    - Limitations to the FDA reporting system include the lack of a control group, reliance on spontaneous reports which may not reflect the true incidence of an adverse event, and the low overall occurrence of rhabdomyolysis. FDA reporting rates are more useful to signal a trigger of concern, rather than to quantify relative risks between different drugs in a class.
    - Despite the differences between rosuvastatin and the other marketed statins in terms of reporting rates and incidence rates of myotoxicity, definitive conclusions cannot be drawn. However, concerns remain with rosuvastatin, particularly at intensive doses.

Drug interactions: Fluvastatin, pravastatin, and rosuvastatin have the most favorable drug-drug interaction profiles as they are not appreciably metabolized via the CYP3A4 system. Atorvastatin, lovastatin, and simvastatin do undergo CYP3A4 metabolism, which results in concerns of drug-drug interactions with amiodarone, diltiazem, "azoles", and other 3A4 metabolized drugs.

Special populations: Fluvastatin, pravastatin, and rosuvastatin are preferred in patients with renal or hepatic insufficiency, in HIV/AIDS patients, or in recipients of solid organ transplants, as they are not metabolized via the CYP3A4 system. These patient groups represent about 2 to 3% of the 9 million DoD beneficiaries.

Pediatrics: Pravastatin is approved by the FDA for use in children as young as 8 years old. Atorvastatin, simvastatin, and lovastatin are approved for use in children as young as 10 years with heterozygous familial hypercholesterolemia, a rare condition.

Pregnancy: All the statins are rated Pregnancy Category X, due to the risk of fetal malformations.

Tolerability: There is insufficient evidence to determine whether one statin is less tolerable than another due to a lack of meta-analyses or retrospective claims data evaluating this outcome and the varying results reported in head-to-head trials.

4) *Other Factors:*

Dosing titration and initiation: The statins can be initiated at maximum doses, with the exception of rosuvastatin 40 mg. Rosuvastatin 40 mg should only be initiated in patients failing to reach target LDL goals with rosuvastatin 20 mg.

Pleiotropic effects: The majority of the observational data suggesting pleiotropic benefit (e.g., beneficial effects other than LDL lowering) with the statins rests with atorvastatin. None of the pleiotropic markers (e.g., C-reactive protein,) have been shown consistently in randomized trials to cause CHD. There is insufficient evidence to determine the clinical applicability of differences between the statins in terms of pleiotropic effects.

Markers of atherosclerotic progression: Rosuvastatin 40 mg was shown to cause plaque regression in the ASTEROID trial, and atorvastatin 80 mg was shown to slow the progression of plaque formation in the REVERSAL trial; both trials used intravascular ultrasound. Benefits on carotid intima media thickness have been shown with all the statins, except for rosuvastatin for which there is no published study.

5) *Efficacy and safety of ezetimibe:*

- Ezetimibe lowers LDL by a mechanism distinct from that of the statins, as it inhibits absorption of dietary cholesterol.
- Use of ezetimibe as monotherapy attains 15 to 19% LDL lowering and provides a treatment option for patients who are at risk for statin adverse events. Use of ezetimibe in combination with low to moderate statin doses provides greater LDL lowering (12 to 20% LDL lowering) vs. increasing the statin dose alone (5 to 6% LDL lowering).

- The combination of ezetimibe with a statin can be used to reach target LDL goals when statin monotherapy has failed, or to avoid the potential risks with using intensive statin doses as monotherapy.
- The proven benefits of cardiovascular outcomes seen with the statins have yet to be duplicated with ezetimibe, as there are no published trials.
- The most common adverse events with ezetimibe are abdominal pain, diarrhea and headache. The risk of elevations in liver transaminases is slightly increased when ezetimibe is combined with a statin (1.3 to 2%) vs. using statin monotherapy (0.4%). To date, there are only rare case reports of myotoxicity and rhabdomyolysis.
- Current MHS utilization and provider opinion support the need for ezetimibe in the MHS.

6) *Efficacy and safety of ezetimibe/simvastatin:*

- The combination of simvastatin with ezetimibe provides additional efficacy for LDL lowering.
- Doses of ezetimibe/simvastatin greater than 10/20 mg provide 45% to more than 55% LDL lowering, allowing a treatment option in those 15 to 20% of DoD patients unable to meet goal LDL with simvastatin alone.
- The efficacy profile of ezetimibe/simvastatin reflects that of the individual components.
- To date, no clinically important increases in safety issues, such as risk of liver transaminase elevation or myotoxicity have been reported.

7) *Efficacy and safety of niacin*

- Niacin is FDA-approved to raise HDL (along with fibrates). Niacin can raise HDL by 25%, and can be used as monotherapy or in combination with other drugs.
- Clinical outcomes including reduced stroke, MI, and all-cause mortality have been reported with niacin.
- The formulation of niacin extended release is associated with a reduced risk of GI adverse events and hepatotoxicity compared to niacin immediate release or over the counter forms of long-acting niacin (Slo-Niacin).
- The risk of myotoxicity and drug-drug interactions is reduced when niacin is used in combination with a statin, vs. using the combination of fibrates with a statin.
- The benefits of niacin extended release are limited to those patients who can tolerate the associated adverse effects (flushing and GI disturbances).

8) *Clinical issues with lovastatin/niacin extended release, atorvastatin/amlodipine, lovastatin extended release, and fluvastatin extended release*

- Lovastatin/niacin extended release is difficult to initiate and titrate, since it is available in a fixed dose formulation.

- Atorvastatin/amlodipine contains a statin in combination with the dihydropyridine calcium channel blocker amlodipine. Amlodipine (Norvasc) was designated non-formulary under the UF in August 05. No outcomes trials have specifically assessed the benefits of the fixed dose Caduet formulation, and there is no evidence to suggest improved adherence or additional LDL lowering with the combination.
- Lovastatin extended release does not offer additional LDL lowering or safety benefits over lovastatin. Unlike lovastatin, lovastatin extended release is available in a 60 mg tablet, but does not attain a >45% LDL lowering.
- Fluvastatin extended release has proven benefits from one trial assessing revascularization (LIPS) and is a non-CYP3A4 metabolized statin. However, it does not offer additional benefits over fluvastatin immediate release and does not attain a >45% LDL lowering.
- Overall, these drugs do not offer additional clinical benefits over the other antilipidemic agents and have low utilization in the MHS (<5,000 Rxs/month dispensed).

9) A survey of MTF providers, including cardiologists, was overwhelmingly in support of simvastatin for treating the 80-85% of MHS patients requiring LDL lowering <45%, and also supported use of ezetimibe. Providers were also concerned with the safety profile of rosuvastatin.

Overall Clinical Effectiveness Conclusion – The Committee concluded that:

1) Across equipotent doses, the statins achieve similar %LDL lowering, with rosuvastatin 40 mg and ezetimibe/simvastatin 10/80 mg as the only statins capable of attaining LDL lowering >55%.
2) Across equipotent doses, the statins achieve similar %HDL raising ability, but all statins show a plateau and drop-off of HDL raising effect at increasing doses.
3) There are no head-to-head trials comparing equivalent doses of statins that evaluate clinical outcomes for reducing mortality or other clinical outcomes (e.g., myocardial infarction, stroke, need for revascularization).
4) In low to moderate doses, the effects of atorvastatin, pravastatin and simvastatin appear similar for long-term cardiovascular protection, based on one meta-analysis (Zhou 2006).
5) In trials assessing the primary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin 10 mg, lovastatin 20 to 40 mg, pravastatin 40 mg, and simvastatin 40 mg.
6) In trials assessing the secondary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin 10 to 80 mg, lovastatin 40 to 80 mg, pravastatin 40 mg, simvastatin 20-40 mg, and fluvastatin 40 mg (administered BID).

7) In one trial assessing acute coronary syndrome (ACS) patients, beneficial effects on clinical outcomes were noted with atorvastatin 80 mg when it was compared to pravastatin 40 mg (PROVE-IT 2004).

8) There are no published trials assessing the benefits of rosuvastatin on clinical outcomes.

9) There is no evidence that increases in liver function tests (ALT) or minor adverse events (GI disturbances, headaches, rash, itching) are less likely to occur with one statin vs. another, and these adverse effects are dose-related.

10) Concerns of proteinuria and myotoxicity remain with rosuvastatin; the overall incidence of rhabdomyolysis occurs rarely with statins.

11) Fluvastatin, pravastatin, and rosuvastatin have the most favorable drug-drug interaction profiles,

12) There is insufficient evidence to determine whether one statin is less tolerable than another.

13) In terms of other factors, the statins can be initiated at maximum doses, with the exception of rosuvastatin 40 mg.

14) There is insufficient evidence to determine the clinical applicability of differences between the statins in terms of pleiotropic effects or effects on markers of atherosclerotic progression (intravascular ultrasound or carotid intima media thickness).

15) Ezetimibe offers an additional 15-20% LDL lowering by a mechanism distinct to that of the statins, but has not yet been evaluated for clinical outcomes.

16) Ezetimibe/simvastatin provides added efficacy in terms of LDL lowering and has a safety and efficacy profile reflecting that of its two individual components.

17) Niacin extended release is required in the MHS as its primary benefit is to raise HDL by 25%.

18) Lovastatin/niacin extended release, atorvastatin/amlodipine, lovastatin extended release, and fluvastatin extended release do not offer additional clinical benefits over the other LIP-1 agents and have low utilization in the MHS (<5,000 Rxs/month dispensed).

19) A survey of MTF providers, including cardiologists, was overwhelmingly in support of simvastatin for treating the 80-85% of MHS patients requiring LDL lowering ≤45%, and also supported use of ezetimibe.

20) Based on clinical issues alone, none of the LIP-1 agents are sufficiently less effective than the others agents within the class to be classified as non-formulary.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

B. LIP-1 Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the LIP-1 agents in relation to the effectiveness, safety, tolerability, and clinical outcomes of the other agents

in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2). A series of cost-effectiveness analyses were used to determine the relative cost-effectiveness of agents within the LIP-1 therapeutic class.

For the high % LDL lowering agents (>45%, intensive) in the LIP-1 class (atorvastatin 40 and 80 mg; rosuvastatin 10, 20, and 40 mg; ezetimibe/simvastatin 10/20, 10/40, and 10/80 mg; and simvastatin 80 mg), four separate cost-effectiveness models were constructed.

1) The Annual Cost per 1% LDL Decrease model compared the cost-effectiveness of the high % LDL lowering agents on annual cost per 1% LDL decrease using a decision analytical model.
2) The Annual Cost per Patient Treated to Goal model compared the cost-effectiveness of these agents on annual cost per patient successfully treated to NCEP goal using a Monte Carlo simulation model.
3) The Medical Cost Offset Model compared the cost-effectiveness of these agents based on their predicted outcomes and total predicted health care expenditures for CHD and CHD risk-equivalent patients.
4) The Cost per Event-Free Patient model, based on the results of the IDEAL Trial, compared the cost-effectiveness of the agents included in that trial – high-dose (80mg) atorvastatin (Lipitor) vs. low-dose (20-40 mg) simvastatin – using a decision analytic model.

The results of the first three cost-effectiveness analyses showed ezetimibe/simvastatin (Vytorin) to be the most cost effective high % LDL lowering agent. The results of the fourth analysis revealed that high-dose (80 mg) atorvastatin was more effective but considerably more costly compared to low dose (20-40mg) simvastatin. The results of this analysis support use of high dose atorvastatin only in patients who cannot be successfully treated to goal with simvastatin.

For the low to moderate % LDL lowering agents (≤ 45%) in the LIP-1 class (simvastatin 5, 10, 20, and 40 mg, atorvastatin 10 and 20 mg; rosuvastatin 5 mg; ezetimibe/simvastatin 10/10 mg; and all strengths of pravastatin, fluvastatin, fluvastatin extended release lovastatin, lovastatin extended release, niacin/lovastatin, niacin extended release, niacin immediate release, and ezetimibe), the cost-effectiveness of the agents within this subclass was evaluated using the Annual Cost per 1% LDL Decrease model. In pharmacoeconomic terms, lovastatin, lovastatin extended release, simvastatin, and rosuvastatin were located along the cost efficiency frontier and were considered to be the optimal agents. Although these agents differed in terms of cost-effectiveness relative to each other, they were more cost-effective than (dominated) the other agents evaluated.

With respect to atorvastatin/amlodipine, an earlier review did not show additional clinical benefit for amlodipine versus other dihydropyridine CCBs. Single ingredient amlodipine (Norvasc) is non-formulary under the UF. In order to assess the cost effectiveness of atorvastatin/amlodipine, it was compared to the combination of atorvastatin and a UF dihydropyridine calcium channel blocker, based on the weighted average cost per day of therapy. The results of this analysis revealed that atorvastatin/amlodipine was

considerably more costly compared to the combination of atorvastatin and a UF dihydropyridine calcium channel blocker, regardless of point of service.

To account for other factors and costs associated with a UF decision (market share migration, switch costs, non-formulary cost shares, and medical necessity processing fees), a budget impact analysis was performed. The goal of the BIA was to assist the Committee in determining which group of high % LDL lowering LIP-1 agents best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA focused on high % LDL lowering agents because 1) simvastatin could meet the vast majority of the needs of patients requiring low % LDL lowering agents; 2) some low % LDL lowering agents were considered to be clinically necessary (pravastatin, ezetimibe, and niacin extended release); and 3) of the remaining low % LDL lowering agents, nothing would be gained clinically or economically by making them non-formulary, especially considering their low market share. Based on the BIA results and other clinical and cost considerations, the Committee agreed that the UF scenario that included the high % LDL lowering agents atorvastatin and ezetimibe/simvastatin on the UF best achieved this goal when compared to other alternative UF scenarios, and thus was determined to be more cost-effective relative to other UF scenarios.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstention, and 0 absent) to accept the LIP-1 relative cost-effectiveness analysis as presented by the PEC. The P&T Committee concluded that the Uniform Formulary scenario that included atorvastatin, ezetimibe/simvastatin, and simvastatin 80 mg as the high % LDL lowering agents on the UF was the most cost effective UF scenario.

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the LIP-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 1 opposed, 1 abstained, and 0 absent) to recommend that atorvastatin, fluvastatin immediate and extended release, pravastatin, simvastatin, lovastatin immediate and extended release, lovastatin/niacin, ezetimibe/simvastatin, niacin immediate and extended release, and ezetimibe be maintained as formulary on the UF and that rosuvastatin and atorvastatin/amlodipine be classified as non-formulary under the UF.

C. LIP-1 UF Medical Necessity Criteria

Based on the clinical evaluation of the LIP-1 agents, 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 medical necessity criteria for rosuvastatin:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Treatment with the formulary alternatives has resulted, or is likely to result, in therapeutic failure.
4) The patient previously responded to rosuvastatin and changing to a formulary alternative would incur unacceptable clinical risk.

The P&T Committee noted that some specific situations in which rosuvastatin might be considered medically necessarily were 1) if a patient requires a high % LDL lowering agent in order to meet his or her LDL goal *and* requires a non-CYP3A4-metabolized statin due to potential drug interactions, or 2) if a patient requires a high % LDL lowering agent in order to met his or her LDL goal *and* is not able to reach that goal with any of the formulary high % LDL lowering agents. The P&T Committee also noted that criterion #4 would apply rarely, since changes in statin therapy are unlikely to present a risk of destabilization or serious adverse effects in the vast majority of patients and since rosuvastatin does not offer any significant safety advantages compared to other statins other than not being metabolized through CYP3A4.

Based on the clinical evaluation of the LIP-1 agents, 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 medical necessity criterion for atorvastatin/ amlodipine:

1) Use of formulary alternatives is contraindicated.

The P&T Committee noted that the other conditions for establishing medical necessity provided for in the UF rule do not apply to atorvastatin/amlodipine since the components of this product are available as single ingredients and there is no evidence to support improved efficacy, safety, or tolerability with the combination product vs. its individual components given separately. Amlodipine, a dihydropyridine calcium channel blocker used for hypertension and coronary artery disease, has not been shown to enhance the lipid-lowering effects of atorvastatin. The P&T Committee further noted that since single ingredient amlodipine is non-formulary under the UF, the closest therapeutic alternative to atorvastatin/amlodipine on the UF would be atorvastatin or another UF statin plus a UF dihydropyridine calcium channel blocker [felodipine (Plendil, generics), nifedipine extended release (Adalat CC, Procardia XL, generics), or nisoldipine (Sular)].

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

D. LIP-1 Implementation Plan:

Because of contractual considerations associated with the statin drug class affecting MTFs and TMOP, the P&T Committee recommended an effective date no sooner than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

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

COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 2 abstained, 0 absent) an effective date no sooner than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

E. LIP-1 BCF Review and Recommendations

The P&T Committee had previously determined that one or more low to moderate % LDL lowering agents and no more than one high % LDL lowering agent could be considered for addition to the BCF. Based on the relative clinical effectiveness and cost effectiveness of the agents and taking into account the following considerations, the P&T Committee recommended the following LIP-1 agents for BCF status:

- *Simvastatin* – Simvastatin provides LDL-lowering of up to 40 to 45% at doses ≤ 40 mg/day; can be used to treat 85% of MHS patients who require a statin; has shown proven mortality benefits in primary and secondary prevention trials [HPS; 4S]; is labeled for pediatric use in patients as young as 10 years of age; has an acceptable adverse event profile compared to other statins; and is familiar to MHS providers as evidenced by its current high utilization in the MHS.
- *Pravastatin* – Pravastatin is one of three statins not metabolized via the CYP3A4 system, which is necessary in order to avoid drug interactions in special populations *requiring* treatment with interacting medications (e.g., HIV/AIDS patients, solid organ transplant patients); has shown proven mortality benefits in primary and secondary prevention trials [WOSCOPS, CARE, LIPID]; is labeled for pediatric use in patients as young as 8 years of age; and has the highest utilization in the MHS of the three non-CYP3A4-metabolized statins.
- *Ezetimibe/simvastatin*– The combination of simvastatin and ezetimibe provides additional efficacy for LDL lowering; the 45% to more than 55% LDL lowering attainable with doses higher than 10/20 mg can be used to treat the estimated 15 to 20% of patients who cannot meet goal with simvastatin alone.
- *Niacin extended release* – Niacin is the only agent in the class that has been shown to raise HDL by 25%; has shown proven benefits for mortality, MI, and stroke [Coronary Drug Project]; and has a lower risk for GI adverse events and hepatotoxicity compared to other niacin formulations.

The Committee commented that while atorvastatin is recommended to remain on the UF, MTFs are strongly advised to avoid adding it to local formularies. Simvastatin doses of 20 to 40 mg provide similar efficacy for LDL lowering as atorvastatin but 10 to 20 mg, at a much lower cost due to generic availability. Patient migration from simvastatin to atorvastatin, particularly for patients requiring lower doses, will erode the cost-savings anticipated to occur as generic prices for simvastatin continue to decrease without providing additional clinical benefit. One possible exception to this may be ACS patients, in whom atorvastatin may be preferable based on the results of the PROVE-IT trial (for most patients, this would most likely entail use of 80 mg dose of atorvastatin, based on the lower LDL goals in this patient population).

COMMITTEE ACTION: The P&T Committee voted (15 for, 1 opposed, 1 abstained, 0 absent) to recommend simvastatin, pravastatin, ezetimibe/simvastatin and niacin extended release as the BCF selections in this drug class.

10. CLASS OVERVIEWS. ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY MEDICATIONS; SEDATIVE HYPNOTICS I (NON-BENZO-DIAZEPINE SEDATIVE HYPNOTICS); SEDATIVE HYPNOTICS II

Portions of the clinical reviews for each class were presented to the Committee. The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review, and for developing the appropriate cost effectiveness models. Both the clinical and economic analyses of these three classes will be completed during the November 2006 meeting; no action necessary.

11. ADJOURNMENT

The second day of the meeting adjourned at 1600 hours on 16 August 2006. The dates of the next meeting are 14-16 November 2006.

_____signed_____

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

List of Appendices

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations/Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications)	**Effective Date for Non-Formulary Medications** (Implementation period)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	Pending approval	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) - excludes gelcaps and effervescent tablets	Pending approval	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	Pending approval	Pending approval
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 July 06	27 Sept 06 (60 days)
May 06	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospironone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospironone (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 July 06	24 Jan 07 (180 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 July 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 July 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	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications)	**Effective Date for Non-Formulary Medications** (Implementation period)
Nov 05	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
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)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	**Decision Date** (DoD P&T minutes signed, effective date for BCF/ECF medications)	**Effective Date for Non-Formulary Medications** (Implementation period)
May 05	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	**-**
Feb 05	ARBs	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary

ER = extended release; IR = immediate release; SR = sustained release

ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs = thiazolidinediones

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

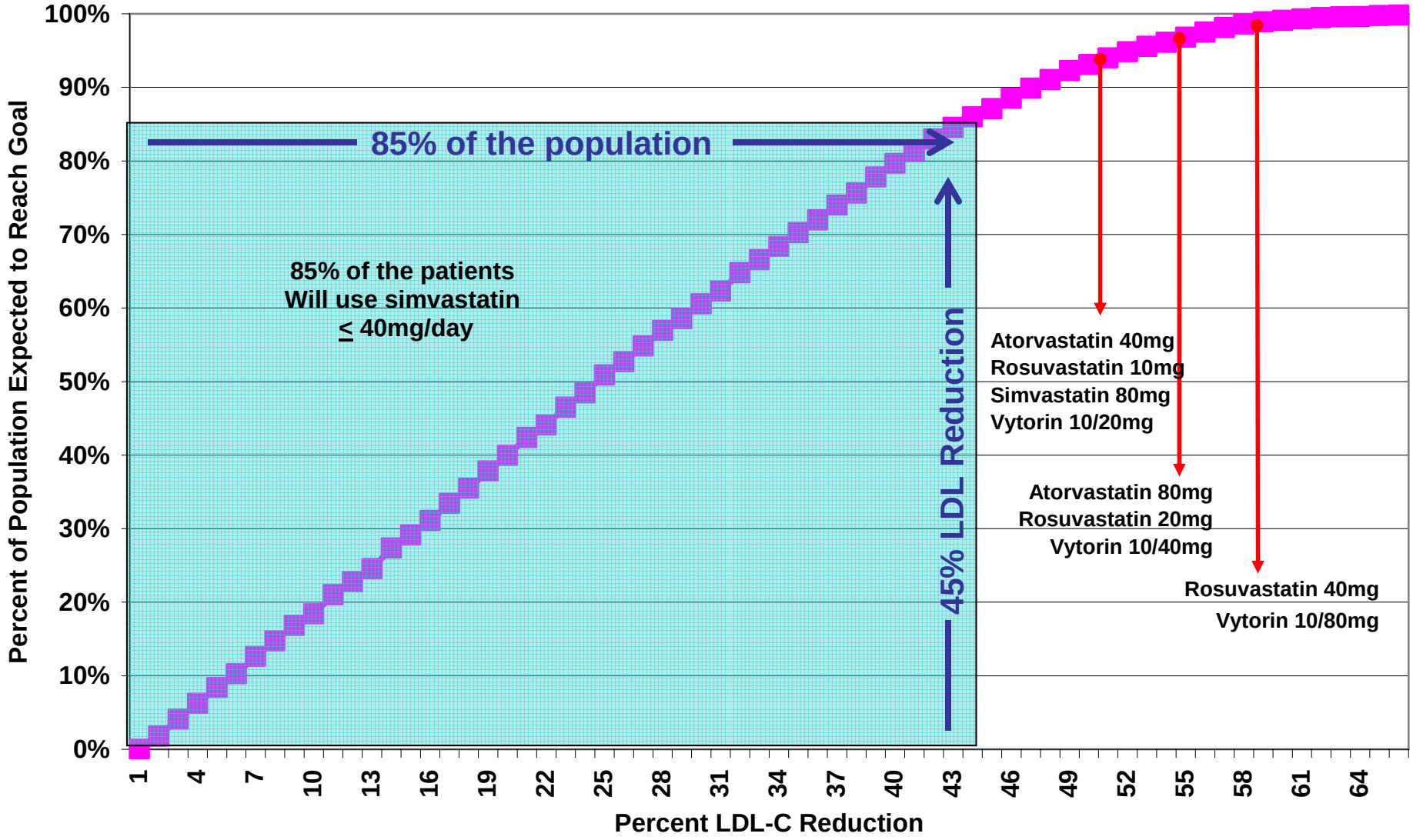
Appendix B – Table 2. Newly Approved Drugs. August 2006 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Dasatinib tabs (Sprycel; BMS) oral multi-kinase inhibitor	Jun 06 ▪ Treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib (Gleevec) ▪ Treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy	No UF recommendation at this meeting. Consideration of UF status deferred until oral cancer medications reviewed. Quantity limits recommended: ▪ TMOP o Days supply limit 45 days o 20 mg: 180 tabs per 45 days o 50 mg: 180 tabs per 45 days o 70 mg: 90 tabs per 45 days ▪ Retail Network o Days supply limit 30 days o 20 mg: 120 tabs per 30 days o 50 mg: 120 tabs per 30 days o 70 mg: 60 tabs per 30 days
Selegiline transdermal system (Emsam; BMS / Somerset) MAO A/B inhibitor	Mar 06 ▪ Acute and longer-term treatment of major depressive disorder in adult patients	No UF recommendation at this meeting. Consideration of UF status deferred until MAO inhibitors reviewed.
Rasagiline tabs (Azilect; Teva) MAO B inhibitor	May 06 ▪ Treatment as monotherapy of early Parkinson's Disease and combination use with levodopa in patients with moderate to advanced stages of Parkinson's Disease	No UF recommendation at this meeting. Consideration of UF status deferred until Parkinson's medications reviewed.
Methylphenidate transdermal system (Daytrana; Shire/Noven) amphetamine	Apr 06 ▪ Treatment of attention deficit hyperactive disorder (ADHD) in children 6-12 yrs of age	No UF recommendation at this meeting. Consideration of UF status deferred until ADHD / narcolepsy drug class reviewed in Nov 06.
Lubiprostone caps (Amitiza; Sucampo / Takeda) chloride channel activator	Jan 06 ▪ Treatment of chronic idiopathic constipation in adults	No UF recommendation at this meeting. Consideration of UF status deferred until drug class reviewed.

Appendix C – Table 3. Table of Abbreviations

ACS	acute coronary syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BPA	blanket purchase agreement
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CHD	coronary heart disease
CI	confidence interval
CMA	cost minimization analysis
CYP450	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DM	diabetes mellitus
DoD	Department of Defense
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FY	fiscal year
GERD	gastrointestinal reflux disease
GI	gastrointestinal
H2	histamine-2
HDL	high density lipoprotein
HbA1c	glycosylated hemoglobin A1c
IV	intravenous
LDL	low density lipoprotein
MI	myocardial infarction
MHS	Military Health System
MTF	military treatment facility
NSAID	non-steroidal anti-inflammatory drug
PA	prior authorization
P&T	Pharmacy and Therapeutics
PDTS	Pharmacy Data Transaction Service
PEC	Pharmacoeconomic Center
PPARs	peroxisome proliferator-activated receptors
PPIs	proton pump inhibitor
QD	once daily
QID	four times daily
TC	total cholesterol
TG	triglyceride
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
TZD	thiazolidinedione
ULN	upper limit of normal
UF	Uniform Formulary

Figure 1. Estimated Percent of Population Expected to Reach ATP-III LDL Goals with Increasing LDL Reduction
(NHANES3 Data Modeling by DoD PEC)



Appendix E – Table 4. Expected Mean LDL Reductions, by Statin and Dose

Expected Mean LDL Reduction	Statin					
	Lovastatin	**Pravastatin**	**Simvastatin**	**Fluvastatin**	**Atorvastatin**	**Rosuvastatin**
	IR - Mevacor, generics ER - Altoprev	Pravachol, generics	Zocor, generics	IR - Lescol, generics ER - Lescol XL	Lipitor	Crestor
25 to 30%	20 mg	20 mg	10 mg	40 mg		
30 to 40%	40 – 80 mg	40 mg	20 mg	80 mg (ER only)	10 mg	
40 to 45%	IR: 80 mg (40 mg x 2) ER: 60 mg	80 mg	40 mg or Vytorin 10/10 mg		20 mg	5 mg
45 to 50%	Please note: ezetimibe (Zetia) or niacin generally decrease LDL up to an additional 15%		80 mg or Vytorin 10/20 mg		40 mg	10 mg
50 to 55%			Vytorin 10/40 mg		80 mg	20 mg
>55%			Vytorin 10/80 mg			40 mg

IR = immediate release; ER = extended release
Vytorin = ezetimibe/simvastatin

DECISION PAPER:

May 2006
DEPARTMENT OF DEFENSE PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

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

The P&T Committee was briefed on six new drugs that had been approved by the Food and Drug Administration (FDA). None of the medications fall into drug classes already reviewed by the P&T Committee, therefore Uniform Formulary (UF) consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits. Sunitinib (Sutent) is an oral multi-kinase inhibitor approved for treatment of patients with advanced renal cell carcinoma and for the treatment of gastrointestinal stromal tumor (GIST). It is available in 12.5, 25 and 50 mg capsules and is administered once daily for a schedule of four weeks on treatment followed by two weeks off treatment. Quantity limits were recommended for sunitinib since there is a risk of discontinuation of therapy due to poor patient prognosis or drug-related adverse effects, and due to the dosing regimen. Other oral chemotherapy drugs (imatinib, erlortinib, sorafenib) also have quantity limits.

COMMITTEE ACTION: The DoD Pharmacy and Therapeutics (P&T) Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend that sunitinib (Sutent) have quantity limits in the TRICARE Mail Order Pharmacy (TMOP) Program of 60 capsules for the 50 mg formulation, 120 capsules for the 25 mg formulation, and 180 capsules for the 12.5 mg formulation per 84 days. In the TRICARE Retail Pharmacy Network (TRRx), the recommended quantity limits were 30 capsules for the 50 mg formulation, 60 capsules for the 25 mg formulation, and 120 capsules for the 12.5 mg formulation per 30 days. (See paragraph 5 on pages 10-11 of the P&T Committee minutes).

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

6. QUANTITY LIMITS:

A. ORAL TRANSMUCOSAL FENTANYL CITRATE (ACTIQ) – Actiq is indicated only for breakthrough cancer pain in patients already receiving opioids and who are opioid tolerant, with a recommended daily maximum of four or fewer units (“lollipops”) per day. If consumption increases to more than four per day, the dose of the long-acting opioid for persistent cancer pain

should be reevaluated. The Committee agreed that a quantity limit of 120 units per 30 days, 360 units per 90 days should be established for Actiq, based on the daily maximum of four per day recommended in product labeling, in order to address potential concerns of overuse (i.e., use in lieu of appropriate increases in long-acting opioid treatment) and diversion.

***COMMITTEE ACTION*.** The Committee voted (13 for, 1 opposed, 1 abstained, 3 absent) to recommend that a quantity limit of 120 units per 30 days, 360 units per 90 days be established for oral transmucosal fentanyl citrate (Actiq). (See paragraph 6A on page 11 of P&T Committee minutes for rationale).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. Rizatriptan (Maxalt, Maxalt MLT) – The current quantity limit for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) is 12 tablets per 30 days, or 36 tablets per 90 days, which is consistent with the maximum recommended dose in product labeling. However, rizatriptan tablets are now available in packages of nine rather than six tablets. The Committee agreed that the 30-day quantity limit for rizatriptan tablets should be increased to 18 tablets, but that the 90-day quantity limit should remain at 36 tablets. This quantity limit would take into account the fact that a substantial number of patients currently fill prescriptions at the maximum quantity limit of 12 tablets per 30 days, allow for dispensing of whole packages, and avoid increasing the 90-day limit to 54 tablets (3 times 18), which is in excess of safety recommendations and not consistent with quantity limits for other triptans.

***COMMITTEE ACTION*.** The Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to recommend changing the quantity limit for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) to 18 tablets per 30 days, or 36 tablets per 90 days. (See paragraph 6B on pages 11-12 of P&T Committee minutes for rationale).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

7. ANTIEMETIC DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost-effectiveness of the antiemetic agents marketed in the United States. The drugs in the class were broken into two subclasses, newer and older antiemetics. The newer agents include the type 3 serotonin receptor (5-HT3) antagonists ondansetron (Zofran), granisetron (Kytril), and dolasetron (Anzemet); and the neurokinin-1 (NK-1) receptor antagonist aprepitant (Emend). The older antiemetic subclass is comprised of the cannabinoid dronabinol (Marinol); the phenothiazines prochlorperazine and thiethylperazine (Torecan); the antihistamines meclizine and promethazine; and the anticholinergics transdermal scopolamine (Transderm Scop) and trimethobenzamide. The newer and older antiemetics together account for approximately $37.4 million dollars annually, and are ranked 48th in Military Health System (MHS) drug class expenditures.

The Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) that: (1) the 5-HT3 antagonists ondansetron, granisetron and dolasetron have shown similar complete response rates in patients with chemotherapy-induced nausea and vomiting (CINV), radiation-induced nausea and vomiting (RINV), and post-operative nausea and vomiting (PONV); (2) the NK-1 receptor antagonist aprepitant serves a unique role in preventing CINV caused by highly emetogenic chemotherapy regimens and is required for adequate clinical coverage; (3) for nausea and vomiting in pregnancy, ondansetron should be reserved for use as third-line therapy in pregnant women requiring intravenous hydration who have not responded to other therapies; (4) there is insufficient evidence to suggest that there are major differences in the adverse effect profiles of the 5-HT3 antagonists or aprepitant; headache and gastrointestinal effects are the most commonly reported adverse events; (5) aprepitant is the newer antiemetic that has the most clinically important drug interaction profile, due to its metabolism via the CYP3A4 enzyme system; (6) there are differences among the newer antiemetics in terms of availability of oral formulations, approval for use in children, and number of FDA-approved indications; (7) none of the newer antiemetics are sufficiently less clinically effective than the others to be classified as non-formulary based on clinical issues alone; (8) none of the older antiemetics has a significant, clinically meaningful therapeutic disadvantage in terms of safety, effectiveness , or clinical outcome compared to the other agents to warrant classification as non-formulary, based on clinical issues alone.

Based on the results of the cost-effectiveness analysis (CEA) and other clinical and cost considerations, the Committee concluded (16 for, 0 opposed, 0 abstained, 2 absent) that granisetron and ondansetron were the more cost effective 5HT-3 antiemetic drugs; that it is also cost-effective for aprepitant to be used as an adjunct for the treatment of CINV; and that the older antiemetics are all relatively cost-effective.

A. COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the anti-emetic drugs, and other relevant factors, the P&T Committee voted (14 for, 1 opposed, 2 absent, 1 abstained) to recommend that dolasetron be classified as non-formulary under the UF, with granisetron, ondansetron, aprepitant, dronabinol, meclizine, prochlorperazine, promethazine, scopolamine, thiethylperazine, and trimethobenzamide remaining on the UF. (See paragraphs 7A and 7B on pages 12-18 P&T Committee minutes)

In addition, the P&T Committee agreed that the current quantity limits for the newer antiemetics should remain unchanged; it also agreed that a more systematic set of criteria addressing severe nausea and vomiting associated with pregnancy should be developed to assist military treatment facilities (MTFs).

Director, TMA, Decision: ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluation of dolasetron (Anzemet) and the conditions for establishing medical necessity for a non-formulary medication provided in the

UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) medical necessity criteria for the antiemetics. (See paragraphs 7C on page 18 of the P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P & T Committee voted (14 for, 1 opposed, 1 abstained, 2 absent) to recommend an effective date no later than the first Wednesday following an implementation period of 60 days. The implementation will begin immediately following the approval of director, TMA. (See paragraph 7D on pages 18-19 of the P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost-effectiveness analysis, the P & T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend oral and rectal promethazine as the Basic Core Formulary (BCF) agent. (See paragraphs 7E on page 19 of the P&T Committee minutes)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

8. CONTRACEPTIVE AGENTS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the oral, transdermal, injectable, and vaginal ring contraceptives available in the U.S. A total of 36 products were divided into 11 subgroups, based on estrogen content, phasic formulation, and route of administration. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 3 absent) that: 1) contraceptives vary in estrogen content, progestin content, regimen (e.g., extended use), phasic formulation, desirability for non-contraceptive uses, and routes of administration; 2) there is wide intra- and inter-patient variability in pharmacokinetics; 3) differences may affect safety, adverse effects/tolerability, convenience/compliance, or effectiveness for non-contraceptive uses; 4) there do not appear to be substantial differences in contraceptive effectiveness across products; 5) providers desire a wide variety of choices (based on both estrogen and progestogen content), patient response is variable, and there are clinical niches for which multiple choices are required; 6) the alternative formulations (vaginal ring, patch, intramuscular and subcutaneous injection) are required for adequate clinical coverage; 7) none of the reviewed contraceptives are sufficiently less clinically effective than others to be classified as non-formulary based on clinical issues alone.

Based on the results of the CEA and other clinical and cost considerations, the P&T Committee agreed (15 for, 0 opposed, 0 abstained, 3 absent) that: 1) all generically available oral contraceptives (OCs) should remain on the UF, because they are generally more cost-effective than brand name contraceptives and non-orally administered contraceptives and because further opportunity exists to negotiate lower prices for generic agents through contracting; 2) all of the non-oral products (Nuvaring, Ortho Evra, Depo Provera and equivalents, Depo-subq Provera 104) should remain on the UF to ensure clinical coverage for patients who need these methods of administration; 3) the brand-only products Yasmin, Yaz, and Ortho Tri-Cyclen Lo should remain on the UF, because they offer clinical and/or economic value; and 4) the brand-only products Seasonale, Ovcon-35, Ovcon-50, and Estrostep Fe should be classified as non-formulary under the UF, because clinically similar alternatives are available at a significantly lower cost. The P&T Committee also agreed (12 for, 1 opposed, 3 abstained, 2 absent) that Plan B should continue on the UF because of the clinical advantages of this progestogen-only product over other OCs for emergency contraception.

In addition, the P&T Committee voted (11 for, 2 opposed, 3 abstained, 2 absent) to recommend that Plan B be available from the TMOP, with a quantity limit of one Plan B package per co-pay applying to purchased care prescriptions.

A. COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend that Seasonale (EE 30 mcg; levonorgestrel 0.15 mg in special packaging for extended use); Ovcon 35 (EE 35 mcg; 0.4 mg norethindrone); Ovcon 50 (EE 50 mcg; norethindrone 1 mg), and Estrostep Fe (EE 20/30/35 mcg; norethindrone 1 mg) be classified as non-formulary under the UF and that the brand-only products Yasmin, Yaz, Ortho Tri-Cyclen Lo, Ortho Evra, Nuvaring, Depo-Provera, Depo-subq Provera 104, and all generically-available products listed in Table 1 (on pages 18-19 of the P&T Committee minutes) be classified as formulary on the UF. The P&T Committee voted (12 for, 1 opposed, 3 abstained, 2 absent) that Plan B should continue to be classified as formulary on the UF. (See paragraphs 8A and 8B on pages 19-30 of P&T Committee minutes)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluation of the contraceptive agents and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 3 absent) medical necessity criteria for the contraceptive agents. (See 8C on page 30 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 3 absent) an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 8D on pages 30-31 of P&T Committee minutes for rationale)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend the following products as the BCF agents.

- 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; levonorgestrel 0.15 mg (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)

(See paragraph 8E on pages 31-32 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ■ Approved □ Disapproved

Approved, but modified as follows:

9. ABBREVIATED CLASS REVIEWS: HISTAMINE-2 (H2) BLOCKERS; HMG-Co A REDUCTASE INHIBITORS (STATINS), COMBINATION PRODUCTS, AND ADD-ON THERAPIES OF EZETIMIBE AND NIACIN; AND NEWER SEDATIVE HYPNOTIC AGENTS

Portions of the clinical reviews for each class were presented to the Committee. The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review, and for developing the appropriate cost effectiveness models. Both the clinical and economic analyses of these three classes will be completed during the August 2006 meeting; no action necessary.

APPENDIX A – TABLE 1: Implementation status of UF Decisions

APPENDIX B – TABLE 2: Newly Approved Drugs

APPENDIX C – TABLE 3: Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____signed_____
William Winkenwerder, Jr., M.D.
Date: 26 July 2006

Department of Defense
Pharmacy and Therapeutics Committee Minutes

11 May 2006

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 9 May 2006 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
CDR Mark Richerson, MSC, USN	DoD P& T Committee Recorder
CAPT Bill Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Maj David Carnahan, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
LtCol Brian Crownover, MC	Air Force, Physician at Large
LtCol Charlene Reith *for* LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer
CDR Brian Alexander, MC	Navy, Physician at Large
LCDR Joe Lawrence MSC *for* CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Joel Schmidt, MC	Army, Physician at Large
LTC Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CDR Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
CDR Jill Pettit, MSC, USN	TMOP COR
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

LCDR Chris Hyun, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatrics Physician
CAPT David Price, MSC	Navy, Pharmacy Officer
LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer
COL Isiah Harper, MSC	Army, Pharmacy Officer

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Mr. Lynn T. Burleson	Assistant General Counsel, TMA
Mr. John Felicio *for* Ms Martha Taft	Health Plan Operations, TMA
Major Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

None	

E. Others Present

CAPT Don Nichols, MC, USN	DoD Pharmacoeconomic Center
Col Nacy Misel, BSC, USAF Reserve	IMA DoD Pharmacoeconomic Center
Lt Col David Bennett, BSC, USAF	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Mr. Dan Remund	DoD Pharmacoeconomic Center
Ms Shana Trice	DoD Pharmacoeconomic Center
Mr. David Bretzke	DoD Pharmacoeconomic Center
Ms Angela Allerman	DoD Pharmacoeconomic Center
Mr. Eugene Moore	DoD Pharmacoeconomic Center
Ms Julie Liss	DoD Pharmacoeconomic Center
Ms Elizabeth Hearin	DoD Pharmacoeconomic Center
Mr. Dave Flowers	DoD Pharmacoeconomic Center
Mr. David Meade	DoD Pharmacoeconomic Center
Ms Harsha Mistry	DoD Pharmacoeconomic Center
Ms Elaine Furmaga	Department of Veterans Affairs

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the minutes – February 2006 DoD P&T meeting minutes were approved as written, with no corrections noted.

B. February minutes approval – Dr. William Winkenwerder, Jr., M.D. approved the minutes of the February 2006 DoD P&T Committee on 26 April 2006.

4. ITEMS FOR INFORMATION

TMA and DoD PEC staff members briefed the P&T Committee on the following:

A. Interim Fluoroquinolone Basic Core Formulary (BCF) Administrative Action: CAPT Buss and CDR Richerson briefed the DoD P&T Committee on the justification and process employed for the 16 March 2006 fluoroquinolone administrative change to the BCF (replacement of gatifloxacin with levofloxacin).

B. Tikosyn Availability in the TRICARE Mail Order Pharmacy (TMOP) Program: Ms. Libby Hearin briefed the DoD P&T Committee that, as of 24 April 2006, Tikosyn is now available through the TMOP. This drug is an anti-arrhythmic which is subject to a controlled distribution program.

C. Beneficiary Advisory Panel (BAP) Briefing: CAPT Buss, CDR Richerson, and CPT Dacus briefed the members of the DoD P&T Committee regarding the 30 March 2006 BAP meeting. The Committee was briefed on BAP comments regarding DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

D. Implementation Status of UF Decisions: Mr. Dave Bretzke briefed the members of the Committee on the progress of implementation for drug classes reviewed for UF status since August of 2005. The Committee made the following observations:

- Utilization in all UF classes continues to remain stable, suggesting continued access to drugs within the reviewed classes.
- Collective utilization of UF agents across all reviewed drug classes and points of service (military treatment facility (MTF), TMOP, TRICARE Retail Pharmacy (TRRx) Network) continues to increase as a percentage of prescriptions dispensed, while utilization of non-formulary agents has decreased. Based on the UF decisions that have been fully implemented since the first UF DoD P&T meeting in February 2005, there has been a 27% reduction in the use of non-formulary agents. Based on all drug classes reviewed by the Committee to date, including those classes where implementation has only just begun, there has been an 18% reduction in the use of agents designated as non-formulary.
- Success in terms of generating increased market share for UF agents (while decreasing market share for non-formulary agents) varies by class and by point of service.
- Market shares by point of service continue to reflect the degree of utilization management applied to each point of service. The more highly managed points of service (i.e., MTFs) are generating higher market shares of UF agents than the unmanaged points of service (i.e., TMOP and TRRx).
- For drug classes fully implemented, MTFs have reduced the use of non-formulary drugs by 81% as projected, but the decrease in the use of non-formulary medications at mail (-2%) and retail (-13%) is significantly less.
- It appears that more beneficiaries are electing to receive non-formulary medications through TMOP. It is unclear at this time whether these beneficiaries are former MTF patients or former TRRx patients.

5. REVIEW OF RECENTLY-APPROVED AGENTS

The P&T Committee was briefed on six new drugs that had been approved by the Food and Drug Administration (FDA). None of the medications fall into drug classes already reviewed by the P&T Committee; therefore, UF consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits. Sunitinib (Sutent) is an oral multi-kinase inhibitor approved for treatment of patients with advanced renal cell carcinoma and for the treatment of gastrointestinal stromal tumor (GIST). It is available in 12.5, 25 and 50 mg capsules and is administered once daily for a period of four weeks followed by two weeks off treatment. Dosage reductions are recommended in 12.5 mg intervals, if needed. There is no 37.5 mg capsule available. Quantity limits were recommended for sunitinib since there is a risk of discontinuation of therapy due to poor patient prognosis or

drug-related adverse effects, and likelihood of changes to individual dosing regimens. Other oral chemotherapy drugs (imatinib, erlortinib, sorafenib) also have quantity limits.

One of the new drugs, mecasermin rinfabate (Iplex), is a new version of a medication for which a prior authorization (PA) is already in place. Mecasermin rinfabate was added to the existing PA criteria and forms for mecasermin.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 against, 1 abstained, 2 absent) to recommend that sunitinib (Sutent) have quantity limits in the TMOP for 60 capsules for the 50 mg formulation, 120 capsules for the 25 mg formulation, and 180 capsules for the 12.5 mg formulation per 84 days. In the TRRx, the recommended quantity limits were 30 capsules for the 50 mg formulation, 60 capsules for the 25 mg formulation, and 120 capsules for the 12.5 mg formulation per 30 days.

6. QUANTITY LIMITS:

A. ORAL TRANSMUCOSAL FENTANYL CITRATE (ACTIQ) – Actiq is indicated only for breakthrough cancer pain in patients already receiving opioids and who are opioid tolerant. Based on safety recommendations in product labeling, the daily limit for Actiq is four or fewer units ("lollipops") per day. If consumption increases to more than four per day, the dose of the long-acting opioid for persistent cancer pain should be reevaluated. The product is available in multiple strengths—200, 400, 600, 800, 1200, and 1600 mcg—to accommodate individual patient needs and increases in opioid requirements associated with long-term opioid treatment.

The major potential concerns with Actiq are overuse (i.e., use in lieu of appropriate increases in long-acting opioid treatment) and diversion. Actiq is costly; average wholesale price per unit ranges from $17.40 to $51.40 per lollipop, with a federal supply schedule price of $4.89 to $14.56.

The Committee voted (13 for, 1 opposed, 1 abstained, 3 absent) to recommend that a quantity limit of 120 units per 30 days, 360 units per 90 days be established for Actiq, based on the daily maximum of four per day recommended in product labeling. The Committee noted that Express Scripts, Inc. (ESI), the contractor for the TMOP and TRRx programs, has established procedures to deal with circumstances that may require temporary overrides of quantity limits (e.g., increases in dose).

COMMITTEE ACTION: The Committee voted (13 for, 1 opposed, 1 abstained, 3 absent) to recommend that a quantity limit of 120 units per 30 days, 360 units per 90 days be established for Actiq, based on the daily maximum of four per day recommended in product labeling.

B. RIZATRIPTAN (MAXALT, MAXALT MLT) – The current quantity limit for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) is 12 tablets per 30 days, or 36 tablets per 90 days. Based on safety recommendations in product labeling, the safety of treating more than four migraine attacks in a 30-day period has not been established. Doses may be repeated after two hours if the first dose is ineffective, with no more than 30 mg taken in any 24-hour period. Based on this, a quantity limit of 12 tablets per 30 days would allow use up to the recommended maximum, assuming that 10-mg tablets are prescribed. However, rizatriptan packaging has been changed to packages of nine rather than six tablets.

The Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to recommend that the quantity unit for rizatriptan tablets and orally disintegrating tablets be increased to 18 tablets per 30 days, 36 tablets per 90 days, based on the following reasoning:

- A substantial number of patients currently fill prescriptions at the maximum quantity limit of 12 tablets per 30 days.
- The proposed quantity limit allows for dispensing of whole packages of rizatriptan tablets.
- Although the proposed quantity limit does violate the usual rule-of-thumb that 90-day limits will be three times 30-day limits, it is technically feasible to implement and avoids increasing the 90-day to 54 tablets, which is in excess of safety recommendations and not consistent with quantity limits for other triptans.

COMMITTEE ACTION: The Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to recommend changing the quantity limit for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) to 18 tablets per 30 days, or 36 tablets per 90 days.

7. ANTIEMETIC DRUG CLASS REVIEW

A. Antiemetic Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the antiemetic agents marketed in the United States. The drugs in the class were broken into two subclasses, the newer and older antiemetics. The newer agents include the type 3 serotonin receptor (5-HT3) antagonists ondansetron (Zofran), granisetron (Kytril), and dolasetron (Anzemet); and the neurokinin-1 (NK-1) receptor antagonist aprepitant (Emend). The older antiemetic subclass is comprised of the cannabinoid dronabinol (Marinol); the phenothiazines prochlorperazine and thiethylperazine (Torecan); the antihistamines meclizine and promethazine; and the anticholinergics transdermal scopolamine (Transderm Scop) and trimethobenzamide. The clinical review included, but was not limited to, the requirements stated in the UF Rule. The newer and older antiemetics together account for approximately $37.4 million dollars annually, and are ranked 48th in Military Health System (MHS) drug class expenditures.

1) Newer Antiemetics

A. Efficacy

Efficacy Measure – The Committee evaluated efficacy of the newer antiemetics in chemotherapy induced nausea and vomiting (CINV), radiation induced nausea and vomiting (RINV), post-operative nausea and vomiting (PONV) and nausea and vomiting in pregnancy. Complete response was the primary efficacy measure considered. Complete response is a composite outcome of two or more of the following components: no emesis; no nausea; or no need for rescue medication.

When reviewing efficacy trials in nausea and vomiting, direct comparisons of trials is difficult due to large heterogeneity in the trials. Trials conducted in the setting of CINV and RINV are differentiated by the type of chemotherapy administered, emetogenicity potential of the chemotherapy regimen, number of chemotherapy or radiotherapy courses given, and type of malignancy; and show widely varying outcomes. For trials conducted in the setting of PONV, differences in the type of surgical procedure, duration of surgery, and type of anesthesia make direct comparisons difficult.

Chemotherapy-induced nausea and vomiting (CINV)

5-HT3 antagonists – For CINV, there are several head-to-head trials comparing the three 5-HT3 antagonists which overall have shown no differences in efficacy between the intravenous (IV) and oral routes and no consistent differences in efficacy between ondansetron, granisetron and dolasetron. However there is large heterogeneity between the trials.

5-HT3 antagonists – Head-to-head trials and national guidelines: In two head-to-head trials comparing oral 5-HT3 formulations, the complete response rates, as measured by no nausea or emesis or need for rescue therapy, were similar between granisetron and ondansetron (47% vs. 48%), and dolasetron and ondansetron (76% vs. 72%). There were no trials comparing oral dolasetron with oral granisetron, but a trial comparing IV formulations of these two drugs reported no differences in efficacy. Clinical practice guidelines from four national professional groups consider the 5-HT3 antagonists therapeutically interchangeable for CINV.

Aprepitant – The NK-1 receptor antagonist aprepitant is approved for preventing nausea and vomiting associated with highly emetogenic chemotherapy regimens, including high dose cisplatin. Aprepitant has been evaluated in four active-controlled trials in patients undergoing highly emetogenic chemotherapy regimens. When aprepitant was used as adjunctive therapy to 5-HT3 antagonists plus dexamethasone and older antiemetics, a significantly higher percentage of patients achieved complete response rates, vs. placebo.

Radiation-induced nausea and vomiting (RINV)

Systematic Reviews – Systematic reviews state that the evidence shows no consistent differences in efficacy for ondansetron, granisetron and dolasetron for RINV.

Head-to-head trials and national guidelines – There are no head-to-head trials comparing the 5-HT3 antagonists for RINV. One indirect comparison of ondansetron 8 mg and granisetron 2 mg with a historical control group in the prevention of RINV found no differences between the two 5-HT3 antagonists in achieving complete control of emesis (27% with ondansetron vs. 28% with granisetron vs. 0% in the historical control group). There are no published studies evaluating aprepitant for RINV. Clinical practice guidelines from four national professional organizations state that the three 5-HT3 antagonists are therapeutically interchangeable as first-line prophylaxis for RINV.

Post-operative nausea and vomiting (PONV)

Prevention of PON – The majority of studies evaluating prevention of PONV used intravenous (IV) therapies, and rarely continued oral medication after hospital discharge. There are seven head-to-head trials comparing the efficacy of IV formulations of the 5-HT3 antagonists for prevention of PONV; five trials comparing dolasetron with ondansetron, and two trials comparing granisetron with ondansetron. Although the heterogeneity between the trials was large, overall the complete response rates were similar between ondansetron, granisetron and dolasetron. There are no head-to-head trials of oral formulations of the 5-HT3 antagonists for prevention of PONV. A systematic review of four placebo-controlled trials comparing either oral or IV 5-HT3 formulations allowed indirect comparisons between oral dolasetron, IV dolasetron, and IV granisetron. The complete response rates were similar between drugs.

Treatment of PONV – Treatment of PONV most commonly occurs with IV therapy, and is of minor importance to this review. There are no head-to-head trials comparing efficacy of the 5-HT3 antagonists for treatment of PONV. Three systematic reviews of active and placebo controlled trials of the 5-HT3 antagonists in the treatment of PONV provided numbers needed

to treat (NNT) to obtain complete control of further nausea and vomiting (complete response). In one review, no statistically significant differences were found between dolasetron and ondansetron in treating PONV occurring within 6 hours of surgery (NNT of 2.0-3.5 with ondansetron vs. 4.2-6.1 with dolasetron). In the same review there were no significant differences between granisetron and ondansetron in treating PONV occurring < 24 hours after surgery (NNT of 3.3-6.3 with ondansetron vs. 2.4-3.3 with granisetron). The NNTs from all three reviews were similar for ondansetron, granisetron, and dolasetron. There are no published studies evaluating aprepitant for PONV.

Nausea and vomiting in pregnancy

Systematic reviews and MHS utilization – No newer antiemetics are FDA-approved for treating nausea and vomiting in pregnancy. An evidenced-based review concluded that there is insufficient data to recommend use of ondansetron as a first-line agent for this indication. A database linking prescription data with diagnosis codes shows that 21% ondansetron usage in the MHS is for nausea and vomiting in pregnancy.

Clinical trials and case reports – One trial compared IV ondansetron 10 mg with IV promethazine 50 mg in 30 women hospitalized with hyperemesis gravidarum. No differences were found in any outcome measure. One published case report showed that ondansetron 8 mg IV given twice daily was effective at reducing emesis, and that ondansetron 4 mg orally given three times daily for 25 weeks was also effective.

National guidelines – Guidelines from the American College of Obstetricians and Gynecologists (ACOG) state that ondansetron may be used IV as third line therapy if dehydration is present, and IV fluid replacement and dimenhydrinate, metoclopramide, or promethazine have failed to control symptoms. The 5-HT3 antagonists and aprepitant are rated as pregnancy category B by the FDA.

B) Safety / Tolerability

Major adverse events – Ondansetron, granisetron and dolasetron all carry a class warning regarding potential prolongation of the QTc interval. The risk is dose dependent. All three 5-HT3 antagonists can rarely cause anaphylaxis; ondansetron and granisetron can rarely cause bronchospasm. Aprepitant has rarely been associated with Stevens-Johnson Syndrome and angioedema.

Minor Adverse events – For the newer antiemetics, the most commonly reported adverse effect is headache, occurring in 8-18% of patients. Asthenia/fatigue, constipation, and increases in liver enzymes also occur with an incidence of greater than 5%. Aprepitant is associated with diarrhea, dizziness, hiccups and increases in liver enzymes, all occurring in <6% of patients. No dosage adjustments are necessary for the four newer antiemetics in patients with renal dysfunction. The maximal dose of ondansetron should be limited to 8 mg in patients with severe hepatic dysfunction.

Drug Interactions – All three 5-HT3 antagonists are metabolized by varying degrees through the Cytochrome P450 (CYP450) enzyme system. The 5-HT3 antagonists are metabolized by multiple pathways within the system. Ondansetron is metabolized to the greatest extent, followed by dolasetron and granisetron; however, there are no requirements for ondansetron dosage adjustments when given with CYP450 inducers. Aprepitant can inhibit Cytochrome P450 3A4 (CYP3A4) enzymes, and is associated with the most clinically important drug interactions of the newer antiemetics. Aprepitant increases concentrations of dexamethasone up

to two and half times, and if administered concomitantly with dexamethasone, the dexamethasone dose should be reduced by 50%.

C) Other Factors

Available formulations – Ondansetron is available in several oral formulations, including an oral tablet, oral solution, and orally dissolving tablet (ODT). Ondansetron ODT may be swallowed without the need to consume additional liquid that could trigger vomiting; however, it should be used with caution in patients with phenylketonuria, as it contains aspartame. Granisetron is available in an oral tablet and oral solution.

Pediatrics – Ondansetron and dolasetron are approved for prevention of CINV in pediatrics. Ondansetron is approved for use in children as young as four years of age, while dolasetron is approved for use in children as young as two years. The oral formulation of granisetron is not approved for use in children; however the IV formulation is approved for use in children older than two years. Aprepitant is not approved for use in the pediatric population.

*FDA indicatio*ns – Of the newer antiemetics, ondansetron has the most FDA-approvals (CINV, RINV, and PONV). Granisetron is approved for CINV and RINV, and dolasetron is approved for CINV and PONV. Aprepitant is approved for prevention of CINV caused by moderately or highly emetogenic chemotherapy regimens.

Quantity Limits – There are existing quantity limits in place for the four newer antiemetics, which take into account FDA-approved indications and dosing recommendations for CINV, RINV, and PONV. Quantity limits may be overridden for individual patients if greater quantities are determined to be medically necessary. A frequent reason for medical necessity is severe nausea and vomiting associated with pregnancy (i.e., hyperemesis gravidarum).

MHS Utilization – The most widely prescribed newer antiemetic in the MHS is ondansetron, with 3,500 prescriptions per month. Over 51% of the MHS usage of the newer antiemetics is for CINV; nausea and vomiting in pregnancy accounts for 15% of the usage of the newer antiemetics, RINV comprises 10% of usage, PONV 2% of usage, and other diagnoses 22% of usage.

Provider Survey – Overall, providers preferred ondansetron, primarily due to more familiarity over the other 5-HT3 antagonists. Several providers commented that they preferred the newer antiemetics over the older antiemetics due to less sedation, which is particularly beneficial for active duty members or those with childcare responsibilities.

Conclusion for the newer antiemetics – The committee concluded that there is insufficient evidence to suggest that the antiemetic effects of the 5-HT3 antagonists differ significantly between drugs. Ondansetron, granisetron and dolasetron show efficacy for CINV, RINV, and PONV. Ondansetron shows efficacy for treating nausea and vomiting in pregnancy, but should be used third line. Aprepitant has shown efficacy in placebo controlled trials for CINV when used as an adjunct to 5-HT3 antagonists for patients undergoing highly emetogenic chemotherapy regimens. The adverse effect profiles of 5-HT3 antagonists and aprepitant are similar in nature. Ondansetron has the largest number of oral formulations, and is approved for use in pediatrics, along with dolasetron.

2) Older Antiemetics

A) Place in therapy and national guidelines – The older antiemetics are still widely used to treat nausea, vomiting and motion sickness. Many of the older antiemetics are mentioned in national guidelines for the treatment of CINV and PONV, and are commonly used in these

settings. Prochlorperazine is used for indications other than nausea and vomiting, including for anxiety and schizophrenia. Promethazine is a second-line therapy for treatment of nausea and vomiting in pregnancy, according to ACOG guidelines. Dronabinol is commonly employed in the treatment of glaucoma, AIDS, chemotherapy-related anorexia and spasticity associated with multiple sclerosis.

B) Adverse effects – All the older antiemetics are associated with drowsiness, dizziness and somnolence. The phenothiazines (prochlorperazine, thiethylperazine) and antihistamines (meclizine, promethazine) can cause rare but serious adverse events including neuroleptic malignant syndrome, reversible dystonic reactions, seizures, irreversible tardive dyskinesias, agranulocytosis and severe leukopenia. Common adverse effects of the anticholinergic agents (trimethobenzamide, scopolamine) include dry mouth and eyes, and urinary retention in elderly patients. Confusion, distorted perception, and rare hallucinations and severe paranoia have been linked to dronabinol.

C) Other factors – Four of the older antiemetics are available in generic formulations; meclizine, promethazine, prochlorperazine, and trimethobenzamide. The older antiemetics are available in various dosage forms that are advantageous for use as rescue therapy in nausea and vomiting when the oral route can not be used. Prochlorperazine, promethazine and trimethobenzamide are available in suppository form. Transdermal scopolamine patches offer a topical route, but should not be used for acute nausea and vomiting, due to delayed absorption. With the exception of meclizine, which has a pregnancy category B rating, all of the older agents are ranked pregnancy category C by the FDA. The older antiemetics are indicated for use in children, with the exception of thiethylperazine. The package insert for promethazine has a black box warning regarding use in children under the age of two due to respiratory depression. Dronabinol is a Drug Enforcement Administration (DEA) controlled schedule III substance. The most widely prescribed older antiemetic in the MHS is promethazine, with 40,000 prescriptions per month.

*Conclusions for the older antiemetic*s – The older antiemetics are frequently used for nausea and vomiting, and several are used for indications other than emesis. The availability of non-oral dosage formulations is useful for rescue therapy of nausea and vomiting. Thiethylperazine is the only older antiemetic not approved for pediatric use, although promethazine should be used with caution in children due to possible respiratory depression. All the older agents can cause sedation and dizziness.

Overall clinical effectiveness conclusion – The Committee concluded: (1) the 5-HT3 antagonists ondansetron, granisetron and dolasetron have shown similar complete response rates in patients with CINV, RINV, and PONV; (2) the NK-1 receptor antagonist aprepitant serves a unique role in preventing CINV caused by highly emetogenic chemotherapy regimens and is required for clinical coverage; (3) for nausea and vomiting in pregnancy, ondansetron should be reserved for use as third-line therapy in pregnant women requiring IV hydration who have not responded to other therapies; (4) there is insufficient evidence to suggest that there are major differences in the adverse effect profiles of the 5-HT3 antagonists or aprepitant; headache and gastrointestinal effects are the most commonly reported adverse events; (5) aprepitant is the newer antiemetic that has the most clinically important drug interaction profile, due to its metabolism via the CYP3A4 enzyme system; (6) there are differences among the newer antiemetics in terms of availability of oral formulations, approval for use in children, and number of FDA-approved indications; (7) none of the newer antiemetics is sufficiently less clinically effective than the others to be classified as non-formulary, based on clinical issues

alone; and (8) none of the older antiemetics has a significant, clinically meaningful therapeutic disadvantage in terms of safety, effectiveness, or clinical outcome compared to the other agents to warrant classification as non-formulary, based on clinical issues alone.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. Antiemetic Relative Cost Effectiveness: In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). Three separate pharmacoeconomic analyses were performed: a cost-minimization analysis (CMA) on the newer 5-HT3 antiemetics subclass, followed by a budget impact analysis (BIA); a cost-effectiveness analysis (CEA) of aprepitant to evaluate its place in therapy; and lastly a cost-analysis on the older antiemetic subclass.

Given the evidenced-based relative clinical effectiveness evaluation conclusion that there was insufficient evidence to suggest that the 5-HT3 antagonists differed in regards to efficacy, safety, tolerability, and clinical outcomes in the treatment of CINV, RINV, and PONV, a CMAwas performed to determine the relative cost-effectiveness of the agents within the 5-HT3 subclass. The cost examined was the total weighted average cost per treatment episode across all points of service. Results of the analysis for the newer antiemetic drugs (5HT-3s) showed granisetron was the most cost effective 5HT-3 antiemetic agent with the lowest average cost per treatment episode across the MHS.

The results of the above analysis were then incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of 5-HT3 antagonists best meet the majority of the clinical needs of the DoD population at the lowest cost to the MHS. Based on the results of the BIA and other clinical and cost considerations (ondansetron is projected to undergo generic competition in 2006), the Committee agreed that a group of 5-HT3 antagonists that included granisetron and ondansetron best achieved this goal when compared to other combination groups of 5-HT3 antagonists, and thus were determined to be more cost-effective relative to other combination groups.

A CEA was also conducted to evaluate the place in therapy for aprepitant, a NK-1 antagonist. Aprepitant is indicated for adjunctive therapy along with other antiemetics for delayed nausea and vomiting associated with chemotherapy. The results of the CEA showed that: 1) the blanket purchase agreement (BPA) offered price for aprepitant improved its cost-effectiveness over baseline, and 2) when total health care costs are considered, aprepitant is cost-effective as an adjunct in the treatment of chemotherapy induced nausea and vomiting.

Finally, a cost analysis for the older antiemetics (promethazine, prochlorperazine, trimethobenzamide, thiethylperazine, meclizine, scopolamine, and dronabinol) was presented. The results of the cost-analysis showed that the cost associated with these agents is about 25% of the overall anti-emetic drug spend. However, 72% of the costs for these older anti-emetic

drugs were generated in the retail setting. Over half of this figure was for promethazine, which is available in generic form. The conclusion of the cost analysis was that no savings would be achieved by placing any of the older antiemetics in the non-formulary tier of the UF.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 2 absent) to accept the antiemetic pharmacoeconomic analyses presented by the PEC. The Committee concluded that granisetron and ondansetron are the more cost effective 5HT-3 antiemetic drugs; that dolasetron is not cost-effective relative to the other 5-HT3 antagonists, that it is cost-effective for aprepitant to be used as an adjunct for the treatment of CINV; and that the older antiemetics are all relatively cost-effective.

The P&T Committee also recommended that the current quantity limits for the newer antiemetics should remain unchanged. They agreed, however, that a more systematic set of criteria addressing severe nausea and vomiting associated with pregnancy should be developed. Such criteria would be particularly beneficial for MTFs.

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the anti-emetic drugs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 1 opposed, 1 abstained, 2 absent) to recommend that dolasetron be classified as non-formulary under the UF, with granisetron, ondansetron, aprepitant, dronabinol, meclizine, prochlorperazine, promethazine, scopolamine, thiethylperazine, and trimethobenzamide remaining on the UF.

C. Antiemetic Medical Necessity Criteria: Based on the clinical evaluation of the antiemetics, 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 medical necessity criteria for dolasetron.

1) Use of formulary antiemetics is contraindicated, and dolasetron is not contraindicated.
2) The patient has experienced significant adverse effects from the formulary antiemetics, or is likely to experience significant adverse effects from formulary antiemetics, and the patient is expected to tolerate dolasetron.
3) Treatment with formulary antiemetics has resulted in therapeutic failure, and the patient is expected to respond to dolasetron.

Because of the clinical differences between antiemetics, the Committee agreed that the most appropriate formulary alternatives for dolasetron are the other 5-HT3 antagonists.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to approve the anti-emetic medical necessity criteria.

D. Antiemetic UF Implementation Period: The P&T Committee recommended an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have dolasetron on their local formularies. MTFs will be able to fill non-formulary requests for dolasetron only if both of the following conditions are met: 1) the prescription is written by an MTF provider, and 2) medical necessity is established. MTFs

may (but are not required to) fill a prescription for dolasetron written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee voted (14 for, 1 opposed, 1 abstained, 2 absent) for an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

E. Antiemetics BCF Review and Recommendations: The P&T Committee had previously determined that zero to one newer antiemetics and at least one older antiemetic should be added to the BCF, based on clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that promethazine be maintained on the BCF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to maintain oral and rectal promethazine on the BCF.

8. CONTRACEPTIVE AGENTS DRUG CLASS REVIEW

A. Contraceptive Relative Clinical Effectiveness Review: The P&T Committee evaluated the relative clinical effectiveness of the oral, transdermal, injectable, and vaginal ring contraceptives available in the U.S. Contraceptive products were divided into the subgroups outlined in Table 1, based on estrogen content, phasic formulation, and route of administration.

Table 1: Oral, Transdermal Patch, Vaginal Ring, and Injectable Contraceptive Products Available in the U.S.
(Source of Prescription Data: Pharmacy Data Transaction Service)

Subgroup	**Generic Product Description** (Ethinyl estradiol = EE; progestogen)	**Brand Name**	**Manufacturer**	**Total MHS Rxs** Jan-Dec 05
Monophasic OCs with 20 mcg EE	EE 20 mcg; 0.1 mg levonorgestrel	Alesse	Wyeth	86,569
		Aviane	Duramed	
		Lutera	Watson	
		Lessina	Barr	
		Levlite	Berlex	
	EE 20 mcg; 1.0 mg norethindrone	Junel 1/20	Barr	2,038
		Loestrin-21 1/20	Warner Chilcott	
		Microgestin 1/20	Watson	
	EE 20 mcg; 1.0 mg norethindrone; ferrous fumarate	Junel Fe 1/20	Barr	18,356
		Loestrin Fe 1/20	Warner Chilcott	
		Microgestin Fe 1/20	Watson	
	EE 20 mcg; 3 mg drospirenone	Yaz	Berlex	Approved March 2006
Monophasic OCs with 30 mcg EE	EE 30 mcg; 0.15 mg levonorgestrel	Levlen 28	Berlex	25,092
		Levora 0.15/30-28	Watson	
		Nordette-28	Duramed/Barr	
		Portia-28	Barr	
	EE 30 mcg; 0.15 mg levonorgestrel	Seasonale	Duramed/Barr	20,153
	EE 30 mcg; 0.3 mg norgestrel	Cryselle	Barr	123,501
		Lo/Ovral	Wyeth	
		Low-Ogestrel	Watson	
	EE 30 mcg; 0.15 mg desogestrel	Apri	Barr	59,086
		Desogen	Organon	
		Ortho-Cept	Ortho	
		Reclipsen	Watson	

Subgroup	Generic Product Description (Ethinyl estradiol = EE; progestogen)	Brand Name	Manufacturer	Total MHS Rxs Jan-Dec 05
		Solia	Prasco	
	EE 30 mcg; 1.5 mg norethindrone acetate	Junel 1.5/30	Barr	1,048
		Loestrin 1.5/30	Duramed/Barr	
		Microgestin 1.5/30	Watson	
	EE 30 mcg; 1.5 mg norethindrone; ferrous fumarate	Junel Fe 1/5/30	Barr	19,472
		Loestrin-FE 1.5/30	Duramed/Barr	
		Microgestin Fe 1.5/30	Watson	
	EE 30 mcg; 3 mg drospirenone	Yasmin	Berlex	125,965
Monophasic OCs with 35 mcg EE	EE 35 mcg; 0.5 mg norethindrone	Brevicon	Watson	144
		Modicon	Ortho	628
		Necon	Watson	
		Nortrel 0.5/35	Barr	
	EE 35 mcg; 0.4 mg norethindrone	Ovcon-35	Warner-Chilcott	6,681
		Ovcon-35 chewable		
	EE 35 mcg; 0.25 mg norgestimate	Mononessa	Watson	46,123
		Ortho-Cyclen	Ortho	
		Previfem	Teva	
		Sprintec	Barr	
	EE 35 mcg; 1.0 mg norethindrone	Necon	Watson	92,114
		Norinyl 1+35	Watson	
		Nortrel	Barr	
		Ortho-Novum 1/35	Ortho	
	EE 35 mcg; 1.0 mg ethynodiol diacetate	Demulen 1/35	Pharmacia/Upjohn	17,171
		Kelnor	Barr	
		Zovia 1/35E	Watson	
Monophasic OCs with 50 mcg EE or mestranol	Mestranol 50 mcg; 1 mg norethindrone	Necon	Watson	3,979
		Norinyl 1+50	Watson	
		Ortho-Novum 1/50	Ortho	
	EE 50 mcg; 1 mg norethindrone	Ovcon-50	Warner Chilcott	2,061
	EE 50 mcg; 1 mg ethynodiol diacetate	Demulen 1/50	Pharmacia/Upjohn	1,368
		Zovia 1/50E	Watson	
	EE 50 mcg; 0.5 mg norgestrel	Ogestrel	Watson	2,938
		Ovral-28	Wyeth	
Biphasic OCPs	EE 35 mcg; 0.5/1.0 mg norethindrone	Necon	Watson	168
		Ortho-Novum 10/11	Ortho	
	EE 20/10 mcg; 0.15 mg desogestrel	Kariva	Barr	22,731
		Mircette	Duramed/Barr	
Triphasic OCPs	EE 25 mcg; 0.18/0.215/0.25 mg norgestimate	Ortho Tri-Cyclen Lo	Ortho	101,349
	EE 35 mcg; 0.18/0.215/0.25 mg norgestimate	Ortho Tri-Cyclen	Ortho	331,429
		Trinessa	Watson	
		Tri-Previfem	Teva	
		Tri-Sprintec	Barr	
	EE 30/40/30 mcg; 0.05/0.075/0.125 mg levonorgestrel	Enpresse	Barr	76,559
		Tri-levlen	Berlex	
		Triphasil	Wyeth	
		Trivora	Watson	
	EE 35 mcg; 0.5/1/0.5 mg norethindrone	Aranelle	Barr	1,516
		Leena	Watson	
		Tri-Norinyl	Watson	

Subgroup	Generic Product Description (Ethinyl estradiol = EE; progestogen)	Brand Name	Manufacturer	Total MHS Rxs Jan-Dec 05
	EE 35 mcg; 0.5/0.75/1 mg norethindrone	Necon 7/7/7	Watson	59,536
		Nortrel 7/7/7	Barr	
		Ortho-Novum 7/7/7	Ortho	
	EE 25 mcg; 0.1/0.125/0.15 mg desogestrel	Cesia	Prasco	5,648
		Cyclessa	Organon	
		Velivet	Barr	
	EE 20/30/35 mcg; 1.0 mg norethindrone	Estrostep Fe	Warner-Chilcott	9,916
Progestogen-Only OCPs	0.35 mg norethindrone	Errin	Barr	71,003
		Ortho Micronor	Ortho	
		Jolivette	Watson	
		Camila	Barr	
		Nora-BE	Watson	
		Nor-QD	Watson	
Contraceptive patch	EE/Norelgestromin ~ 60% higher exposure than oral contraceptive with 35 mcg EE (= >50 mcg EE), but lower peak concentrations	Ortho Evra	Ortho	268,223
Contraceptive vaginal ring	Daily dose: ~ EE 15 mcg; ~0.12 mg etonogestrel	Nuvaring	Organon	55,415
Injectable Contraceptives	104 mg/ 0.65mL depot medroxyprogesterone acetate	Depo-subqProvera104	Pfizer	39
	150 mg/mL depot medroxyprogesterone acetate	Depo-provera (disp syr)	Pharmacia/Upjohn	10,912
		Medroxyprogesterone acetate (disp syr)	Sicor	
		Depo-provera (vial)	Pharmacia/Upjohn	59,931
		Medroxyprogesterone acetate (vial)	Greenstone	
			Sicor	
Emergency Contraceptives	0.75 mg levonorgestrel	Plan B	Duramed/Barr	4,049

Oral contraceptives (OCs) differ from most other drug classes in two regards: 1) unique combinations of varying strengths of specific estrogen and progestogen components are considered to be separate products (e.g., Ortho-Novum 1/35 and Ortho-Novum 1/50) rather than different strengths of the same product; and 2) generic versions of branded contraceptive products typically have brand names of their own. Other factors (such as FDA-approved special packaging/labeling or the content of "placebo" tablets) may also affect generic equivalency. For the purpose of making formulary recommendations, the P&T Committee made its selections at the "generic product" level as outlined in Table 1, consistent with its actions in other drug classes. For example, ethinyl estradiol 35 mcg; 1.0 mg norethindrone constituted a single line item to be considered for placement on the UF. Specific originator products (e.g., Ortho-Novum 1/35) and generic equivalents (Necon, Norinyl, and Nortrel) were not considered individually.

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 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.

During a twelve-month period ending 31 Jan 2006, 552,272 MHS beneficiaries received one or more contraceptive prescriptions, accounting for about $80 million in annual expenditures across the MHS.

1) DoD Provider Input

A total of 79 survey responses were received from providers in time to be tabulated for P&T Committee review. Responders were family practice physicians (26), women's health nurse practitioners (21), obstetricians /gynecologists (18), family nurse practitioners (6), certified nurse-midwives (4), or other providers (4). A number of responses, including some from internal medicine physicians, were received too late for tabulation, but were not qualitatively different from other providers' responses.

2) Potential Differences between Contraceptive Products

There are a wide variety of contraceptive products. Points of difference include estrogen content; progestogen content; regimen (e.g., extended use, 24-day cycle products); phasic formulation; proven or potential usefulness for other conditions in addition to contraception (e.g., acne); and route of administration. Most OCs contain both an estrogen and a progestogen component. Progestogen-only OCs are used much less commonly than combined OCs, but fill a distinct clinical niche for women who should not receive estrogen.

Estrogen content – The estrogen component in almost all combined contraceptives is ethinyl estradiol; mestranol (a prodrug of ethinyl estradiol) is used in a few older products. The amount of ethinyl estradiol included in specific products varies from as little as 15-20 mcg per day to as much as 50 mcg per day in older products. Low-estrogen products (20-30 mcg of ethinyl estradiol) are most commonly used. The availability of a wide array of contraceptive products with differing ethinyl estradiol levels is necessary because of the need to maintain contraceptive effectiveness and control irregular bleeding (cycle control) while minimizing common adverse effects and thromboembolic risk. Considerable intra- and inter-patient variability in estrogen metabolism contributes to the need for multiple products. Another contributing factor may be the fact that adverse effects and cycle control problems with all contraceptive products tend to occur more frequently in the first few cycles after initiation of treatment; switching products prematurely may lead women to falsely believe that they cannot tolerate specific products.

Progestogen content – Contraceptive products available in the U.S. include a variety of progestogens. Based on chemical structure, a recent Cochrane review (Maitra et al, 2005) classified progestogens (not including non-U.S. products) as follows:

- First generation: norethindrone, ethynodiol diacetate
- Second generation: levonorgestrel, norgestrel
- Third generation: desogestrel, norgestimate (some authors classify norgestimate as second generation, since it is partially metabolized to levonorgestrel)
- Unclassified: drospirenone

The injectable contraceptives (Depo-Provera and generics, Depo-subq Provera 104) contain depot medroxyprogesterone acetate (DMPA), a derivative of progesterone.

Regimen – While most combined contraceptives—including the transdermal patch and vaginal ring—are based on a 21-day "on", 7-day "off" cycle, this regimen is often modified in clinical practice by either extending the active treatment period and/or shortening the medication-free period. Extended treatment cycles or continuous (daily) use of combined OCs have been used

clinically for many years to treat menstrual migraines, dysmenorrhea, endometriosis, and other conditions associated with menses. Over time, extended or continuous use of OCs for practical or convenience reasons (reducing or eliminating menstrual periods) has come into more common use. A Cochrane review [Edelman et al, 2005] concluded that extended or continuous use of contraceptives was reasonable for women without contraindications, based on the results of six trials. A single contraceptive product, Seasonale, is labeled and specially packaged for extended cycle use (84 days on, 7 days off), although any monophasic OC could be used for extended or continuous treatment by eliminating unneeded placebo tablets.

A majority of DoD providers surveyed indicated that extended or continuous cycle offered advantages over conventional dosing, with 29 citing convenience/lifestyle advantages, and 36 citing advantages in treating menstrual-related problems. A total of 43 providers (out of 62 commenting) did not agree that Seasonale provided a benefit relative to another OC given on the same dosing schedule (84 days on, 7 days off); 19 commented on the greater convenience of packaging. Many providers without experience with Seasonale reported using other OCs on an extended-cycle basis.

Two newly approved low-estrogen contraceptive products, Loestrin 24 Fe and Yaz, are labeled for use as a 24-day on, 4-day off regimen. The shortened "off" cycle is intended to decrease adverse effects associated with hormone withdrawal. It may also provide a greater safety margin for contraceptive effectiveness by decreasing the likelihood of follicle development during the "off" cycle.

Phasic formulations – Biphasic and triphasic oral contraceptives attempt to "mimic" changes in levels of estrogen and progesterone seen during the normal menstrual cycle, in an attempt to decrease adverse effects by decreasing hormonal steroid exposure. The introduction of these products was probably primarily a reaction to the controversy about the relationship between thromboembolic events and progestogen content, since lower total amounts of progestogens can be achieved by providing a varying amount throughout the cycle. The biphasic OCs initially introduced to the market were rapidly superseded by triphasic OCs, resulting in infrequent use of the older biphasic products. Triphasic products, which vary doses of progestogen and/or estrogen three times during the treatment period, remain popular.

Although classified as a biphasic product, Mircette and its generic equivalents (21 days of EE 20 mcg/desogestrel 150 mcg followed by 2 days of placebo and 5 days of 10 mcg EE) are more similar to a low-estrogen monophasic product plus supplemental estrogen than to the older biphasic products. Mircette may be useful in perimenopausal women due to the more constant estrogen levels.

Usefulness for other conditions – Most if not all combined contraceptives offer non-contraceptive benefits, including control of heavy menstrual bleeding or irregular cycles, reduction of acne and dysmenorrhea, and favorable effects on other conditions, such as endometriosis pain and menstrual migraines. Relatively few contraceptive products have FDA-approved indications in addition to prevention of pregnancy. However, given the lack of substantial differences between products with regard to contraceptive effectiveness, the choice of a specific contraceptive product may depend on its proven or potential usefulness for another condition.

Alternative routes of administration – Contraceptive products offering alternative routes of administration include DMPA injections, a transdermal patch (Ortho Evra), and a vaginal ring (Nuvaring). Two DMPA formulations are available: 150 mcg, given by deep intramuscular (IM) injection (Depo-Provera, generics), and 104 mcg (Depo-subq Provera 104), given by

subcutaneous (SC) injection (less painful and may allow patient self-administration). DMPA injections are given every 11 to 13 weeks. In addition to prevention of pregnancy, the 104 mcg formulation is also approved by the FDA for endometriosis pain. The transdermal patch is applied weekly for three weeks, followed by a patch-free week, while the vaginal ring is inserted on a monthly basis and then removed after 3 weeks, followed by a 7-day ring-free period.

Emergency contraception – The only product currently labeled as emergency contraception is levonorgestrel 0.75 mg (Plan B), which is given as one dose (1 tablet) within 72 hours after unprotected intercourse and a second dose 12 hours later. A combination emergency contraception product (Preven) was discontinued in 2004. In addition to Plan B, the FDA has declared several brands of combined OCs to be safe and effective for emergency contraception, including Ovral, Alesse, Nordette or Levlen, Lo/Ovral, Triphasil or Tri-Levlen. Progestogen-only regimens such as Plan B have been shown to be more effective and better tolerated for emergency contraception than combination OCs.

3) Efficacy / Effectiveness

Contraceptive effectiveness – All of the reviewed contraceptives are highly effective at preventing pregnancy when used correctly. Progestogen-only OCs may be slightly less effective than combined OCs and for that reason have stricter use requirements (i.e., they must be taken at the same time each day, without an "off" period). There is some question as to whether the lowering of estrogen content in combined OCs over time has resulted in a decrease in contraceptive effectiveness, although data are lacking. Methods that reduce the potential for user error (e.g., injectable contraceptives) are known to decrease "actual use" failure rates. Whether or not potentially improved compliance related to less-frequent dosing of the transdermal patch and vaginal ring results in decreases in "actual use" failure rates remains to be seen; contraceptive effectiveness so far appears similar to combined OCs. Drug interactions and patient weight may also affect contraceptive effectiveness.

Overall, the differences in contraceptive effectiveness among the reviewed contraceptive products appear minor, with no reliable evidence to suggest substantial differences in contraceptive effectiveness based on progestogen content, phasic formulation, or regimen.

Efficacy in treating other conditions

Acne – All combined contraceptives are likely to have beneficial effects on acne, based on several potential mechanisms, including decreased production and increased binding of free testosterone, blocking androgen receptors, and inhibiting conversion of testosterone to dihydrotestosterone in the hair follicles and skin. Clinically, progestogens with relatively low binding to androgen receptors have been preferred for patients with androgenic adverse effects (such as acne or hirsutism), although actual differences between products are unclear. A 2005 Cochrane review [Arowojolu et al] reviewed 14 head-to-head contraceptive trials (9 different comparisons) focusing on acne; unfortunately, most products included in the review are not currently available in the U.S. The three trials remaining either reported no difference between products or inconclusive results.

Contraceptive products with an additional FDA approved indication for acne include Ortho Tri-Cyclen (a triphasic product containing 35 mcg EE and varying amounts of norgestimate, which is now generically available) and Estrostep Fe (a triphasic product containing varying amounts of estrogen and 1 mg norethindrone). Trials with products containing drosperinone, which has anti-androgen properties, have reported comparable to somewhat superior results

compared to a product containing cyproterone (a progestogen traditionally favored in the United Kingdom for acne treatment, but not available in the U.S.) [Van Vloten et al, 2002] and Ortho Tri-Cyclen [Thorneycroft et al, 2004].

The vast majority of DoD providers surveyed (76/79) agree that other OCs work as well for acne as Ortho Tri-Cyclen, despite its FDA indication.

Premenstrual Syndrome (PMS) / Premenstrual Dysphoric Disorder (PMDD) – Continuous use of OCs may decrease premenstrual symptoms. Several clinical trials with drospirenone-containing OCs have reported favorable effects on PMDD, a severe form of PMS, especially with regard to fluid retention and weight fluctuations ("bloating").

Endometriosis pain – OCs with higher progestational activity and/or continuous use of contraceptives may be preferred in patients with endometriosis pain, which is related to the menstrual cycle. Progestogen-only DMPA injections are associated with improvements in endometriosis; the subcutaneous administered 104 mg strength (Depo-subq Provera 104) has an FDA-approved indication for endometriosis pain.

Heavy menstrual bleeding and dysmenorrhea (menstrual pain) – Combined OCs have been used to treat dysmenorrhea (by decreasing prostaglandins and thus uterine motility/cramping) and heavy menstrual bleeding (by promoting regular shedding of a thinner endometrial lining) since their introduction in 1960. While clinical evidence supports efficacy, most of the literature addresses the older products (≥ 50 mcg EE) and does not support conclusions about the efficacy or comparative efficacy of currently used low estrogen products.

4) Safety and Tolerability

Serious adverse events/contraindications – Use of combined OCs is associated with increased risk of several serious conditions, including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the absolute risk of these events is very low in women without additional risk factors. Much of the available epidemiological data was obtained from studies using higher estrogen and progestogen doses than those currently in use; the effect of long-term, low-estrogen OC use has yet to be determined. Risks associated with the patch and vaginal ring are largely unknown, although they are presumed to be similar to those of combined OCs.

Use of combined OCs is associated with an increased risk of venous thromboembolism (VTE) (e.g., deep vein thrombosis, pulmonary embolism). Most data relate to products with higher doses of estrogen than are currently used; low estrogen products may be associated with a lower risk. The issue of whether third-generation progestogens (e.g., desogestrel) are associated with an increased thromboembolic risk compared to second-generation progestogens has been controversial; however, many sources now appear to agree that there is a modestly increased risk with products containing desogestrel, compared to those containing levonorgestrel. The risk of VTE with norgestimate appears similar to levonorgestrel and lower than desogestrel, based on limited data [Gomes et al, 2004]. Epidemiological data for drospirenone is not yet available. A 2004 safety review reporting 3-year interim results from a large, controlled, postmarketing surveillance study [Heinemann & Dinger, 2004] did not suggest an excess risk with drospirenone-containing products compared to those containing levonorgestrel or other progestogens.

An increased risk of myocardial infarction (MI) and stroke has been associated with OC use, primarily in smokers or women with underlying risk factors for coronary artery disease. Most data relate to products with higher doses of estrogen than are currently used; low estrogen

products may be associated with lower risk. Whether progestogen content affects the risk of MI or stroke is unclear.

Absolute contraindications to the use of combined contraceptives include: previous thromboembolic event or stroke, cerebral vascular or coronary artery disease, or valvular heart disease with complications; severe hypertension; headaches with focal neurologic symptoms; known or suspected estrogen-dependent tumor (e.g., endometrial, breast cancer); liver disease; cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use; major surgery with prolonged immobilization; pregnancy; undiagnosed abnormal uterine bleeding; and women over age 35 years who smoke.

Common adverse effects – In general, adverse effects of oral, transdermal, or vaginal ring contraceptives may include: breast tenderness, headache, migraine, nausea, nervousness, vomiting, dizziness, weight gain, fluid retention, tiredness, decline of libido, and increased blood pressure.

Estrogen content and adverse effects – Logically, lower estrogen products (e.g., ≤ 20 mcg EE) are associated with a lower risk of estrogen-related adverse effects and a lower risk of thromboembolic events (although data are limited). However, this must be balanced against a greater vulnerability to compromises in contraceptive effectiveness due to missed doses or drug interactions, a potential decrease in non-contraceptive benefits (e.g., reduction in risk of ovarian cancer or protection against functional ovarian cysts), and a higher incidence of cycle control problems (e.g., breakthrough bleeding and spotting). Determination of the "best" estrogen dose – reliable pregnancy prevention with acceptable cycle control and minimal adverse effects – is complicated by wide inter-patient variability in hormonal blood levels.

Progestogen content and adverse effects – There is considerable difference of opinion among providers concerning the extent to which the choice of progestogen affects tolerability. Products containing third-generation progestogens appear to have fewer androgenic effects than the first- and second-generation products, and may be favored in patients with androgenic adverse effects such as acne or hirsutism (although all combined OCs reduce free testosterone levels and therefore tend to have favorable effects on acne). According to a Cochrane review last updated in 2005 (Maitra et al), second- and third-generation products may offer some advantage over first generation products with respect to cycle control (e.g., minimizing spotting or breakthrough bleeding). The magnitude of the difference is unclear.

Drospirenone is a derivative of spironolactone with anti-mineralocorticoid and anti-androgenic properties similar to progesterone. In addition to progesterone receptors, drospirenone binds to aldosterone receptors in the kidney; the effect is similar to 25 mg of spironolactone. As a consequence, drospirenone reduces fluid retention and weight fluctuations ("bloating"). It may cause concerns about hyperkalemia in patients with a predisposing condition or on other medications that increase potassium levels (women receiving daily, long-term treatment with medications that can increase potassium should have their serum potassium levels checked during the first treatment cycle). While precautions are indicated, there appears to be little evidence to cause serious concern. About 14 million women worldwide have received drospirenone-containing products, according to the manufacturer.

Adverse effects with the transdermal patch – Based on a comparative trial, adverse effects of the transdermal patch appear similar to a combined OC comparator, with the exception of a higher incidence of site reactions, breast symptoms (e.g., breast tenderness), and dysmenorrhea. Another obvious concern with the patch is adhesion; about 5% of patches used during clinical trials had to be replaced, because they fell off or partially detached. A small study cited in

labeling showed a relatively small percentage of patches falling off under conditions of heat, humidity, or exercise; anecdotal reports and survey results from deployment sites suggest a much larger percentage. Site reactions, reported in about 17% of patients, were mostly mild to moderate (92%). Skin pigmentation changes were rarely reported (overall in <1% of patients), with one severe case reported in labeling.

Based on pooled data from North American pivotal trials (Archer et al, 2002), the patch may have compliance advantages compared to combined OCs, with perfect compliance (21 days of drug-taking followed by 7 drug-free days) in 79% of cycles for patients receiving comparator OCs vs. 98% receiving the patch.

DoD providers surveyed cited advantages of the transdermal patch as being improved compliance with infrequent dosing and availability of a different dosing option; disadvantages included the patch coming off, the uncertainty regarding estrogen exposure and VTE risk, the incidence of skin reactions, and weight limitations.

A recent pharmacokinetic study noted that systemic exposure (area under the curve and steady state concentrations) with the patch was about 60% higher than a combined OC with 35 mcg ethinyl estradiol and 0.25 norgestimate, although peak concentrations are about 25% lower. This information, which has been added to product labeling, has caused uncertainty regarding safety of the patch with respect to estrogen content and associated thromboembolic risk. Epidemiological data is limited to one published and one unpublished study, with conflicting results.

Adverse effects with the vaginal ring – Adverse effects with the vaginal ring appear low compared to rates typically reported with combined OCs. Overall, 5-14% of women reported the most common adverse effects (vaginitis, headache, vaginal secretion, weight gain, and nausea). A cross-over study focusing on genital symptoms (Veres et al, 2004) showed a higher percentage of women reporting vaginal wetness during ring use compared to a combined OC (63% vs. 43%), but did not find evidence of any pathological conditions associated with ring use. Specific to the vaginal ring are issues such as interference with intercourse (about 85% of women and 71% of partners say they cannot feel the device during intercourse), premature expulsion (occurring in about 0.5% of cycles), and lack of comfort with inserting and removing the vaginal ring (which does not require exact positioning). After insertion, the product remains effective for about 35 days, providing a safety margin if the patient fails to remove the ring on schedule and making extended or continuous use feasible.

DoD providers surveyed cited advantages of the vaginal ring as being improved compliance with infrequent dosing and a good adverse effect profile; disadvantages included a substantial number of patients who are not comfortable with the method and deployment limitations related to storage requirements.

Adverse effects with DMPA injections – Women receiving injectable DMPA may lose significant bone mineral density, an effect which may not be completely reversible. It is unclear whether use during adolescence or early adulthood reduces peak bone mass and increases the risk of osteoporotic fracture in the future. Injectable DMPA products carry a black box warning advising that it be used as a long-term birth control method (e.g., longer than two years) only if other birth control methods are inadequate.

Of the contraceptives reviewed, only injectable DMPA appears to be associated with progressive (and substantial) weight gain, with labeling for the 150 mg IM strength reporting an average weight gain of 5.4 lb in women completing 1 year of treatment, 8.1 lb after 2 years,

13.8 lb after 4 years, and 16.5 lb after 6 years. Labeling for the 104 mg SQ strength provides one-year results from three large clinical trials (average weight gain 3.5 lbs in the first year of use) and 2-year results from a small study comparing the two strengths (average weight gain of about 7.5 lbs with either strength).

Other issues with DMPA injections include amenorrhea in a high percentage of users (may be an advantage or disadvantage); irregular menses and unpredictable spotting/bleeding in the first several months of use; and lack of immediate reversibility (10 months to return to baseline fertility).

Drug interactions – A large number of medications may interact with hormonal contraceptives. Oral contraceptives may also affect levels of other medications. Data do not suggest a higher incidence of clinically significant drug interactions based on differences in progestogen content, phasic formulation, regimen, or route of administration.

Use in special populations – There are multiple considerations which may affect the choice of contraceptives in women with concomitant conditions (e.g., endometriosis). Progestogen-only OCs may be preferred in women who are breastfeeding, due to concerns about estrogen effects on the content and quality of breast milk, and the potential for infant exposure.

5) Other Factors – One practical concern with the vaginal ring is storage. Refrigeration is required prior to dispensing. After dispensing, the product may remain at controlled room temperature for up to 4 months, but should not be exposed to excessive heat. Heat, humidity, and exercise may also affect adhesion of the transdermal patch.

6) Overall Clinical Effectiveness Conclusion – The P&T Committee concluded that: 1) contraceptives vary in estrogen and progestogen content, regimen (e.g., extended use), phasic formulation, desirability for non-contraceptive uses, and routes of administration; 2) there is wide intra- and inter-patient variability in pharmacokinetics; 3) differences may affect safety, adverse effects/tolerability, convenience/compliance, or effectiveness for non-contraceptive uses; 4) there do not appear to be substantial differences in contraceptive effectiveness across products; 5) providers desire a wide variety of choices based on estrogen and progestogen content consistent with variable patient response and the clinical niches for which multiple are required; 6) the alternative formulations (vaginal ring, patch, IM and SQ injection) are required for adequate clinical coverage; and 7) none of the reviewed contraceptives are sufficiently less clinically effective than the others to be classified as non-formulary based on clinical issues alone.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to accept the clinical conclusion as stated above.

B. Contraceptive UF Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the contraceptive agents in relation to safety, tolerability, effectiveness, 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 C.F.R. 199.21(e) (2).

The clinical review identified 35 unique contraceptive entities, the majority of which are available generically. For clinical comparison, these agents were classified into one of 11 categories based upon their estrogen content, phasic formulation, or route of administration. This classification system was also used in the economic review. However, for the initial cost assessment, the contraceptives were stratified into three broad groups: 1) OCs available only as brand-name products; 2) OCs available generically; and 3) non-oral contraceptives.

Respectively, these groups represented 20%, 53%, and 27% of the total annual contraceptive drug spend.

The initial cost assessment was based on average weighted cost per cycle across the MHS. This assessment found generically available oral contraceptives to be, in general, more cost-effective than brand name oral contraceptives and non-orally administered contraceptives. Additionally, it was determined that further opportunity exists to obtain lower prices for generic agents through national pharmaceutical contracts. For these reasons, the P&T Committee concluded that all generically available contraceptives should be maintained on the UF.

The P&T Committee also concluded that despite a somewhat higher average weighted cost per cycle for non-orally administered contraceptives (Nuvaring, Ortho Evra, Depo-Provera and equivalents, Depo-subq Provera 104) compared to generically available OCs, these agents should remain on the UF to ensure clinical coverage for patients who need these methods of administration. Likewise, the P&T Committee concluded that Plan B should remain on the UF, because of the clinical advantages of this progestogen-only product over other OCs for emergency contraception. The P&T Committee also discussed availability of Plan B from the TMOP, which currently does not fill prescriptions for Plan B. Although Plan B must be used within 72 hours of unprotected intercourse to be effective, which is not possible via mail order, the P&T Committee agreed that: (1) Under 32 CFR 199.21(h)(2)(i), formulary pharmaceutical agents are required to be available under the Pharmacy Benefits Program from all four points of service identified in paragraph 199.21(h)(1), except for military treatment facilities which are required only to have available BCF agents, with other formulary agents based upon their scope of practice; (2) consistent with this requirement, other medications which must be used acutely are available through mail order (e.g., antibiotics); and (3) this requirement of availability through mail order can ameliorate access problems.

A CMA and BIA were performed to determine the relative cost-effectiveness of the brand name oral contraceptives. The comparators for these analyses were the OCs within the same subgroup (as defined by the clinical review) as the brand name agent being analyzed. The brand name contraceptives considered in these analyses were: Estrostep Fe, Ovcon-35, Ovcon-50, Yasmin, Yaz, Ortho Tri-Cyclen Lo, and Seasonale.

The results of each category-specific CMA were incorporated into a BIA to account for other factors and costs associated with a potential decision to recommend non-formulary status for one or more brand-name contraceptive agents. The BIA accounted for market share migration, cost reductions associated with non-formulary cost shares, and medical necessity processing fee. Based on the CMA and BIA results of the combined category-specific analyses, the P&T Committee agreed that Yasmin, Yaz, and Ortho Tri-Cyclen Lo offered clinical and/or economic value for retention on the UF. The P&T Committee agreed that Seasonale, Ovcon-35, Ovcon-50, and Estrostep Fe should be non-formulary, because the category-specific cost-minimization analyses showed clinically similar alternatives were available at a significantly lower cost.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 3 absent) to accept the UF cost analysis presented by the PEC. The P&T Committee concluded that Seasonale (EE 30 mcg; levonorgestrel 0.15 mg in special packaging for extended use); Ovcon 35 (EE 35 mcg; 0.4 mg norethindrone); Ovcon 50 (EE 50 mcg; norethindrone 1 mg), and Estrostep Fe (EE 20/30/35 mcg; norethindrone 1 mg) were not cost-effective relative to other contraceptive agents with similar clinical attributes. Taking into consideration the conclusions from the relative clinical effectiveness and relative

cost-effectiveness determinations of the contraceptive agents, and other relevant factors, the P&T Committee recommended that Seasonale, Ovcon-35, Ovcon-50 and Estrostep Fe be classified as non-formulary under the UF, and that Yasmin, Yaz, Ortho Tri-Cyclen Lo, Ortho Evra patches, Nuvaring, Depo-Provera, Depo-subq Provera 104, Plan B, and all generically available OCs be retained on the UF (See Table 1 on Pages 19-20 for a complete list of generically available OCs).

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend Seasonale, Ovcon-35, Ovcon-50 and Estrostep Fe be classified non-formulary under the UF, with Yasmin, Yaz, Ortho Tri-Cyclen Lo, Ortho Evra patches, Nuvaring, Depo-Provera, Depo-subq Provera 104, and all generically available contraceptives (and equivalents) being added to the UF. In a separate vote, the P&T Committee recommended (12 for, 1 opposed, 3 abstained, 2 absent) that Plan B should continue to be classified as formulary on the UF.

The P&T Committee also voted (11 for, 2 opposed, 3 abstained, 2 absent) to recommend that Plan B be available from the TMOP; with a quantity limit of one Plan B package per copay applying to prescriptions filled by TMOP and retail network pharmacies.

C. Contraceptive Agents UF Medical Necessity Criteria: Based on the clinical evaluation of contraceptive agents, 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 medical necessity criteria for the combined OCs that were recommended for non-formulary status:

1) Use of formulary combined OCs is contraindicated.

2) The patient has experienced significant adverse effects from formulary combined OCs, or is likely to experience significant adverse effects from formulary combined OCs, and is expected to tolerate a non-formulary contraceptive agent.

3) Use of formulary combined OCs has resulted in therapeutic failure.

The P&T Committee agreed that it was extremely unlikely that a non-formulary contraceptive agent would truly be medically necessary, given the number and variety of contraceptive agents recommended for formulary status and the inclusion of contraceptives that are very similar to the recommended non-formulary agents.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 3 absent) to approve the medical necessity criteria.

D. Contraceptive Agents UF Implementation Plan: Because a high proportion of beneficiaries who would be affected by this formulary action are receiving Seasonale, which necessarily requires a 90-day prescription (about 11,000 DoD beneficiaries receive one or more prescriptions for Seasonale annually, out of about 23,000 patients with one or more prescriptions annually for Seasonale, Ovcon-35, Ovcon-50, or Estrostep Fe), the P&T Committee recommended an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have Seasonale, Ovcon-35, Ovcon-50, or Estrostep Fe on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and

2) medical necessity is established. MTFs may (but are not required to) fill a prescription for non-formulary contraceptives written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 3 absent) an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

E. Contraceptive Agents BCF Review and Recommendations

The P&T Committee had previously determined that at least one but no more than two contraceptive products would be added to the BCF in each of the following subgroups. The P&T Committee could also consider addition of contraceptives in other subgroups, if needed. Based on the relative clinical effectiveness and cost effectiveness of the agents within each subgroup recommended for UF addition and taking into account the desire to maximize clinical coverage by providing a wide array of products within the most commonly used subgroups, the P&T Committee recommended the following OCs for BCF status.

- *Monophasic OCs with 20 mcg EE*
  - EE 20 mcg; 3 mg drospirenone (Yaz)
  - EE 20 mcg; 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent)
- *Monophasic OCs with 30 mcg EE*
  - EE 30 mcg; 3 mg drospirenone (Yasmin)
  - EE 30 mcg; levonorgestrel 0.15 mg (Nordette or equivalent; excludes Seasonale)
- *Monophasic OCs with 35 mcg EE*
  - EE 35 mcg; 1 mg norethindrone (Ortho-Novum 1/35 or equivalent)
  - EE 35 mcg; 0.25 mg norgestimate (Ortho-Cyclen or equivalent)
- *Triphasic OCs*
  - 25 mcg EE; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo)
  - 35 mcg EE; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent)
- *Progestogen-only OCs*
  - 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)

The P&T Committee extensively discussed addition of the vaginal ring product (Nuvaring) to the BCF. Factors supporting addition included potential compliance advantages with once monthly dosing, a low adverse effect profile, and positive provider comments. The major factor opposing addition was the P&T Committee's uncertainty as to whether the clinical advantages outweighed the substantially higher cost per cycle compared to the OCs recommended for the BCF. The P&T Committee ultimately voted not to recommend Nuvaring for the BCF (6 for, 7 opposed, 2 abstained, 3 absent).

The P&T Committee noted that BPA prices submitted by manufacturers contingent upon UF and BCF status had a substantial impact on cost-effectiveness, particularly for some of the brand-name products (e.g., Yasmin, Yaz, and Ortho Tri-Cyclen Lo), which resulted in BCF recommendations that should broaden clinical coverage and reduce the unit cost of these widely used contraceptive products at MTFs. MTFs considering formulary status for products previously on the BCF should take into consideration local needs, as well as the potential that further cost reductions for generically available products may result from national contracting initiatives.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend the following contraceptive agents for 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; levonorgestrel 0.15 mg (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)

9. ABBREVIATED CLASS REVIEWS: HISTAMINE-2 (H2) BLOCKERS; HMG-Co A REDUCTASE INHIBITORS (STATINS), COMBINATION PRODUCTS, AND ADD-ON THERAPIES OF EZETIMIBE AND NIACIN; AND NEWER SEDATIVE HYPNOTIC AGENTS

Portions of the clinical reviews for each class were presented to the Committee. The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review, and for developing the appropriate cost effectiveness models. Both the clinical and economic analyses of these three classes will be completed during the August 2006 meeting; no action necessary.

10. ADJOURNMENT

The second day of the meeting adjourned at 1600 hours on May 10, 2006. The dates of the next meeting are August 15-17, 2006.

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

List of Appendices

Appendix A – Table 1. Implementation Status of UF Decisions

Appendix B – Table 2. Newly Approved Drugs

Appendix C – Table 3. Abbreviations

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations/Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	**Effective Date of Decision**	**Comments**
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 July (90 day implementation period)	
Feb 06	Misc Antihypertensive Agents	felodipine/enalapril (Lexxel) verapamil/trandolapril (Tarka)	BCF	amlodipine/benazepril (Lotrel) hydralazine clonidine tablets	26 Apr 06	26 July (90 day implementation period)	
Feb 06	GABA-analogs	pregabalin (Lyrica)	BCF	gabapentin (Neurontin)	26 Apr 06	28 Jun (60 day implementation period)	
Nov 05	Alzheimer's Drugs	tacrine (Cognex)	ECF	donepezil (Aricept)	19 Jan 06	19 April (90 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Nasal Corticosteroids	beclomethasone dipropionate (Beconase AQ, Vancenase AQ) budesonide (Rhinocort AQ) triamcinolone (Nasacort AQ)	BCF	fluticasone (Flonase)	19 Jan 06	19 April (90 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Macrolide/ Ketolide Antibiotics	azithromycin 2gm (Zmax) telithromycin (Ketek)	BCF	azithromycin (Z-Pak) erythromycin salts and bases	19 Jan 06	22 March 2006 (60 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Antidepressants (excluding MAOIs and TCAs)	paroxetine HCL CR (Paxil) fluoxetine 90mg (weekly regimen – Prozac Weekly) fluoxetine (special packaging for PMDD – Sarafem) escitalopram (Lexapro) duloxetine (Cymbalta) buproprion extended release (Wellbutrin XL)	BCF	citalopram fluoxetine (excluding weekly regimen and special packaging for PMDD) sertraline (Zoloft) trazadone buproprion sustained release	19 Jan 06	19 July 2006 (180 day implementation period)	BCF selections effective 19 Jan 06

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Decision	Comments
Aug 05	Alpha Blockers for BPH	tamsulosin (Flomax)	BCF	terazosin alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05
Aug 05	CCBs	amlodipine (Norvasc) isradipine IR (Dynacirc) isradipine ER (Dynacirc CR) nicardipine IR (Cardene, generics) nicardipine SR (Cardene SR) verapamil ER (Verelan) verapamil ER for bedtime dosing (Verelan PM, Covera HS) diltiazem ER for bedtime dosing (Cardizem LA)	BCF	nifedipine ER (Adalat CC) verapamil SR diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150-day implementation period)	BCF selections effective 13 Oct 05
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-day implementation period)	BCF selection effective 13 Oct 05
May 05	PDE-5 Inhibitors	sildenafil (Viagra) tadalafil (Cialis)	ECF	vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90-day implementation period)	ECF selection effective 14 Jul 05
May 05	Topical Antifungals*	econazole ciclopirox oxiconazole (Oxistat) sertaconazole (Ertaczo) sulconazole (Exelderm)	BCF	nystatin clotrimazole	14 Jul 05	17 Aug 05 (30-day implementation period)	BCF selection effective 14 Jul 05
May 05	MS-DMDs	-	ECF	interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-	ECF selection effective 14 Jul 05
Feb 05	ARBs	eprosartan (Teveten) eprosartan/HCTZ (Teveten HCT)	BCF	telmisartan (Micardis) telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	**Effective Date of Decision**	**Comments**
Feb 05	PPIs	esomeprazole (Nexium)	BCF	omeprazole rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = UF
ER = extended release; IR = immediate release; SR = sustained release
ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors
*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs May 2006 DoD P&T Committee Meeting

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Insulin detemir Injection (Levemir); Novo Nordisk**;** long-acting insulin	Jun 05: Treatment of insulin dependent diabetes mellitus in adults requiring long acting insulin for control of hyperglycemia. Oct 05: Treatment of pediatric Type I DM	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until the injectable medications for diabetes drug class is reviewed.
Insulin glulisine injection (Apidra); Sanofi-Aventis; ultra short acting insulin analogue	Apr 04: Treatment of insulin dependent diabetes mellitus in adults requiring ultra short acting insulin for control of hyperglycemia	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until the injectable medications for diabetes drug class is reviewed.
Ranolazine tablets (Ranexa); CV Therapeutics**;** partial fatty oxidase inhibitor	Jan 06: Treatment of chronic angina when used in combination with amlodipine, beta blockers or nitrates	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until the miscellaneous cardiovascular drug class is reviewed.
Sunitinib capsules (Sutent); Pfizer**;** multi-kinase inhibitor	Dec 05 (priority review); Treatment of gastrointestinal stromal tumor after disease progression on, or intolerance to, imatinib (Gleevec). Treatment of advanced renal cell carcinoma	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until oral cancer drug class is reviewed. Quantity limits recommended: TMOP: 50 mg: #60 caps/84 days, 25 mg: #120 caps/84 days, 12.5 mg: #180 caps/84 days. Retail Network: 50 mg: #30 caps/30 days, 25 mg:#60 caps/30 days, 12.5 mg: #120 caps/30 days
Lenalidomide capsules (Revlimid); Celgene**;** immunomodulatory drug (thalidomide analogue)	Dec 05: Treatment of myelodsyplastic syndromes in transfusion dependent patients with del 5q cytogenetic abnormality	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until oral cancer drug class is reviewed.
Mecasermin rinfabate injection (Iplex); Insmed Pharmaceuticals; recombinant human insulin-I-like growth factor-1 (IGF-1)	Aug 05: Long-term treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until growth hormone / IGF-1 drug class is reviewed. Added to existing PA criteria and forms for mecasermin (Increlex).

Appendix C – Table 3. Table of Abbreviations

5-HT3	type 5 serotonin antagonists
ACOG	American College of Obstetricians and Gynecologists
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BPA	blanket purchase agreement
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CINV	chemotherapy-induced nausea and vomiting
CMA	cost minimization analysis
CYP450	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DEA	Drug Enforcement Administration
DMPA	depot medroxyprogesterone acetate
DoD	Department of Defense
EE	ethinyl estradiol
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
GIST	gastrointestinal stromal tumor
H2	histamine-2
IV	intravenous
MHS	Military Health System
MTF	military treatment facility
NK-1	neurokinin-1
NNT	number needed to treat
OCs	oral contraceptives
ODT	orally dissolving tablet
PA	prior authorization
P&T	Pharmacy and Therapeutics
PEC	Pharmacoeconomic Center
PONV	post-operative nausea and vomiting
RINV	radiation-induced nausea and vomiting
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
TZDs	thiazolidinediones
UF	Uniform Formulary
VTE	venous thromboembolism

DECISION PAPER:

FEBRUARY 2006
DEPARTMENT OF DEFENSE PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

1. CONVENING

2. ATTENDANCE

3. REVIEW MINUTES OF LAST MEETING

4. ITEMS FOR INFORMATION

5. REVIEW OF RECENTLY APPROVED AGENTS

The P&T Committee was briefed on two new agents that had been approved by the Food and Drug Administration (FDA) (Appendix B – Table 2). Neither of the medications fall into drug classes already reviewed by the P&T Committee, therefore Uniform Formulary (UF) consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits. Sorafenib (Nexavar) is an oral multi-kinase inhibitor approved for treatment of patients with advanced renal cell carcinoma. It is available in 200 mg tablets and is administered in a dose of 2 tabs given twice daily. Quantity limits were recommended for sorafenib since there is a risk of discontinuation of therapy due to poor patient prognosis or drug-related adverse effects. Other oral chemotherapy drugs (imatinib, erlortinib) have quantity limits. The manufacturer of sorafenib has instituted a restricted distribution system which limits the quantity dispensed to a 30-day supply. Sorafenib is not currently available from the TMOP, due to the restricted distribution system.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend that sorafenib have quantity limits of 180 tablets per 45 days (TMOP), should the product become available from the TMOP, or 120 tablets per 30 days from the TRRx. (See paragraph 5 on pages 10-11 of P&T Committee minutes.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

6. OVERACTIVE BLADDER (OAB) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the antimuscarinic drugs used to treat over active bladder. The overactive bladder therapeutic class was defined as: oxybutynin immediate release (Ditropan tablets/solution or generic) oxybutynin sustained release (Detrol XL), oxybutynin transdermal (Oxytrol), tolterodine immediate release (Detrol), tolterodine sustained release (Detrol LA), trospium (Sanctura),

solifenacin (Vesicare), and darifenacin (Enablex). This class is now ranked 28th in Military Health System (MHS) drug class expenditures at a cost of $55 million annually.

The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) that for the purposes of the UF clinical review none of the OABs have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other OABs.

Based on the results of the cost-effectiveness analysis (CEA) and other clinical and cost considerations, the Committee agreed (15 for, 0 opposed, 0 abstention, 3 absent) that a group of OAB agents including tolterodine sustained release, oxybutynin sustained release, oxybutynin immediate release, solifenacin, and darifenacin represented the best overall value to the DoD for the treatment of OAB across all three points of service.

A. COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the OAB agents, and other relevant factors, the P&T Committee voted (15 for, 0 opposed, 0 abstention, 3 absent) to recommend that tolterodine immediate release, oxybutynin patch, and trospium be classified as non-formulary under the UF and that tolterodine sustained release, oxybutynin sustained release, oxybutynin immediate release, solifenacin and darifenacin classified as formulary on the UF. (See paragraphs 6A and 6B on pages 11-16 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of tolterodine immediate release, oxybutynin patch, trospium 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, 2 absent) medical necessity criteria for the OAB agents. (See paragraph 6C on pages 16-17 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P&T Committee recommended (13 for, 2 opposed, 1 abstained, 2 absent) an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 6D on page 17 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ☐Approved ☑ Disapproved

~~Approved, but modified as follows~~: *"I note that the BAP recommended a 120 day implementation period. I have increased the implementation period to 90 days."*

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend oxybutynin immediate release and tolterodine sustained release as the Basic Core Formulary (BCF) agents. (See paragraph 6E on page 17 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

7. MISCELLANEOUS ANTIHYPERTENSIVE AGENTS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the miscellaneous antihypertensive agents marketed in the United States. The class was defined to include the angiotensin converting enzyme (ACE) inhibitor/calcium channel blocker (CCB) combinations amlodipine/benazepril (Lotrel), felodipine/enalapril (Lexxel), and verapamil sustained release/trandolapril (Tarka); the direct acting vasodilators (hydralazine, minoxidil); the centrally acting alpha-2 agonists (clonidine, methyldopa, guanabenz, guanfacine); the peripheral alpha-1 antagonists (prazosin); the adrenergic antagonists (reserpine, guanadrel, guanethidine); and the ganglionic blockers (mecamylamine). Together these drugs account for approximately $27M annually and are ranked 53rd in MHS drug class expenditures.

The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) that for the purposes of the UF clinical review the following clinical conclusions applied: (1) there is no evidence that any one ACE/CCB combo is more effective relative to another for lowering blood pressure; (2) there is more evidence to support the use of amlodipine/benazepril and verapamil sustained release/trandolapril in sub-populations of patients with hypertension than felodipine/enalapril; (3) there is insufficient evidence to conclude that any one ACE/CCB combo is superior to another for reducing risk of cardiovascular outcomes in patients with hypertension; (4) safety/tolerability profiles of the ACE/CCB combos are primarily dictated by the CCB component; (5) there is no evidence to suggest that amlodipine/benazepril or felodipine/ enalapril would be superior to the other in terms of safety/tolerability. Verapamil sustained release/trandolapril has unique safety issues, due to the verapamil component; (6) persistence rates with amlodipine/benazepril may be improved by 7%-22% compared to the individual agents administered together; (7) transdermal clonidine is not a candidate for non-formulary designation on the UF due to its unique niche in several patient sub-groups and lower risk of rebound hypertension upon drug discontinuation; (8) Use of the remaining miscellaneous antihypertensive drugs is limited by bothersome tolerability profiles, however, several drugs maintain unique roles for treating hypertension and non-cardiovascular conditions.

Based on the results of the CEA and other clinical and cost considerations, the Committee agreed (16 for, 0 opposed, 1 abstention, 1 absent) that a group of miscellaneous antihypertensive agents including amlodipine/benazepril, the direct acting vasodilators (hydralazine, minoxidil); the centrally acting alpha-2 agonists [(clonidine tablets and patches), methyldopa, guanabenz, guanfacine]; the peripheral alpha-1 antagonists (prazosin); the adrenergic antagonists (reserpine, guanadrel, guanethidine); and the ganglionic blockers

(mecamylamine) represented the best overall value to the DoD in the class of miscellaneous antihypertensive agents.

A. COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (11 for, 4 opposed, 2 abstention, 1 absent) to recommend that felodipine/ enalapril (Lexxel) and verapamil/trandolapril (Tarka) be classified as non-formulary under the UF, with clonidine tablets, clonidine patches, amlodipine/benazepril (Lotrel), hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine remaining on the UF. (See paragraphs 7A and 7B on pages 18-24 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows: *"I note the BAP's concern about having Lotrel as UF agent when amlodipine is non-formulary. 50K beneficiaries use Lotrel. Keeping this drug on the UF maintains the option of an ACE/CCB combo for these and other beneficiaries."*

B. COMMITTEE ACTION: Based on the clinical evaluation of felodipine/enalapril (Lexxel) and verapamil/trandolapril (Tarka) 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, 2 absent) medical necessity criteria for these agents. (See paragraph 7C on page 24 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 absent) an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 7D on page 24 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ☐Approved ☑ Disapproved

~~Approved, but modified as follows~~: *"I note that the BAP recommended a 120 day implementation period. I have increased the implementation period to 90 days."*

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) to recommend one combination agent [amlodipine/benazepril (Lotrel)] and two single agents (hydralazine and clonidine tablets) as the BCF agents. (See paragraph 7E on page 24 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

8. GAMMA-AMINOBUTYRIC ACID (GABA)-ANALOG DRUG CLASS REVIEW

The DoD P&T Committee evaluated the relative clinical effectiveness of the GABA-analog agents marketed in the United States. The class was defined to include gabapentin (Neurontin and various generics), pregabalin (Lyrica) and tiagabine (Gabatril). Although gabapentin, pregabalin, and tiagabine all have FDA indicates as adjunctive therapy (added to other antiepileptic drugs) in the treatment of partial seizures, the Committee's review focused most heavily on the use of these agents for the treatment of various types of neuropathic pain. Together these drugs account for approximately $148M annually and are ranked 6th in MHS drug class expenditures.

The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) that for the purposes of the UF clinical review the following clinical conclusions applied: (1) the efficacy of gabapentin and pregabalin for treating pain associated with either diabetic peripheral neuropathy (DPN) or post-herpetic neuropathy (PHN) appears similar; (2) gabapentin is the only GABA-analog that has shown modest efficacy in treating other types of neuropathic pain based on published clinical trials; (3) there is insufficient data regarding the efficacy of tiagabine in patients with neuropathic pain syndromes to make definitive conclusions; (4) there appear to be no major differences in the efficacy of gabapentin, pregabalin, or tiagabine for use as adjunctive treatment of partial seizures; (5) the safety and tolerability profiles of gabapentin and pregabalin are more favorable compared to tiagabine; (6) there appear to be only minor differences in the tolerability profiles of gabapentin and pregabalin, when evaluating the incidence of somnolence, dizziness, and peripheral edema; (7) there are minor differences in other factors between the drugs, including use in pediatrics, pharmacokinetic profiles, titration schedules, onset of effect, and controlled substance status. Overall the Committee agreed based on clinical usefulness alone, there was no basis for classifying any of the GABA analogs as non-formulary.

Based on the results of the clinical and cost-effectiveness analyses, the Committee agreed (16 for, 0 opposed, 0 abstained, 2 absent) that gabapentin was the more cost effective GABA-analog drug for the treatment of neuropathic pain.

A. COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the GABA-analog drugs, and other relevant factors, the P&T Committee recommended (14 for, 2 opposed, 0 abstained, 2 absent) that pregabalin be classified as non-formulary under the UF, with gabapentin and tiagabine remaining on the UF. (See paragraphs 8A and 8B on pages 24-31 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows: *"I agree with the concerns noted by some BAP members re off-label use of new drugs as first-line therapy when there are "tried and true" alternatives with known safety profiles. Lyrica remains available to those who need it under medical necessity criteria."*

B. COMMITTEE ACTION: Based on the clinical evaluations of pregabalin 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, 1 opposed, 0 abstained, 2 absent) medical necessity criteria for the GABA-analog agents. (See paragraph 8C on pages 31-32 of P&T Committee minutes for criteria.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Due to the relatively low number of patients that will be affected by this formulary action, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 3 absent) an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 8D on page 32 of P&T Committee minutes for rationale.).

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to recommend gabapentin as the BCF agent. (See paragraph 8E on page 32 of P&T Committee minutes for rationale.)

*Director, TMA, Decision***:** ☑Approved ☐ Disapproved

Approved, but modified as follows:

9. ABBREVIATED CLASS REVIEWS: THIAZOLIDINEDIONES (TZDS), ORAL ANTIEMETIC AGENTS; CONTRACEPTIVE AGENTS

Portions of the clinical reviews of each class were presented to the Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing appropriate cost effectiveness models. Both the clinical and economic analyses of each class will be completed during the May 2006 meeting; no action necessary.

APPENDIX A – TABLE 1. Implementation Status of UF Decisions

APPENDIX B – TABLE 2. Newly Approved Drugs

APPENDIX C – TABLE 3. Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

_____//signed//_____
William Winkenwerder, Jr., M.D.
Date: 26 April 2006

Department of Defense
Pharmacy and Therapeutics Committee Minutes

17 February 2006

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 14 February 2006 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
CDR Mark Richerson, MSC, USN	DoD P& T Committee Recorder
CDR Bill Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Maj David Carnahan, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
LtCol Brian Crownover, MC	Air Force, Physician at Large
LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer
LCDR Scott Akins, MC	Navy, Pediatrics Physician
CDR Brian Alexander, MC	Navy, Physician at Large
LCDR Joe Lawrence MSC *for* CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
MAJ Paul Garrett MC *for* COL Joel Schmidt, MC	Army, Physician at Large
LTC Peter Bulatao, MS *for* COL Isiah Harper, MS	Army, Pharmacy Officer
CDR Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
CDR Jill Pettit, MSC, USN	TRRx/TMOP COR
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

LCDR Chris Hyun, MC	Navy, Internal Medicine Physician
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Joel Schmidt, MC	Army, Physician at Large
COL Isiah Harper, MS	Army, Pharmacy Officer

C. Non-Voting Members Present

COL Kent Maneval, MS, USA	Defense Medical Standardization Board
Mr. Lynn T. Burleson	Assistant General Counsel, TMA
Mr. John Felicio *for* Ms Martha Taft	Health Plan Operations, TMA

Capt Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

None	

E. Others Present

Col Nacy Misel, BSC, USAF Reserve	IMA DoD Pharmacoeconomic Center
Lt Col David Bennett, BSC, USAF	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC, USA	DoD Pharmacoeconomic Center
CPT Ryan Young, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Dan Remund	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Julie Liss	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Dave Flowers	DoD Pharmacoeconomic Center
David Meade	DoD Pharmacoeconomic Center
Harsha Mistry	DoD Pharmacoeconomic Center
Catherine Kelly	Department of Veterans Affairs
Charles R. Brown	TMA/CMB

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the minutes – November 2005 DoD P&T meeting minutes were approved as written, with no corrections noted.

B. November minutes approval – Dr. William Winkenwerder, Jr., M.D. approved the minutes of the November 2005 DoD P&T Committee on 19 January 2006.

4. ITEMS FOR INFORMATION

TMA and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing: CAPT Buss, LtCol Bennett and LtCol Crownover briefed the members of the DoD P&T committee regarding the 15 December 2005 BAP meeting. The Committee was briefed on BAP comments regarding DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions: Mr. Dave Bretzke briefed the members of the Committee on the progress of implementation for drug classes reviewed for UF status since

February of 2005 (see Appendix A – Table 1). The Committee made the following observations:

- Utilization in all UF classes remains stable suggesting continued access to drugs within the reviewed classes.
- Collectively, as a percent of prescriptions dispensed, utilization of UF agents across all reviewed drug classes and points of service (MTF, mail, retail) have increased, while utilization of non-formulary agents has decreased. Among the UF decisions that have been implemented since the first UF DoD P&T meeting in February 2005 DoD there has been a 34% reduction in the use of non-formulary agents. Among all drug classes reviewed by the Committee to date, including those classes where implementation has only just begun, there has been a 17% reduction in the use of agents designated as non-formulary.
- Success in terms of generating increased market share for UF agents (while decreasing market share for non-formulary agents) varies by class and by point of service.
    - Formulary decisions resulting in a higher degree of drug class restrictiveness (i.e., phosphodiesterase-5 inhibitors) are generating better market share results than formulary decisions allowing multiple UF options within a drug class (i.e., angiotensin receptor blockers).
    - Market shares by point of service reflect the degree of utilization management applied to each point of service. The more highly managed points of service (ie., MTF, mail) are generating higher market shares of UF agents than the unmanaged point of service (i.e., retail).
- Overall market share projections for UF agents of 80% have not yet been realized. Although these projections were based on an implementation plan utilizing a one year time horizon, it is unlikely this degree of conversion will be achieved across all three points of service.
    - Models used to describe the relative economic comparison of agents within a drug class have been adjusted to reflect this information.
    - For the February 2006 drug classes evaluated for UF status, switch rates were reduced from 80% at all three points of service to approximately 70% at the MTF point of service and 30% in the retail and mail order sectors.

5. REVIEW OF RECENTLY-APPROVED AGENTS

The P&T Committee was briefed on two new agents recently approved by the Food and Drug Administration (FDA) (Appendix B – Table 2). Neither of the medications fall into drug classes already reviewed by the P&T Committee, therefore UF consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits. Sorafenib (Nexavar) is an oral multi-kinase inhibitor approved for treatment of patients with advanced renal cell carcinoma. Sorafenib is available in 200 mg tablets and is administered in a dose of 2 tabs given twice daily. Quantity limits were recommended for sorafenib since there is a risk of discontinuation of therapy due to poor patient prognosis or drug-related adverse effects. Other oral chemotherapy drugs (imatinib, erlortinib) do have quantity limits. The manufacturer of sorafenib has instituted a restricted distribution system

which limits the quantity dispensed to a 30-day supply. Sorafenib is not currently available from the TMOP, due to the restricted distribution system.

COMMITTEE ACTION: The DoD Pharmacy and Therapeutics (P&T) Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend that sorafenib have quantity limits of 180 tablets per 45 days (TMOP), should the product become available from the TMOP, or 120 tablets per 30 days (TRRx).

6. OVERACTIVE BLADDER (OAB) DRUG CLASS REVIEW.

A. OAB Medications Relative Clinical Effectiveness Review: The P&T Committee evaluated the relative clinical effectiveness of all the FDA-approved antimuscarinic drugs available in the U.S. for the treatment of overactive bladder. The OAB therapeutic class was defined as the antimuscarinics: oxybutynin immediate release (Ditropan tablets/solution or generic), oxybutynin sustained release (Detrol XL), oxybutynin transdermal (Oxytrol), tolterodine immediate release (Detrol), tolterodine sustained release (Detrol LA), trospium (Sanctura), solifenacin (Vesicare), and darifenacin (Enablex). 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 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.

During a twelve month period ending 30 Sept 2005, 147,508 Military Health System (MHS) patients were prescribed an antimuscarinic drug for overactive bladder. This class is now ranked 28th in MHS drug class expenditures at a cost of $55 million annually.

1) Efficacy

Efficacy measures. The antimuscarinic drugs reviewed are FDA-approved for the treatment of OAB. Efficacy measures used in clinical trials include the following:

a. Weekly number of urge incontinence episodes and total (urge plus non-urge) urinary incontinence episodes
b. Daily micturition frequency for up to 7 consecutive days during the baseline period and for one or more periods prior to clinic visits
c. Daily frequency of urgency episodes
d. Daily severity of urgency episodes
e. Volume voided per micturition
f. Number of incontinence episodes resulting in a change of pad or clothing per week
g. Nocturnal awakenings per week due to OAB symptoms
h. Volume to first urge sensation
i. Volume to first detrusor contraction
j. Bladder capacity (volume)
k. Post-void residual volume

Efficacy results: No differences in efficacy were reported when the following trials were assessed: four studies comparing oxybutynin immediate release and tolterodine immediate

release; one study of trospium versus oxybutynin immediate release; four studies of oxybutynin sustained release versus oxybutynin immediate release; and one study comparing of tolterodine sustained release versus tolterodine immediate release.

Oxybutynin sustained release was found to be superior to tolterodine immediate release in one trial; conversely tolterodine sustained release was reported as superior in one comparative trial against oxybutynin immediate release. Conflicting results were reported in the trials comparing oxybutynin sustained release and tolterodine sustained release, however, the two products showed similar efficacy in the comparative clinical trial that had the most rigorous study design. Solifenacin (flexible dose) showed greater efficacy over tolterodine sustained release (fixed dose) in one trial, however the results may be explained by lack of dosage titration allowed in the tolterodine sustained release group. Another short term trial showed greater efficacy with solifenacin vs tolterodine immediate release in some, but not all, efficacy measures. There were no trials comparing darifenacin vs. other OAB drugs.

A comparison of the OAB drugs' effects on the primary efficacy was made by adjusting for placebo effect and standardizing for 24 hour results. This comparison was not designed to demonstrate superiority, but designed to provide a range of improvement. All of the OAB agents decreased incontinence episodes by 0.32 - 1.04 events per 24 hours and urinary frequency by 0.6 - 1.3 voids per 24 hours.

Efficacy conclusion: In controlled clinical trials in overactive bladder, there was a high placebo efficacy rate. All of the OAB drugs have shown statistical superiority over placebo in controlled trials, however the results are of questionable clinical significance. Despite the availability of several head-to-head comparative trials for the OAB drugs, it is difficult to determine superiority of one product over another, due to differences in study design. When the results of the comparative clinical trials are compared in terms of incontinent episodes, urinary frequency and volume/void, there is insufficient evidence to conclude that any one OAB drug is more efficacious than another.

2) Safety and Tolerability

Contraindications: All the OAB drugs carry a similar contraindication of use in patients with gastric retention, urinary retention and uncontrolled narrow angle glaucoma.

Serious side effects: Irreversible urinary retention is a possible serious side effect with all the drugs in the OAB class. Cases are rare especially with the use of long acting agents.

Common Side effects: The majority of the side effects are due to the anti-cholinergic properties inherent to the class. The most prevalent side effects are dry mouth, constipation, dry eyes, somnolence and nausea. The newer agents (solifenacin, darifenacin and trospium) cause similar rates of dry mouth as the older agents (tolterodine and oxybutynin). These newer OAB drugs cause more constipation than tolterodine and oxybutynin. In the clinical trials with the oxybutynin patch, patients treated with the patch had a lower anti-cholinergic side effect profile verses patients receiving tolterodine and oxybutynin oral formulations. However, the patch was associated with significant dermatological side effects resulting in patient withdrawal. Oxybutynin immediate release is listed on the Beer's Criteria indicating the drug's use should be limited in the elderly.

Evidence from short-term head-to-head comparison trials indicate a higher incidence of adverse events overall, and dry mouth specifically, with oxybutynin. The sustained release forms of each drug resulted in fewer adverse events and dry mouth when compared to formulations. Trospium causes less severe dry mouth although the overall incidence of dry mouth and short

term adverse events are similar to oxybutynin immediate release. The difference between drugs based on withdrawals is less clear. Two trials of solifenacin versus tolterodine showed similar rates of adverse events overall; one trial showed lower rates of dry mouth for tolterodine sustained release versus solifenacin.

Discontinuation Rates: One comparative long-term study assessed the discontinuation rate of tolterodine and oxybutynin immediate release over a 6-month period. Oxybutynin immediate release treatment resulted in a higher discontinuation rate and earlier withdrawal from therapy than patients receiving tolterodine. The discontinuation rates and withdrawal rates were high for both drugs. Uncontrolled studies reported that dry mouth is the most common adverse event, and found similar rates of adverse events and withdrawals between oxybutynin and tolterodine. One head-to-head trial of trospium versus oxybutynin reported more adverse effects attributed with oxybutynin, especially dry mouth.

Drug interactions: There is the potential for induction or inhibition of hepatic cytochrome P450 isoenzymes with all the OAB drugs except trospium. There are few studies evaluating the clinical effects of these drug interactions. All the OAB drugs have the potential to increase the anti-cholinergic effects when used concomitantly with other anti-cholinergic drugs, which increases the risk for adverse effects and toxicity. All the OAB drugs can potentially increase the risk for sedation when taken with other drugs with sedating effects.

Persistence: Persistence rates of less than 10% with the OAB drugs have been reported in the literature. In the MHS, after a 12 month evaluation period, the persistence rates for tolterodine sustained release, oxybutynin sustained release, and oxybutynin immediate release were 5% to 16%. There were insufficient numbers of prescriptions refilled for the three newest OAB drugs to determine persistent rates. MHS beneficiaries using TMOP were more persistent with OAB therapy than those beneficiaries using other points of service. Noted in the study were a number of patients refilling OAB drug prescriptions well after the due date. It is possible that patients are using the OAB drugs on an as needed basis as dictated by social situations

Safety/tolerability conclusion: Anti-cholinergic effects are the most bothersome adverse events with all the OAB drugs. The most frequently encountered adverse event is dry mouth, which occurs with a higher rate for immediate release formulations than with SR formulations. The highest frequency of dry mouth occurs with oxybutynin immediate release. The three newest OAB drugs (trospium, solifenacin, and darifenacin) do not substantially lower the rate of dry mouth compared with tolterodine or oxybutynin sustained release, but do cause a higher rate of constipation. An evaluation of prescription refill patterns in DoD shows low persistence rates with tolterodine and oxybutynin. There was not enough data available to adequately evaluate MHS persistence rates for trospium, solifenacin, and darifenacin.

3) Other Factors

Dosing: All of the agents in the class are dosed once daily except for trospium, oxybutynin immediate release, and tolterodine immediate release. Once daily dosing theoretically increases compliance. Oxybutynin sustained release is frequently dosed in a range of 5 mg to 15 mg daily in clinical trials. In contrast, DoD usage shows 20 mg to 30 mg daily more commonly used, which can potentially increase the risk of adverse events.

Special populations: Pediatrics: Oxybutynin immediate release and sustained release are FDA-approved for use in children 6 years and older. The manufactures of tolterodine are pursuing an indication for use in pediatric patients.

Pregnancy: All the OAB drugs are rated as pregnancy category C with the exception of oxybutynin which is rated category B.

DoD Provider Comments: DoD providers were most comfortable prescribing oxybutynin immediate release and tolterodine sustained release; these two drugs have been included on the BCF since 2002. Most providers favored tolterodine sustained release. A majority of respondents had heard of the newer agents, trospium, solifenacin and darifenacin, but over 80% had not yet prescribed the agents. Most providers reported that the side effect profiles seen with clinical usage were similar to what is reported in the literature. DoD providers overestimated MHS persistence rates at 43% compared to the actual rates of between 5% and 16%.

Other Factors Conclusion: There is no evidence to suggest clinical superiority of any one OAB drug over another based on differences in dosing and titration schedules or DoD provider opinion. For pediatric patients, oxybutynin is preferred at this time.

Overall Clinical Effectiveness Conclusion: The DoD P&T Committee concluded that: 1) when the results of the comparative clinical trials are compared in terms of incontinent episodes, urinary frequency and volume/void, there is insufficient evidence to conclude that any one OAB drug is more efficacious than another; 2) When similar dosage forms are compared (immediate release to immediate release; sustained release to sustained release) the side effect profiles are similar; 3) immediate release forms of the overactive bladder drugs induce more anti-cholinergic side effects than the sustained release forms; 4) the new agents, solifenacin and darifenacin, and trospium have an increased rate of constipation compared to oxybutynin sustained release and tolterodine sustained release; 5) oxybutynin is the only product which is approved for use in children at this time; 6) MHS persistence rates with all drugs in this class are very low, ranging between 16% and 55% at the end of a one year evaluation period; 7) DoD providers were most comfortable prescribing oxybutynin and tolterodine and had little experience with the newer agents.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) that for the purposes of the UF clinical review, all the drugs reviewed for OAB were similar in terms of effectiveness and clinical outcome.

B. OAB UF Relative Cost Effectiveness:

The P&T Committee evaluated the relative cost-effectiveness of the OAB agents in relation to safety, tolerability, effectiveness, 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).

To determine the relative cost effectiveness of the OAB agents, two separate economic analyses were performed, a pharmacoeconomic analysis and budget impact analysis (BIA). From the preceding evidence-based relative clinical effectiveness evaluation, the P&T Committee concluded that, when comparing immediate release agents to immediate release agents and sustained release agents to sustained release agents, there was insufficient evidence to suggest that the OAB agents differed in regards to efficacy, safety, and tolerability in the treatment of OAB. Normally, such a conclusion would suggest cost-minimization to be the appropriate pharmacoeconomic analysis, however, in this case, to account for the differences in relative clinical effectiveness between the immediate release and sustained release agents in this therapeutic class, a cost-effectiveness analyses (CEA) was used. This was done based on the results of a sample based retrospective cohort database analysis. In a CEA, the agents within a therapeutic class are competed on two dimensions, cost and effect (outcomes).

A one-year sample-based retrospective cohort database analysis was performed on DoD MHS prescription data. The study population was comprised of DoD patients filling prescriptions for oxybutynin immediate release, oxybutynin sustained release, oxybutynin patch, tolterodine immediate release, tolterodine sustained release, and trospium between 01 July 2004 and 30 September 2005. Patients taking any OAB agent, in the 6 month period prior of their observed period of enrollment, were excluded to capture new users only. Note, darifenacin and solifenacin were not included in the study since these agents are new and lacked a year's worth of utilization data. The drug cost used in the analysis was the point of service adjusted total weighted average cost per day of treatment (for all three points of service) and the outcome of interest was adherence to treatment, where adherence to treatment was measured by total days of treatment. Theoretically, adherence to treatment is a surrogate indicator of efficacy, safety, and tolerability. In other words, a patient is more inclined to adhere to treatment if the agent works (efficacy) and is tolerated to the extent that the benefits of treatment outweighs the risk of side effects (tolerability and/or safety).

The results from the sample-based retrospective cohort database analysis were incorporated into a CEA. The cost used in the analysis for each agent was the mean cost of treatment for one year and the effect/outcome was the mean days of treatment for one year. Overall, the results of the CEA were as follows:

- Overall, oxybutynin immediate release was determined to be the most cost-effective agent and tolterodine sustained release was determined to be significantly more costly and effective along the efficiency frontier.
- Among the multi-dosed immediate release agents, oxybutynin immediate release was determined to be the most cost-effective agent; tolterodine immediate release was determined to be slightly more effective but significantly more costly (> 15-fold) compared to oxybutynin immediate release; and trospium immediate release was determined to be slightly less effective and significantly more costly (> 15-fold) compared to oxybutynin immediate release
- Among the once daily extended release agents, tolterodine sustained release was determined to be the most cost-effective agent; oxybutynin patch and sustained release tablet were dominated (more costly and less effective) compared to tolterodine sustained release.

Although the evidence-based relative clinical effectiveness evaluation determined that there was insufficient evidence to suggest that the OAB agents differed in regards to efficacy, safety, and tolerability in the treatment of OAB, this CEA based on a sample-based retrospective cohort database analysis suggests that differences do exist among the agents in regards to adherence to treatment.

Since darifenacin and solifenacin lacked sufficient utilization data to be included in the CEA analysis, the agents were evaluated on their point of service adjusted total weighted average cost per day of treatment only. The manufacturers of darifenacin and solifenacin submitted highly competitive prices for their respective agents, which made them significantly less costly compared to the most cost-effective single-dosed extended release agent, tolterodine sustained release. For purposes of this evaluation, the DoD P&T Committee assumed that darifenacin and solifenacin would have similar relative clinical effectiveness compared to tolterodine sustained release, based upon the conclusion of the overall relative clinical effectiveness presentation.

The results of the CEAs were subsequently incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of OAB agent's best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. Based on the BIA results and other clinical and cost considerations (oxybutynin sustained release is projected to go generic in 2006), the Committee agreed that a group of OAB agents that included: darifenacin, oxybutynin immediate release, oxybutynin sustained release, solifenacin, and tolterodine sustained release best achieved this goal when compared to other combination groups of OAB agents, and thus were determined to be more cost-effective relative to other combination groups.

*Conclusion**:*** The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 2 abstention, 1 absent) to accept the OAB pharmacoeconomic analyses presented by the PEC. The P&T Committee concluded that: tolterodine immediate release, oxybutynin patch, and trospium were not cost-effective relative to the other OAB agents. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the OAB agents, and other relevant factors, the P&T Committee recommended that tolterodine immediate release, oxybutynin patch, and trospium be classified as non-formulary under the UF and that darifenacin, oxybutynin immediate release, oxybutynin sustained release, solifenacin, and tolterodine sustained release be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstention, 3 absent) to recommend that tolterodine immediate release, oxybutynin patch, and trospium be classified as non-formulary under the UF, with darifenacin, oxybutynin immediate release, oxybutynin sustained release, solifenacin, and tolterodine sustained release remaining on the UF. In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, 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).

C. OAB Drug UF Medical Necessity Criteria: Based on the clinical evaluation of overactive bladder drugs, 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 medical necessity criteria for these agents.

1) Use of the formulary overactive bladder drugs (oxybutynin immediate release, oxybutynin sustained release, tolterodine sustained release, solifenacin and darifenacin) are contraindicated, and the use of tolterodine immediate release, trospium, or oxybutynin patch is not contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from the formulary overactive bladder drugs (oxybutynin immediate release, oxybutynin sustained release, tolterodine sustained release, solifenacin and darifenacin) and the patient is expected to tolerate tolterodine immediate release, trospium, or oxybutynin patch.

3) Use of the formulary overactive bladder drugs (oxybutynin immediate release, oxybutynin sustained release, tolterodine sustained release, solifenacin and darifenacin) resulted in

therapeutic failure, and the patient is expected to respond to tolterodine immediate release, trospium, or oxybutynin patch (therapeutic failure as outlined on medical necessity form).

4) The patient has previously responded to the oxybutynin patch, and changing to the formulary overactive bladder drugs (oxybutynin immediate release, oxybutynin sustained release, tolterodine sustained release, solifenacin and darifenacin) would incur unacceptable risk. The Committee agreed that this criterion could apply because of the potentially lower risk of CNS effects with the oxybutynin patch.

5) There is no alternative formulary agent: The Committee agreed that this criterion could apply to the oxybutynin patch if the patient could not take oral medications.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to approve the medical necessity criteria.

D. OAB Drug UF Implementation Plan: Because of the low number of beneficiaries who would be affected by this formulary action (19,118 patients known to be taking tolterodine immediate release, trospium, or oxybutynin patch across the MHS), the P&T Committee recommended an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have tolterodine immediate release, trospium, or oxybutynin patch on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) medical necessity is established. MTFs may (but are not required to) fill a prescription for tolterodine immediate release, trospium, or oxybutynin patch written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee recommended (13 for, 2 opposed, 1 abstained, 2 absent) an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

E. OAB Drug Basic Core Formulary (BCF) Review and Recommendations. The P&T Committee had previously determined that at least one but no more that two overactive bladder drugs would be added to the BCF based on the clinical and cost effectiveness reviews. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that oxybutynin immediate release and tolterodine sustained release be added to the BCF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to include oxybutynin immediate release and tolterodine sustained release on the BCF.

7. MISCELLANEOUS ANTIHYPERTENSIVE AGENTS DRUG CLASS REVIEW

A. Miscellaneous Antihypertensive Agents UF Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the miscellaneous antihypertensive agents marketed in the United States. The drugs in the class included the angiotensin converting enzyme (ACE) inhibitor/calcium channel blocker (CCB) combinations amlodipine/ benazepril (Lotrel), felodipine/enalapril (Lexxel), and verapamil sustained release/trandolapril (Tarka); the direct acting vasodilators (hydralazine, minoxidil); the centrally acting alpha-2 agonists (clonidine, methyldopa, guanabenz, guanfacine); the peripheral alpha-1 antagonists

(prazosin); the adrenergic antagonists (reserpine, guanadrel, guanethidine); and the ganglionic blockers (mecamylamine). Information regarding the safety, effectiveness, clinical outcomes, and patient persistence rates of the ACE inhibitor/CCB combinations (ACE/CCB combos) was considered in depth. For the other miscellaneous antihypertensive agents, the Committee considered the place in therapy of the drugs in national hypertension guidelines, significant usage for conditions other than hypertension, existing MHS utilization, and adverse effect profiles. The clinical review included, but was not limited to, the requirements stated in the UF Rule.

1) *ACE inhibitor/CCB combinations:* The relative clinical effectiveness of the individual ACE inhibitors and calcium channel blockers was reviewed previously by the Committee. Refer to the minutes from the August 2005 P&T Committee meeting for the relative clinical effectiveness conclusion for these two drug classes.

   a) Pharmacology: Both amlodipine/benazepril and felodipine/enalapril contain a dihydropyridine (DHP) CCB. The verapamil component of verapamil sustained release /trandolapril is a non-dihyropyridine CCB. Verapamil reduces myocardial contractility and slows conduction through the atrioventricular node. The physiologic effect of slowed heart rate with the non-DHP CCBs is frequently used as a beneficial effect in patients with increased heart rate (e.g. atrial fibrillation). The DHPs do not slow cardiac conduction, but have peripheral vasodilatory effects. The individual ACE inhibitor components of the combo products (benazepril, enalapril, trandolapril) exhibit similar pharmacologic properties.

   The benefits of combining an ACE inhibitor with a CCB include additive blood pressure (BP) lowering effect due to differing mechanisms of action, attenuation of CCB-induced edema through addition of the ACE inhibitor, patient convenience due to simplified drug regimens, decreased pill burden, and potentially improved adherence with antihypertensive therapy.

   b) Efficacy for Hypertension:

   Place in Therapy: The three ACE/CCB combinations are all approved for the treatment of mild to moderate hypertension. The Joint National Commission VII (JNC VII) guidelines acknowledge that combination antihypertensive therapy may be necessary, and is likely to be used as first-line treatment of hypertension. The guidelines recommend use of a combination regimen, which should usually include a diuretic, as first-line therapy for stage 2 hypertension (BP $\geq$160/100 mm Hg), or for patients with compelling indications. Compelling indications for use of an ACE inhibitor include heart failure, post-myocardial infarction, high risk of coronary artery disease, diabetes, chronic kidney disease, or previous stroke; compelling indications for use of a CCB include diabetes and patients with high risk of coronary artery disease.

   Efficacy for lowering BP: All three products have clinical trial data showing enhanced efficacy when the combination product is compared to the single components administered individually. Data from the individual package inserts was used to compare BP lowering effects. Amlodipine/benazepril reduces systolic blood pressure (SBP) by 10-25 mmHg and diastolic blood pressure (DBP) by 6-13 mmHg, felodipine/enalapril reduces SBP by 14.2 mmHg and DBP by 12.6 mmHg, and verapamil/trandolapril reduces SBP by 13-22 mmHg, and DBP by 8-17 mmHg.

Effects in sub- populations of patients with hypertension: There are no published trials of felodipine/enalapril (Lexxel) in sub-populations of patients with hypertension. Both amlodipine/benazepril and verapamil sustained release /trandolapril have several published trials supporting efficacy in patients with type 2 diabetes, patients with moderate to severe hypertension, and African Americans. Direct comparisons of BP lowering effects in the sub-populations are difficult, due to differences in study design.

Effect on proteinuria: The verapamil CCB component of verapamil sustained release/ trandolapril physiologically decreases resistance of the afferent renal arteriole, which reduces glomerular pressure and proteinuria. DHP CCBs do not have this effect on the afferent arteriole. Evidence from one large clinical trial showed that a combination of verapamil with trandolapril over a 3 year period prolonged the time to onset of microalbuminuria in patients with type-2 diabetes and hypertension.

Cardiovascular Outcomes: There are no published trials with felodipine/enalapril showing a benefit of the drug in reducing cardiovascular outcomes. There are no completed trials with amlodipine/benazepril assessing cardiovascular outcomes; two ongoing trials are assessing cardiovascular mortality/morbidity (ACCOMPLISH trial) and progression to overt nephropathy (GUARD). There are no published trials assessing the efficacy of the specific Tarka formulation at reducing cardiovascular outcomes. Although a regimen comprised of verapamil sustained release and trandolapril used as add-on therapy showed a reduction in all-cause death, non-fatal myocardial infarction, and non-fatal stroke (INVEST trial), this open label trial did not show a difference in outcomes between a regimen of CCB and ACE inhibitor vs. beta blocker and diuretic. The INVEST trial did not randomize patients prospectively to the combination, thus cannot be used to support efficacy of the specific Tarka formulation in reducing cardiovascular outcomes.

Clinical Efficacy Conclusion: The Committee concluded that there is insufficient evidence to suggest that the BP lowering effects of the ACE/CCB combos differ significantly. The formulations of amlodipine/benazepril and verapamil sustained release/trandolapril have shown efficacy in treating sub-populations of patients with hypertension; there is no data with Lexxel. Clinical trials assessing cardiovascular outcomes with the combination products Lexxel, amlodipine/benazepril and verapamil sustained release/trandolapril have not been conducted, but there is some evidence of benefit with the individual components.

c) Safety and Tolerability:

Serious Adverse Effects: Verapamil sustained release/trandolapril is contraindicated for use in patients with impaired cardiac contractility (e.g. severe left ventricular dysfunction, SBP < 90 mm Hg), due to the verapamil component. All three ACE/CCB combos are contraindicated for use in patients with a history of angioedema to any ACE inhibitor.

Common Adverse Effects: The safety profiles of the ACE/CCB combos are reflected by their individual CCB components. The products containing a DHP CCB (amlodipine/benazepril and felodipine/enalapril) commonly causes edema and headache, while the non-DHP CCB (verapamil sustained release/trandolapril) more commonly causes dyspnea, fatigue, and constipation. Comparison of the product labeling between amlodipine/benazepril and felodipine/enalapril do not suggest major differences in the incidence of edema, headache, or dizziness.

Discontinuations due to Adverse Effects: Pooled data from clinical trials was used to compare the products in terms of the percentage of patients discontinuing therapy due to

adverse events. For felodipine/enalapril, 2.8% of patients discontinued treatment vs. 1.3% with placebo, most commonly due to headache. The percentage of patients discontinuing therapy with amlodipine/benazepril was 4%, vs. 3% with placebo, most commonly due to edema. The discontinuation rate with verapamil sustained release/trandolapril was 2.6% vs. 1.9% with placebo, most commonly due to dyspnea and fatigue.

Safety and Tolerability Conclusion: The DoD P&T Committee concluded that the discontinuation rate due to adverse events appears similar between the three ACE/CCB combos, based on pooled analysis from placebo controlled trials. The non-DHP component of verapamil sustained release/trandolapril imparts unique risks of impaired cardiac contractility. There is no evidence that amlodipine/benazepril and felodipine/enalapril differ markedly in adverse event profiles.

d) Other Factors - Adherence/Persistence with antihypertensive therapy: For the purposes of this review, the measure used to define persistence is the medication possession ratio, which is calculated based on the daily possession of drugs. There are no published trials with felodipine/enalapril or verapamil sustained release/trandolapril showing improved rates of patient persistence. Data from two studies (one published, the other in abstract form) using pharmacy claims databases reported medication possession ratios ranging from 81%-88% with patients continuously refilling prescriptions for amlodipine/benazepril, compared to 69%-73.8% for regimens containing an ACE inhibitor and CCB administered as separate components.

Conclusion for Other Factors (Adherence/Persistence): Two database claims studies suggest that patient persistence with amlodipine/benazepril is improved by 7%-22%, compared to regimens containing an ACE inhibitor and CCB administered as separate components.

2) *Other Miscellaneous Antihypertensive Agents:* The Committee evaluated the other miscellaneous antihypertensive agents by considering the place in therapy of the drugs in national hypertension guidelines, significant usage for conditions other than hypertension, existing MHS utilization, and adverse effect profiles. The Committee also specifically evaluated the relative clinical effectiveness of clonidine tablets vs. clonidine patch.

a) Clonidine oral tablets vs. Clonidine transdermal patches: The JNC VII guidelines recommend clonidine as a second or third line choice for treating hypertension, due to adverse effects. Clonidine is frequently used for off-label indications, including treatment of menopausal symptoms, smoking cessation, pediatric behavioral problems, and alcohol or opiate withdrawal symptoms. Clonidine tablets require twice daily to three times a day dosing, and there is a high risk of rebound hypertension, if the tablets are abruptly discontinued. The clonidine patches are changed weekly and are associated with a lower risk of rebound hypertension, since plasma levels of drug slowly decline over a one-week period when the patch is removed. Other benefits of transdermal clonidine include that it is frequently used in patients with swallowing difficulties (e.g. stroke patients), its use can potentially improve compliance in patients requiring several drugs for BP control, and that its use can simplify the medication regimen in patients requiring several antihypertensive drugs. In the entire MHS, approximately 20,000 prescriptions for clonidine tablets are dispensed monthly, compared to 5,000 prescriptions for clonidine patches.

b) Remaining miscellaneous antihypertensive agents in the class: The remaining miscellaneous antihypertensive drugs in the class include hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, prazosin, reserpine, guanadrel, guanethidine, and

mecamylamine. All of these drugs are available in generic formulations and some no longer have marketed proprietary formulations (e.g. reserpine, guanethidine). Utilization of these drugs in the MHS is low (<5,000 prescriptions dispensed in fiscal year 2005), with the exception of hydralazine (40,000 Rxs), prazosin (22,000 Rxs), methyldopa (13,000 Rxs), and minoxidil (12,000 Rxs). Some of these products have been available for several decades; including reserpine, mecamylamine, hydralazine, methyldopa, and guanethidine, thus rigorously conducted clinical trials are not available.

Place in therapy: JNC VII guidelines support use of methyldopa, hydralazine, minoxidil, reserpine, and guanfacine as antihypertensive drugs, although clinical use is often limited due to tolerability issues. Methyldopa is commonly used for treating hypertension in pregnant patients, due to long-term studies supporting its safety. Hydralazine also has a role in treating symptoms of heart failure in patients who are intolerant of or who have contraindications to use of ACE inhibitors. Guanfacine is also utilized in the setting of pediatric patients with behavioral problems. Guanabenz is rarely used clinically (<500 Rxs dispensed in the MHS in fiscal year 2005), as it requires twice daily dosing and has bothersome side effects. Minoxidil is an option for patients with stage 2 hypertension (SBP 160-179 / DBP 100-109 mm Hg) who have not responded to conventional antihypertensive drug regimens. Reserpine has evidence from randomized controlled trials that it reduces cardiovascular mortality and morbidity (VA trials, SHEP trials). Use of prazosin as an antihypertensive agent has fallen into disfavor, based on the results of the ALLHAT trial that showed an increased risk of development of heart failure in patients receiving the alpha blocker doxasozin. Guanadrel, guanethdine, and mecamylamine are rarely used today.

Adverse Effects: The use of the other miscellaneous antihypertensive agents has largely been replaced by other drugs (e.g. ACE inhibitors, diuretics, CCBs, angiotensin receptor blockers, beta blockers) due to their side effect profiles. Hydralazine may cause drug-induced systemic lupus erythematosus. Minoxidil can cause hypertrichosis; and fluid retention and reflux tachycardia are frequent problematic effects. Common adverse effects of methyldopa, guanabenz and guanfacine include fluid retention, sedation, lethargy, postural hypotension, dizziness, dry mouth and headache. First-dose syncope is a risk with prazosin and other alpha blockers. Clinical use of reserpine is limited due to nasal stuffiness and the perception of increased risk of depression. Orthostatic hypotension is an issue with guanadrel and guanethidine, as is diarrhea, and sexual dysfunction. Postural hypotension is a limiting side effect of mecamlyamine. Other effects of mecamylamine due to its ganglionic blockading properties include tachycardia, mydriasis, paralytic ileus, syncope, and urinary retention.

COMMITTEE RECOMMENDATION: *Overall clinical effectiveness conclusion for the miscellaneous antihypertensive agents:* The Committee concluded that: (1) for lowering blood pressure, there is no evidence that any one ACE/CCB combo is more effective relative to another; (2) there is more evidence to support the use of amlodipine/benazepril and verapamil sustained release/trandolapril in sub-populations of patients with hypertension than felodipine/ enalapril; (3) there is insufficient evidence to conclude that any one ACE/CCB combo is superior to another for reducing risk of cardiovascular outcomes in patients with hypertension; (4); the safety/tolerability profiles of the ACE/CCB combos are primarily dictated by the CCB component; (5) there is no evidence to suggest that amlodipine/benazepril or felodipine/ enalapril would be superior to the other in terms of safety/tolerability. Verapamil sustained release/trandolapril has unique safety issues, due to the verapamil component; (6) persistence rates with amlodipine/benazepril may be improved by 7%-22% compared to the individual

agents administered together; (7) transdermal clonidine is not a candidate for non-formulary designation on the UF due to its unique niche in several patient sub-groups and lower risk of rebound hypertension upon drug discontinuation; (8) Use of the remaining miscellaneous antihypertensive drugs is limited by bothersome tolerability profiles, however, several drugs maintain unique roles for treating hypertension and non-cardiovascular conditions.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 1 absent; 1 abstain) to accept the clinical effectiveness conclusion as stated above.

B. Miscellaneous Antihypertensives UF Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the miscellaneous antihypertensive agents in relation to safety, tolerability, effectiveness, 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).

As with the relative clinical effectiveness evaluation, the primary focus of the relative cost-effectiveness presentation was limited to the combination antihypertensives (amlodipine/benazepril, felodipine/enalapril, verapamil/trandolapril) and clonidine patches. The DoD P&T Committee concluded that the other agents listed in the class, as previously described, should be maintained on the UF given their generic availability, low utilization, and low cost.

To determine the relative cost effectiveness of the miscellaneous antihypertensive agents, two separate economic analyses were performed, a pharmacoeconomic analysis and BIA.

A cost analysis was performed to compare clonidine patches and clonidine tablets. The comparison of cost was based on the point-of-service adjusted total weighted average cost per day of treatment. As expected, the results of the cost-analysis revealed that clonidine patches were significantly more costly compared to clonidine tablets.

Two different types of pharmacoeconomic analysis could have been performed to determine the cost-effectiveness of the combination antihypertensive agents within this therapeutic class. One alternative was to use cost-minimization to compare the combination antihypertensives to their respective agents given separately solely based on cost. However, this alternative would have neglected to account for the primary potential benefit of combination products, improved patient compliance with medication therapy. Therefore, to account for the potential differences in relative clinical effectiveness, a CEA was performed based on the results of three observational studies examining compliance with combination antihypertensives.

The observational studies included two studies that examined compliance with the combination product amlodipine/benazepril and another study that examined compliance with combination ACE/hydrochlorothiazide (HCTZ) products (enalapril/HCTZ and lisinopril/HCTZ). These studies revealed increased compliance ranging from 7% to 20% with the combination antihypertensives compared to the respective agents given separately. For purposes of the CEA, the increased compliance associated with combination antihypertensive products was assumed to be 10%. To determine the relative cost-effectiveness of the combination products, two simple cost-effectiveness decision models were constructed, one comparing the DHP/ACE combination products (amlodipine/benazepril and felodipine/enalapril) to their respective agents given separately and another comparing the verapamil/ACE combination product (verapamil/trandolapril) to its respective agents given separately. The cost used in the model was the total cost of drug treatment for one-year. The outcome/effect was ‘days of treatment.’

Theoretically, 'days of treatment' is a surrogate indicator of compliance. Likewise, compliance with drug therapy theoretically results in overall improved blood pressure control.

The results from the CEAs are as follows:

- DHP/ACE combination
    - The two agents given separately were more cost-effective compared to Lexxel (felodipine/enalapril) and Lotrel (amlodipine/benazepril). However, the incremental cost-effectiveness ratio was relatively low, indicating that the combination products may be a cost-effective alternative therapy.
- Verapamil/ACE combination
    - The two agents given separately were more cost-effective compared to Tarka (verapamil/trandolapril). For this comparison, the incremental cost-effectiveness ratio was relatively high, indicating that the combination product is not a cost-effective alternative therapy.

The results of the CEAs were subsequently incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of miscellaneous antihypertensive best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. Based on the BIA results and other clinical and cost considerations, the Committee agreed that a group of miscellaneous antihypertensive agents that included: clonidine patches and amlodipine/ benazepril best achieved this goal when compared to other combination groups of miscellaneous antihypertensive agents, and thus were determined to be more cost-effective relative to other combination groups.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 1 abstention, 1 absent) to accept the miscellaneous antihypertensive cost-analysis presented by the PEC. The P&T Committee concluded that felodipine/enalapril and verapamil/trandolapril were not cost-effective relative to the other miscellaneous antihypertensive agents. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the miscellaneous antihypertensive agents, and other relevant factors, the P&T Committee recommended that felodipine/enalapril and verapamil/trandolapril be classified as non-formulary under the UF. The P&T Committee also recommended that clonidine tablets, clonidine patches, amlodipine/ benazepril, hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted 11 for, 4 opposed, 2 abstention, 1 absent) to recommend that felodipine/ enalapril and verapamil/trandolapril be classified as non-formulary under the UF, with clonidine tablets, clonidine patches, amlodipine/benazepril, hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine remaining on the UF.

C. Miscellaneous antihypertensive agents Medical Necessity Criteria. The P&T Committee concluded that because the only miscellaneous antihypertensive agents classified as non-formulary under the UF are the combination agents felodipine/enalapril and verapamil/

trandolapril, and because the individual components of both of these agents are available separately on the UF, only two of the five general medical necessity criteria could potentially apply. Therefore, based on the clinical evaluation of felodipine/enalapril and verapamil/ trandolapril and conditions for establishing medical necessity for a non-formulary medication provided in the UF rule, the following medical necessity criteria may apply:

1) Use of a formulary pharmaceutical agent is contraindicated, and the use of a non-formulary agent is not contraindicated.

2) The patient previously responded to the non-formulary pharmaceutical agent and changing to a formulary pharmaceutical agent would incur an unacceptable clinical risk.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to accept the miscellaneous medical necessity criteria.

D. Miscellaneous Antihypertensive Agents UF Implementation Period: The Committee recommended an effective date no later than the first Wednesday following a 60-day implementation.

COMMITTEE ACTION: The DoD P&T Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to recommend an implementation period of 60 days.

E. Miscellaneous Antihypertensive Agents Basic Core Formulary (BCF) Review and Recommendations. The P&T Committee had previously determined that at least one but no more that two miscellaneous antihypertensive agents would be added to the BCF based on the clinical and cost effectiveness reviews. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that amlodipine/benazepril, hydralazine and clonidine tablets be added to the BCF.

Conclusion: Lotrel (amlodipine /benazepril), hydralazine and clonidine tablets were recommended for inclusion on the BCF.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) to include Lotrel (amlodipine /benazepril), hydralazine and clonidine tablets on the BCF

8. GAMMA-AMINOBUTYRIC ACID (GABA)-ANALOG DRUG CLASS REVIEW

A. GABA-Analogs Relative Clinical Effectiveness: The DoD P&T Committee evaluated the relative clinical effectiveness of the GABA-analogs marketed in the US: gabapentin (Neurontin and various generics), pregabalin (Lyrica), and tiagabine (Gabitril). Information regarding the safety, effectiveness, and clinical outcome of these drugs was considered. Although gabapentin, pregabalin, and tiagabine are all FDA indicated as adjunctive therapy (added to other antiepileptic drugs) in the treatment of partial seizures, the Committee's review focused primarily on the use of these agents for the treatment of various types of neuropathic pain. The clinical review included, but was not limited to the requirements stated in the UF Rule, 32 CFR 199.21.

1) Efficacy

a) Endpoints: The primary efficacy measure used in the clinical trials was pain experienced by the patients during the previous 24 hours, rated on an 11-point numerical scale (0= no pain; 10= worst possible pain). The primary efficacy parameter was the change in the mean daily pain

score from baseline to the study end; the proportion of patients responding to therapy was a secondary outcome. A >50% reduction in mean pain scores between baseline and study end are considered relevant. Numbers needed to treat (NNT), defined as the number of patients needed to be treated with the drug to result in one patient obtaining a >50% reduction in mean pain score, were then calculated to give a measure of the effect size.

b) Efficacy of GABA analogs for treatment of pain associated with diabetic peripheral neuropathy (DPN):

Place in Therapy: Guidelines from the American Diabetes Association recommend gabapentin and pregabalin and other therapies as initial therapy for the treatment of pain associated with DPN. There is no preference stated for gabapentin or pregabalin in the guidelines. The guidelines do not mention tiagabine.

Clinical Trials for DPN-related pain: There are no head-to-head clinical trials comparing pregabalin with gabapentin for DPN-related pain, and there are no clinical trials evaluating efficacy of tiagabine for this condition. The Committee reviewed the following trials evaluating the use of the GABA-analogs in DPN: one comparative trial of gabapentin vs. amitriptyline; one active controlled trial of pregabalin and amitriptyline vs. placebo; a Cochrane review of four placebo controlled trials with gabapentin; and three placebo controlled trials with pregabalin.

In the comparative trial of gabapentin (900-1800 mg/day) vs. amitriptyline (25-75 mg/day), both treatments resulted in significant reductions in mean pain score from baseline; there was no difference between the two drugs at study endpoint. This trial was limited by small patient enrollment (N=28). In the active controlled trial of pregabalin (600 mg/day) and amitriptyline (75mg/day) vs. placebo, pregabalin did not differ from placebo in the change in mean pain score from baseline or in the proportion of patients achieving at least a 50% decrease in mean pain score at endpoint. These endpoints reached statistical significance when amitriptyline was compared to placebo. Direct comparisons of the efficacy of pregabalin vs. amitriptyline were not conducted in the trial. Overall, treatment with pregabalin 600 mg/d (200 mg three times a day) was no more effective than placebo in the treatment of DPN-related pain in this study.

A Cochrane review of four placebo controlled trials enrolling 281 patients that evaluated the efficacy of gabapentin for DPN pain favored gabapentin [relative risk 2.21 (95% confidence interval 1.65, 2.96)]. The gabapentin doses ranged from 900-3600 mg/day. Overall, 64% of patients improved with gabapentin compared to 28% with placebo. The combined NNT for effectiveness of gabapentin in DPN compared to placebo was 2.9.

The results of the three double-blinded, placebo controlled trials evaluating pregabalin in DPN were reported to the Committee. In two of the three trials, patients were excluded if they had not previously responded to gabapentin doses >1200 mg/day. Pregabalin in doses of 100 mg three times a day (300 mg/day) and 200 mg three times a day (600 mg/day) resulted in statistically significant improvements in the mean pain score at endpoint and in the proportion of patients obtaining at least a 50% reduction in pain score from baseline compared to placebo. The mean pain score at endpoint was 1.26 to 1.45 points lower with pregabalin (300 mg/day and 600 mg/day doses, respectively) than placebo. The percentage of patients responding to pregabalin 300 mg/day ranged from 40% to 46%; the percentage of responders to pregabalin 600 mg/day ranged from 39% to 48%, while the placebo responder rate was 15%. Although 600 mg/day was evaluated in these trials, the product labeling for pregabalin does not recommend doses above 300 mg/day for DPN, as doses of 600 mg/day do not provide greater

benefit. The NNT with pregabalin to achieve a 50% reduction in mean pain score at endpoint ranged from 3.4 to 4.0 for the three studies.

DPN Conclusion: Based on the primary efficacy measures of change in mean pain score at baseline, the percentage of patients responding to therapy, and the NNT, the Committee concluded that there is no evidence to suggest that gabapentin or pregabalin is superior to the other in treating pain associated with DPN, when the individual results from the placebo controlled trials are compared. There are no trials evaluating efficacy of tiagabine in pain due to DPN.

c) Efficacy of GABA analogs for treatment of pain associated with post-herpetic neuralgia (PHN):

Place in therapy: Practice guidelines endorsed by the American Academy of Neurology for the treatment of pain in patients with PHN give a Level A, class I recommendation (strongest evidence for efficacy) to gabapentin and pregabalin. First-line options for the treatment of PHN included gabapentin, pregabalin, lidocaine patch, tricyclic antidepressants and controlled release morphine or oxycodone. The guideline does not give a preference to either pregabalin or gabapentin for the treatment of PHN-related pain, and does not mention tiagabine.

Clinical Trials for PHN pain: There are no head to head clinical trials comparing pregabalin with gabapentin for treatment of pain in patients with PHN. There are no trials evaluating efficacy of tiagabine for PHN-related pain. The Committee evaluated two placebo controlled trials with gabapentin, and three placebo controlled trials with pregabalin for this pain syndrome.

Two double-blind placebo controlled trials compared gabapentin vs. placebo for the treatment of pain associated with PHN. Gabapentin doses ranging from 600 mg three times a day to 900 mg three times a day were evaluated in the two trials. In both trials, patients receiving gabapentin had a statistically significant reduction in mean daily pain score at study end, compared to placebo. The mean pain score at endpoint was 2.1 points lower with gabapentin (all doses) than placebo. In the first trial, 43% of patients receiving gabapentin 900 mg three times a day rated their pain as much improved vs. 12.1% with placebo. In the second trial, the responder rate was 14% with placebo, 32% with gabapentin 600 mg three times a day and 34% with gabapentin 800 mg three times a day.

A Cochrane review of the two placebo controlled trials discussed earlier (enrolling 563 patients) that evaluated the efficacy of gabapentin for PHN pain favored gabapentin [relative risk 2.50 (95% confidence interval 1.80, 3.48)]. Overall, 43% of patients improved with gabapentin compared to 17% with placebo. The combined NNT from these two studies for effectiveness compared to placebo was 2.9.

Three double-blind placebo controlled trials evaluated pregabalin for the treatment of pain associated with PHN. In two of the three trials, patients were excluded if they had not previously responded to gabapentin doses >1200 mg/day. Twice a day dosing of pregabalin was used in one trial, while a three times a day regimen was used in the remaining two trials; doses ranged from 150 mg/day to 600mg/day. All pregabalin doses resulted in significant reductions in mean pain scores compared to placebo. The mean pain score at endpoint was 0.88 to 1.79 points lower with pregabalin (all doses) than placebo. The percentage of patients responding to pregabalin 150 mg/day ranged from 26% to 27%, the percentage of responders to pregabalin 300 mg/day ranged from 27% to 28%, the percentage of responders to pregabalin 600 mg/day ranged from 38% to50%, while the placebo responder rate ranged from 8% to 10%.

The NNT with pregabalin to achieve a 50% reduction in mean pain score at endpoint ranged from 3.3 to 6.3 in the three studies, depending on the dose of pregabalin.

PHN Conclusion: Based on the primary efficacy measures of change in mean pain score at baseline, the percentage of patients responding to therapy, and the NNTs, the Committee concluded that there is no evidence to suggest that gabapentin or pregabalin is superior to the other in treating pain associated with PHN, when the individual results from the placebo controlled trials are compared. There are no trials evaluating efficacy of tiagabine in pain due to PHN.

d) Efficacy of GABA analogs for other neuropathic pain syndromes:

Clinical Trials: The P&T Committee evaluated two trials assessing the efficacy of gabapentin, and one trial assessing the efficacy of tiagabine in other types of neuropathic pain syndromes. Gabapentin was evaluated in doses up to 2.4 g/day in 305 patients with a variety of different types of neuropathic pain syndromes, including complex regional pain syndrome, PHN, radiculopathy, and post laminectomy. The authors reported there was an overall significant difference in mean pain score favoring gabapentin over placebo, however there was no significant difference between gabapentin and placebo at weeks 7 and 8 (the differences at weeks 1,3,5,6 were significant). When gabapentin was compared to placebo in 19 patients with post-amputation limb pain, gabapentin was significantly better than placebo at study endpoint. The effect of tiagabine in painful neuropathy was studied in a 4-week, open-label, non-placebo-controlled pilot trial in 17 adults. Overall pain indices tended to decline, but results did not reach statistical significance for tiagabine vs. placebo, given the high and dropout rate (only 8 patients completed the study).

Other Neuropathic Pain Syndromes Conclusions: The Committee concluded that gabapentin demonstrated modest clinical efficacy for other neuropathic pain syndromes, based on two placebo controlled trials. No conclusion can be made concerning the efficacy of tiagabine for neuropathic pain due to limited evidence (one poorly designed study and overall lack of trials evaluating the efficacy of tiagabine for neuropathic pain). Pregabalin has not been evaluated in other types of neuropathic pain syndromes.

e) Efficacy of GABA Analogs for Treatment of Partial Seizures:

Place in Therapy: A report endorsed by the American Academy of Neurology and the American Epilepsy Society assigned both gabapentin and tiagabine Level A recommendations (highest recommendation) as adjunctive therapy for partial seizures. There was no mention of pregabalin due to publication of the guideline prior to FDA approval.

Clinical Trials: Gabapentin, pregabalin, and tiagabine have all been evaluated in the adjunctive treatment of epilepsy in placebo controlled trials. There are no head to head trials comparing efficacy of one GABA-analog to another in seizure disorders. The results of one meta-analysis conducted with gabapentin and tiagabine, and three double-blinded placebo controlled trials with pregabalin support efficacy of all three agents in patients with epilepsy, based on the endpoint of 50% reduction in seizure frequency.

Partial Seizures Conclusions: The committee concluded that gabapentin, pregabalin, and tiagabine demonstrate clinical efficacy for adjunctive treatment of partial seizures. Since the GABA analogs are added onto regimens comprised of other antiepileptic drugs, there is no evidence to suggest clinical superiority of any GABA agent over another.

Overall efficacy conclusion: The Committee concluded that there is no evidence of superiority of either gabapentin or pregabalin for treatment of pain associated with DPN or PHN. Efficacy of gabapentin for other types of neuropathic pain syndromes appears modest, but there is no efficacy evidence for pregabalin in other types of neuropathic pain. There is insufficient evidence to make conclusions regarding the efficacy of tiagabine in DPN, PHN, or other types of neuropathic pain syndromes.

2) Safety and Tolerability: The Committee assessed the comparative safety and tolerability of gabapentin, pregabalin, and tiagabine including rare but serious adverse effects, common adverse effects, potential for drug interactions, and safety of use in special populations.

Serious Adverse Effects:
All three GABA analogs (gabapentin, pregabalin, and tiagabine) should be gradually tapered when therapy is discontinued, to minimize the potential for increased seizure frequency. Post-marketing reports have linked tiagabine with new onset seizures and status epilepticus in patients who did not have epilepsy. There are reports of sudden unexplained death in patients with epilepsy taking gabapentin or tiagabine, however, it is unknown whether the unexplained deaths were a direct result of gabapentin or tiagabine therapy. Tiagabine has been associated with cognitive/neuropsychiatric events such as impaired concentration, speech and language problems, confusion and fatigue. Pregabalin has been associated with creatine kinase elevations and three reports of rhabdomyolysis in premarketing clinical trials.

Common Adverse effects:
The most commonly reported side effects associated with gabapentin, pregabalin and tiagabine include dizziness, somnolence, and asthenia. These adverse effects appear to be dose related, and tend to decrease over time. Based on clinical trial experience, tiagabine appears more commonly associated with nervousness and tremor, while gabapentin and pregabalin are associated the weight gain, dizziness, somnolence and peripheral edema.

Due to differences in study design for the placebo controlled trials and the lack head to head trials, comparisons of adverse event rates between the GABA analogs are difficult. In general, clinical trials using flexible dosing regimens and slow titration schedules result in fewer patients dropping out of the trial and lower adverse event rates than trials incorporating fixed dosing regimens and quick titration schedules.

A comparison of the product labeling for all three GABA analogs lists the following adverse events, which have been placebo-adjusted. Peripheral edema: 8.3% with gabapentin, and 9% with pregabalin; an incidence is not provided in the tiagabine package insert. Dizziness: 28% with gabapentin, 21% with pregabalin, and 27% with tiagabine. Somnolence: 21.4% with gabapentin, 12% with pregabalin, and 12% with tiagabine.

Numbers needed to harm (NNH) is another way of measuring adverse events and for the purpose of this review was defined as any adverse effect leading to patient withdrawal from a study. NNH could be calculated for two of the trials assessing pain in PHN. For gabapentin, the NNH was 11.2; for pregabalin, the NNH was 3.7. Although the NNH is smaller with pregabalin, possibly indicating a less tolerable drug, the titration period with pregabalin was more rapid (over 1 week) compared to the gabapentin trial (over 4 weeks). A longer titration period may have led to a more favorable NNH in the gabapentin trial. When the NNHs were calculated from a clinical trial evaluating pregabalin for treatment of DPN and PHN in both fixed and flexible doses, the NNH was 10.7 with the flexible dosing regimen, and 5.8 with the fixed dosing regimen. The flexible dosing regimen incorporated a longer titration schedule than

with the fixed dose, which could possibly account for the more favorable NNH with the flexible dosing.

Drug Interactions:

Gabapentin and pregabalin are not metabolized by hepatic CYP450 enzymes, thus are not associated with significant drug interactions. Tiagabine is primarily metabolized by CYP450 and is highly protein bound, thus drug interactions have been reported with concomitant usage with other anticonvulsant drugs (carbamazepine, phenytoin, phenobarbital, primidone).

Special populations:
Renal Impairment: Gabapentin and pregabalin are both renally eliminated, and both drugs require dosage reductions with decreasing renal function. Reductions in gabapentin and pregabalin dosages may be required in patients who have age related compromised renal function.

Hepatic Impairment: Patients with impaired liver function may require reduced initial and maintenance doses of tiagabine or a longer dosing interval compared to patients with normal hepatic function.

Pregnancy: All three GABA analogs are rated as pregnancy category C, and should be used during pregnancy only if the potential benefit justifies the potential risk.

Overall Safety and Tolerability Conclusion: The Committee concluded withdrawal seizures occurring with sudden discontinuation of therapy have been reported with all three GABA analogs. Tiagabine is associated with serious adverse events, including neuropsychiatric and cognitive effects and development of seizures in patients who did not previously have epilepsy. Dizziness and somnolence are the most commonly reported adverse effects with pregabalin and gabapentin, while tremors and nervousness are more commonly reported with tiagabine. Indirect comparisons, based on NNH and the percentage of patients discontinuing therapy due to adverse effects, show only minor differences in tolerability between gabapentin and pregabalin. Tiagabine has a greater drug interaction potential compared to gabapentin and pregabalin, due to hepatic metabolism. Both gabapentin and pregabalin require dose adjustment in patients with renal dysfunction.

3) Other Factors:
FDA Approved indications: Gabapentin and pregabalin are both FDA-approved for treating pain associated with PHN. Pregabalin is the sole agent in the class approved for treating pain associated with DPN, however, controlled clinical trial data support the efficacy of gabapentin. Gabapentin, pregabalin, and tiagabine are all approved as adjunctive therapy in seizure disorders.

Controlled Substance Class: Pregabalin is the only GABA-analog that is a schedule V controlled substance. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms of insomnia, nausea, headache, or diarrhea, suggestive of dependence. Due to the schedule V status, no more than 5 refills can be obtained in a 6-month period.

Use in Pediatrics: Gabapentin is approved in for use as an anticonvulsant in patients as young as three years old. Tiagabine is approved for use in patients as young as 12 years old for treatment of epilepsy. Pregabalin has not been studied in pediatric patients.

Pharmacokinetics: Gabapentin exhibits non-linear pharmacokinetics; as the dose of gabapentin is increased, bioavailability decreases. In contrast, pregabalin exhibits linear pharmacokinetics, and the oral bioavailability of pregabalin is > 90% independent of dose. However, a linear dose response has not resulted in significantly improved pain relief with pregabalin administered at higher doses (600mg/d) vs. lower doses (300 mg/d). In fact, the manufacturer of pregabalin does not recommend greater than 300 mg/d for DPN because 600 mg/d pregabalin has not been proven to significantly improve pain scores compared to 300 mg/d, and greater than 600 mg/d for PHN.

Frequency of Dosing and Titration Schedules: Pregabalin can be dosed twice daily for treatment of pain associated with PHN, while gabapentin requires three times a day dosing. For pain associated with DPN, both pregabalin and gabapentin require three times a day dosing. Twice a day dosing of pregabalin in DPN-related pain is not recommended by the manufacturer, as twice daily dosing did not show significant differences in efficacy as compared to placebo in unpublished trials available from the FDA. The dosage initiation schedule for pregabalin is less complex and requires a shorter time period than the dosage titration recommended with gabapentin. Statistical improvements in mean pain score in clinical trials have occurred within 1-2 weeks of initiation of both gabapentin pregabalin therapy.

Provider Opinion: A survey of DoD providers ranked gabapentin first in terms of clinical efficacy for neuropathic pain, due to more personal clinical experience, compared to tiagabine and pregabalin. Pregabalin was ranked second in terms of clinical efficacy, primarily due to lack of clinical experience, but providers did prefer ease of titration and twice daily dosing in PHN. The majority of providers' therapeutic strategy would include a trial of gabapentin first, followed by pregabalin if therapy with gabapentin was not successful. Tiagabine was rarely used in neuropathic pain, and if chosen, it was preferred as adjunctive therapy to other treatments for neuropathic pain, not as an alternative to gabapentin or pregabalin. All three drugs (gabapentin, pregabalin, and tiagabine) were considered therapeutically interchangeable for use in patients with partial seizures.

Other Factors Conclusions: The Committee concluded that pregabalin is the only GABA-analog that has restrictions in prescribing due to its controlled status. The linear pharmacokinetic profile of pregabalin has not resulted in significant improvement in efficacy with higher doses. Pregabalin may potentially have improved patient compliance compared to gabapentin, due to an easier titration schedule and twice a day dosing in patients with PHN. However, three times a day dosing is recommended for pregabalin in patients with DPN. There is no published data evaluating the efficacy of pregabalin in pediatrics.

Overall Clinical Effectiveness Conclusion: The Committee concluded that (1) the efficacy of gabapentin and pregabalin for treating pain associated with either DPN or PHN appears similar; (2) gabapentin is the only GABA-analog that has shown modest efficacy in treating other types of neuropathic pain based on published clinical trials; (3) there is insufficient data regarding the efficacy of tiagabine in patients with neuropathic pain syndromes to make definitive conclusions; (4) there appear to be no major differences in the efficacy of gabapentin, pregabalin, or tiagabine for the use an adjunctive treatment of partial seizures; (5) the safety and tolerability profiles of gabapentin and pregabalin are more favorable compared to tiagabine; (6) there appear to be only minor differences in the tolerability profiles of gabapentin and pregabalin, when evaluating the incidence of somnolence, dizziness, and peripheral edema; (7) there are minor differences in other factors between the drugs, including use in pediatrics, pharmacokinetic profiles, titration schedules, onset of effect, and controlled substance status.

Overall the Committee agreed that based on clinical usefulness alone, there is no basis for classifying any of the GABA-analog as non-formulary.

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

B. Relative CEA: In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2). A CEA was used to determine the relative cost-effectiveness of agents within the GABA-analog therapeutic class. A Monte Carlo simulation was performed using data from three well designed randomized controlled trials of pregabalin and gabapentin in diabetic peripheral neuropathy and post-herpetic neuralgia. Flexible dose (average 378 mg) and fixed dose (600 mg) pregabalin were compared to daily gabapentin doses of 600, 900, 1200, 1800 and 2400 mg. Costs used in the model were the total weighted average cost per day of treatment across all points of service in the MHS. The principal outcome of interest was the mean reduction in weekly pain scores at the 12th week.

Results of the CEA showed gabapentin at doses of up to 2400 mg to be the most cost effective GABA-analog drug in the treatment of neuropathic pain with the lowest average cost per patient over twelve weeks of treatment, and no clinically significant differences in outcomes.

The results of the above analyses were then incorporated into a BIA, which accounted for other factors and costs associated with a potential decision regarding formulary status of GABA-analog drugs within the UF. These factors included: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and switch costs. The results of the BIA further confirmed the results of the CEA. Gabapentin was found to be the most cost-effective GABA-analog drug overall in the treatment of neuropathic pain.

Conclusion: The P&T Committee concluded that gabapentin was the more cost effective GABA-analog drug for the treatment of neuropathic pain. The cost-effectiveness of tiagabine was also considered, and it was determined that nothing would be gained clinically or economically by making tiagabine non-formulary.

COMMITTEE ACTION: The P&T Committee agreed (16 for, 0 opposed, 0 abstained, 2 absent) with the relative CEA of the GABA-analog drugs presented.

Based on the results of the two analyses, the P&T Committee concluded that pregabalin was much more costly, and had similar relative clinical effectiveness compared to gabapentin in both neuropathic pain and partial seizures. Tiagabine also had similar relative clinical effectiveness in partial seizures as compared to gabapentin and pregabalin. However, due to its low utilization, and small, static market share, it was felt that tiagabine contributed minimally to the amount spent in this drug class. Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the GABA-analog drugs, and other relevant factors, the P&T Committee recommended (14 for, 2 opposed, 0 abstained, 2 absent) that pregabalin be classified as non-formulary under the UF, with gabapentin and tiagabine remaining on the UF.

C. GABA analogs UF Medical Necessity Criteria: Based on the clinical evaluation of the GABA analogs and conditions for establishing medical necessity for a non-formulary

medication provided in the UF rule, the P&T Committee concluded that the following general medical necessity criteria would apply for these agents:

1) Use of formulary agents is contraindicated, and the use of pregabalin is not contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from the formulary agents, and the patient is expected to tolerate pregabalin.

3) Treatment with formulary agents has resulted in a therapeutic failure, and the patient is expected to respond to pregabalin.

4) The patient previously responded to the pregabalin and changing to a formulary agent would incur an unacceptable clinical risk.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 1 opposed, 0 abstained, 2 absent) to accept the GABA-analog medical necessity criteria.

D. GABA-analog UF Implementation Period: The Committee recommended an effective date no later than the first Wednesday following a 60-day implementation.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to recommend an implementation period of 60 days.

E. GABA-analog BCF Review and Recommendations: The P&T Committee reviewed the GABA analogs recommended for inclusion on the UF to select the BCF GABA analog.

Gabapentin is currently included on the BCF. From a clinical and economic standpoint, all strengths and formulations of gabapentin are rational selections for the BCF. Gabapentin is the highest utilized GABA-analog in all three points of service (MTF, TRRx, and TMOP), is efficacious in treating a variety of neuropathic pain syndromes, and is now generically available.

Conclusion: The Committee concurred with the recommendations to place all formulations and strengths of gabapentin on the BCF.

COMMITTEE ACTION: The DoD P&T Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to maintain all formulations and strengths of gabapentin on the BCF.

9. ABBREVIATED CLASS REVIEWS: THIAZOLIDINEDIONES (TZDS), ORAL ANTIEMETIC AGENTS; CONTRACEPTIVE AGENTS

Portions of the clinical reviews were presented to the Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing appropriate cost effectiveness models. Both the clinical and economic analyses of each class will be completed during the May 2006 meeting; no action necessary.

10. ADJOURNMENT

The third day of the meeting adjourned at 1130 hours on February 16, 2006. The dates of the next meeting are May 9 – 11, 2006.

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

List of Appendices

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations/Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	**Effective Date of Decision**	**Comments**
Feb 06	OABs	tolterodine IR (Detrol) oxybutynin patch (Oxytrol) trospium (Sanctura)	BCF	oxybutynin IR (Ditropan tabs/soln) tolterodine SR (Detrol LA)	Pending approval	Pending approval	
Feb 06	Misc Antihypertensive Agents	felodipine/enalapril (Lexxel) verapamil/trandolapril (Tarka)	BCF	amlodipine/benazepril (Lotrel) hydralazine clonidine tablets	Pending approval	Pending approval	
Feb 06	GABA-analogs	pregabalin (Lyrica)	BCF	gabapentin (Neurontin)	Pending approval	Pending approval	
Nov 05	Alzheimer's Drugs	tacrine (Cognex)	ECF	donepezil (Aricept)	19 Jan 06	19 April (90 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Nasal Corticosteroids	beclomethasone dipropionate (Beconase AQ, Vancenase AQ) budesonide (Rhinocort AQ) triamcinolone (Nasacort AQ)	BCF	fluticasone (Flonase)	19 Jan 06	19 April (90 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Macrolide/ Ketolide Antibiotics	azithromycin 2gm (Zmax) telithromycin (Ketek)	BCF	azithromycin (Z-Pak) erythromycin salts and bases	19 Jan 06	22 March 2006 (60 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Antidepressants (excluding MAOIs and TCAs)	paroxetine HCL CR (Paxil) fluoxetine 90mg (weekly regimen – Prozac Weekly) fluoxetine (special packaging for PMDD – Sarafem) escitalopram (Lexapro) duloxetine (Cymbalta) buproprion extended release (Wellbutrin XL)	BCF	citalopram fluoxetine (excluding weekly regimen and special packaging for PMDD) sertraline (Zoloft) trazadone buproprion sustained release	19 Jan 06	19 July 2006 (180 day implementation period)	BCF selections effective 19 Jan 06

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Decision	Comments
Aug 05	Alpha Blockers for BPH	tamsulosin (Flomax)	BCF	terazosin alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05
Aug 05	CCBs	amlodipine (Norvasc) isradipine IR (Dynacirc) isradipine ER (Dynacirc CR) nicardipine IR (Cardene, generics) nicardipine SR (Cardene SR) verapamil ER (Verelan) verapamil ER for bedtime dosing (Verelan PM, Covera HS) diltiazem ER for bedtime dosing (Cardizem LA)	BCF	nifedipine ER (Adalat CC) verapamil SR diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150-day implementation period)	BCF selections effective 13 Oct 05
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-day implementation period)	BCF selection effective 13 Oct 05
May 05	PDE-5 Inhibitors	sildenafil (Viagra) tadalafil (Cialis)	ECF	vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90-day implementation period)	ECF selection effective 14 Jul 05
May 05	Topical Antifungals*	econazole ciclopirox oxiconazole (Oxistat) sertaconazole (Ertaczo) sulconazole (Exelderm)	BCF	nystatin clotrimazole	14 Jul 05	17 Aug 05 (30-day implementation period)	BCF selection effective 14 Jul 05
May 05	MS-DMDs	-	ECF	interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-	ECF selection effective 14 Jul 05
Feb 05	ARBs	eprosartan (Teveten) eprosartan/HCTZ (Teveten HCT)	BCF	telmisartan (Micardis) telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	**Effective Date of Decision**	**Comments**
Feb 05	PPIs	esomeprazole (Nexium)	BCF	omeprazole rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = UF
ER = extended release; IR = immediate release; SR = sustained release
ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors
*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs February 2006 DoD P&T Committee Meeting

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Deferasirox (Exjade; Novartis) tablets for oral suspension; iron chelator	Nov 05; treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years and older	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Sorafenib (Nexavar) tablets; multi-kinase inhibitor	Dec 05 (priority review); treatment of patients with advanced renal cell carcinoma	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed. Quantity limits recommended: TMOP: 180 tablets per 45 days (if the product becomes available in this point of service; Retail Network: 120 tablets per 30 days

Appendix C – Table 3. Table of Abbreviations

ACE	angiotensin converting enzyme
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BP	blood pressure
CCB	calcium channel blocker
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
DHP	dihydropyridine
DM	diabetes mellitus
DoD	Department of Defense
DPN	diabetic peripheral neuropathy
ECF	Extended Core Formulary
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
HCTZ	hydrochlorothiazide
JNC VII	Joint National Commission VII
MHS	Military Health System
MTF	military treatment facility
NNH	number needed to harm
NNT	number needed to treat
OAB	overactive bladder
P&T	Pharmacy and Therapeutics
PEC	Pharmacoeconomic Center
PHN	post-herpetic neuralgia
SBP	systolic blood pressure
SUI	stress urinary incontinence
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
TZDs	thiazolidinediones
UF	Uniform Formulary