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 neither Seasonique nor Loestrin 24 Fe has 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: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows: Implement on 24 January 2007

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: BW ☑ 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: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows: Implement on 24 January 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 August 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 of age 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: BW ☑ 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: BW ☑ 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~~ 30 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: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

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 19-21 of the P&T Committee minutes).

Director, TMA, Decision: BW ☑ 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 August 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: BW ☑ 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 pages 24-25 of the P&T Committee minutes for rationale).

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

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

The drugs in the 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 spheroidal oral drug absorption system (SODAS) (Ritalin LA) are eight- to nine-hour products, while methylphenidate osmotically controlled-release oral delivery system (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 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 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 and sodium oxybate 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: BW ☑ 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 of the P&T Committee minutes).

Director, TMA, Decision: BW ☑ 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 39 of the P&T Committee minutes).

Director, TMA, Decision: BW ☑ 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 pages 39-40 of the P&T Committee minutes).

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

8. PRIOR AUTHORIZATION REQUIREMENT (PA) FOR MODAFINIL

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 40-41 of the P&T Committee minutes.)

Director, TMA, Decision: BW ☑ 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 41-43 of the P&T Committee minutes.)

Director, TMA, Decision: BW ☑ 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.

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 September 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 2006. 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 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 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 2006 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 neither Seasonique nor Loestrin 24 Fe has 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 October 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 August 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 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 2% and clotrimazole 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 or nystatin. 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, miconazole, and nystatin. Other topical antifungals compared included cyclopirox, sertaconazole, oxiconazole, naftifine, butenafine, sulconazole, econazole, and ketoconazole.

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 April 2006 and October 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 2006 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
  - 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. 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, flurazepam, quazepam, temazepam, and triazolam) 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 is frequently preferred over flurazepam, 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 is commonly considered by providers to have an unacceptable adverse effect profile. Quazepam and estazolam 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 and secobarbital. Secobarbital has been used in the short-term treatment of insomnia, and also in the pre-operative setting and in alcohol withdrawal. Butabarbital 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 and butabarbital 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 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, chloral hydrate, temazepam 15 and 30 mg, estazolam, and triazolam 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, secobarbital, chloral hydrate, quazepam, temazepam, estazolam, and triazolam 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 – 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 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 and sodium oxybate are indicated for the treatment of excessive sleepiness associated with narcolepsy. Modafinil 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 is also indicated for the treatment of cataplexy in narcolepsy.

Sodium oxybate 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 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 is a Schedule IV controlled drug. It has not been associated with producing withdrawal symptoms or tolerance.

Drug Interactions: Modafinil 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 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 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 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 Agents 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 UF. 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 – 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 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 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 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 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 (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 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

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, Growth Stimulant Agents, MAOI Antidepressants, 5-Alpha Reductase Inhibitors, 5-HT Receptor Agonists ("Triptans"), Antilipidemics II (LIP-2s), and Proton Pump Inhibitors.

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. 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.

Patricia Buss

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 Recommendations / Decisions

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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