DOD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

INFORMATION FOR THE UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL

I. Uniform Formulary Review Process

Under 10 U.S.C. § 1074g, as implemented by 32 C.F.R. 199.21, the DoD P&T Committee is responsible for developing the Uniform Formulary (UF). Recommendations to the Director, TMA, on formulary status, pre-authorizations, and the effective date for a drug's change from formulary to non-formulary status receive comments from Beneficiary Advisory Panel (BAP), which must be reviewed by the Director before making a final decision.

II. ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY AGENTS

P&T Comments

A. Relative Clinical Effectiveness:

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 GABA. However, there are distinct GHB receptors in the CNS, where GHB is believed to function as a neurotransmitter and cause marked CNS depression.

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

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

and patient registry, compulsory educational materials for both the physician and the patient, and a tracked method of shipping.

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

iv) *Efficacy*

Modafinil (Provigil)

- *Narcolepsy (FDA approved indication):* Four randomized double-blinded placebo controlled trials [US Modafinil in Narcolepsy Multicenter Study Group 1998, 2000; Broughton 1997; Billiard 1994] reported statistically significant improvements in objective and subjective daytime sleepiness. The American Academy of Sleep Medicine rates modafinil as the "standard" of treatment for narcolepsy.
- *Excessive daytime sleepiness associated with OSAHS (FDA approved indication):* Three randomized double-blinded placebo controlled trials evaluated the efficacy of modafinil administered as an adjunct to CPAP treatment [Black 2005, Pack 2005, Kingshott 2001]. In the majority of the patients studied, there were statistically significant improvements (rated both objectively by providers and subjectively by the subjects) in daytime sleepiness.
- *Excessive daytime sleepiness associated with SWSD (FDA approved indication):* Two randomized double-blinded placebo controlled trials [Czeisler 2005, Rosenberg 2003] both showed statistically significant improvement in objective and subjective measures of fatigue in patients during work-time shifts.
- *Depression (non-FDA approved indication)*: Two randomized double-blinded placebo controlled trials [Fava 2005, Frye 2005] reported statistically significant improvement in objective measures of global improvement. There were improvements in some (but not all) depression-specific rating scales. There was no evidence of increased manic emergence in patients with bipolar depression.
- *Multiple Sclerosis (MS) (non-FDA approved indication)*: One randomized double-blinded placebo controlled trial and one single blinded trial [Stankoff 2005, Rammohan 2002] evaluated efficacy of modafinil for fatigue associated with multiple

sclerosis (MS). Stankoff et al showed no statistically significant difference in subjective measures of fatigue and daytime sleepiness. However, Rammohan et al showed a statistically significant improvement in objective measures of fatigue and daytime sleepiness. The National MS Society's expert opinion guideline on management of multiple sclerosis fatigue recommends 200 mg of modafinil daily as a primary treatment of MS fatigue, once secondary causes of fatigue have been addressed.

- *Cocaine dependence (non-FDA approved indication)*: There are two randomized double-blinded placebo controlled trials evaluating use of modafinil to treat cocaine dependency [Dackis 2003, 2005]. One trial showed a statistically significant decrease in self-rated euphoria in treated patients versus placebo. The other trial reported a statistically significant increase in the number of patients who remained abstinent from cocaine abuse for greater than three weeks versus placebo.
- *Myotonic dystrophy (non-FDA approved indication):* Two randomized double-blinded placebo controlled trials [MacDonald 2002, Talbot 2003] showed statistically significant improvements in subjective measures of daytime sleepiness, fatigue, and improvements in subjective quality of life measures.

Sodium oxybate (Xyrem)

- *Excessive daytime sleepiness:* Three randomized, double-blinded placebo controlled trials [Black et al 2006, US Xyrem Multicenter Study Group 2002, 2003] supported the FDA new drug application of sodium oxybate (Xyrem) for excessive daytime sleepiness. All three trials statistically significant improvements in subjective measures of daytime sleepiness with sodium oxybate compared to placebo; in some cases improvements approached normal values. Improvements in sleep quality, alertness, and concentration were also noted.
- *Narcolepsy associated with cataplexy:* Four randomized, double-blinded placebo controlled trials [US Xyrem Multicenter Study Group 2002, 2003, 2005, Scrima 1989] support the use of the drug for narcolepsy associated with cataplexy. All four trials reported statistically significant reductions in the number of cataplexy attacks ranging from 50% to 90%, compared to placebo.
- *Idiopathic hypersomnia:* Two open-label trials [Bastuji 1988, Laffont 1994] showed statistically significant reductions in the number of sleep attacks and daytime drowsiness in most patients treated. This disorder is clinically very similar to

narcolepsy, and is diagnosed only through a sleep study by a sleep specialist.

2) Safety and Tolerability

a) ADHD Drugs

i) Black box warning

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

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

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

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

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

vi) Decreased growth velocity – Early studies conducted with the stimulants showed a relationship between drug treatment and decreased growth velocity. Decreases in height can range from 0.7 to 1.9 cm in treated patients versus control patients. Long-term studies show trends for treated patients to catch up with non-treated peers. Labeling for all stimulant products contains strong warnings for continual evaluation of growth velocity in treated patients.

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

viii) Drug interactions

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

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

ix) Minor adverse events

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

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

x) Tolerability

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

Persistence: One report [Kenner 2003] comparing the once daily stimulant formulations showed that patients taking methylphenidate OROS (Concerta) and mixed amphetamine salts ER (Adderall XR) took their medication more consistently than patients receiving methylphenidate 30% IR/70% ER (Metadate CD). Another report [Marcus 2005] showed that patients were more persistent with

Concerta for longer time periods than methylphenidate IR (Ritalin, generics).

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

b) Narcolepsy Drugs

i) *Modafinil (Provigil)*

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

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

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

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

ii) *Sodium oxybate (Xyrem)*

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

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

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

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

3) Other Factors

a) ADHD Drugs

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

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

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

iv) Dosage formulations – The methylphenidate transdermal system (Daytrana) is the only non-oral formulation in this class. Methylphenidate 30% IR/70% ER (Metadate CD), mixed

amphetamine salts ER (Adderall XR), dexmethylphenidate SODAS (Focalin XR) and methylphenidate SODAS (Ritalin LA) are capsule formulations that can be opened and sprinkled on food for patients with swallowing difficulties. Methylphenidate IR (Methylin) is available in an oral solution and chewable tablets.

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

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

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

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

b) Narcolepsy agents

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

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

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

1) For ADHD, interpretation of the data is limited due to the poor quality of studies, limited number of comparator trials, varying rating scales used, small number of patients enrolled, and short study duration.
2) There is no evidence to suggest a difference in efficacy between IR formulations of methylphenidate (Ritalin, generics), dextroamphetamine (Dexedrine, Dextrostat, generics), dexmethylphenidate (Focalin), and mixed amphetamine salts (Adderall, generics).
3) The overall efficacy of the once daily methylphenidate formulations appears similar based on a few small studies, but differences exist in reported outcomes at specific times of the day, due to the individual release mechanisms of the products. Methylphenidate 30% IR/70% ER (Metadate CD) and methylphenidate SODAS (Ritalin LA) are eight- to nine-hour products, while methylphenidate OROS (Concerta), dexmethylphenidate SODAS (Focalin XR), and methylphenidate transdermal system (Daytrana) are 12-hour products.
4) Mixed amphetamine salts ER (Adderall XR) appears to have similar efficacy to methylphenidate OROS (Concerta), based on one small study.
5) The efficacy of atomoxetine (Strattera) appears to be inferior to the stimulants, but it is the only non-stimulant available in the ADHD class.
6) Between 40% and 80% of patients who do not respond to one type of stimulant (methylphenidate products vs. amphetamine products) may respond to the other.
7) The adverse events and warnings of the stimulants are well-recognized and are similar between products.
8) The methylphenidate transdermal system (Daytrana) can cause significant dermatological adverse events, which can lead to sensitization to oral products.
9) Atomoxetine (Strattera) remains the only alternative for patients who cannot tolerate stimulants, despite its association with an increased risk of hepatotoxicity and suicidal ideation.

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

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

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

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

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

COMMITTEE ACTION: The P&T Committee voted to accept the clinical effectiveness conclusions stated in II(A).

B. Relative Cost Effectiveness:

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 Uniform Formulary suggested dexmethylphenidate IR should be evaluated for non-formulary status.

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

Based on the results of the clinical review and the pharmacoeconomic evaluations, a budget impact analysis (BIA) of various formulary scenarios was

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

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 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 Uniform Formulary scenario.

COMMITTEE ACTION: The P&T Committee voted to accept the cost-effectiveness conclusions stated above

C. Uniform Formulary 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 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 Uniform Formulary and that dexmethylphenidate IR (Focalin), dexmethylphenidate SODAS (Focalin XR), methylphenidate transdermal system (Daytrana) be classified as non-formulary.

D. Implementation Plan:

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 the approval by the Director, TMA.

III. ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY AGENTS (cont.)

BAP Comments

A. Uniform Formulary 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 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 Uniform Formulary and that dexmethylphenidate IR (Focalin), dexmethylphenidate SODAS (Focalin XR), methylphenidate transdermal system (Daytrana) be classified as non-formulary.

BAP Comment:	□ Concur □ Non-concur Additional Comments and Dissentions:

B. Implementation Plan*:* The P&T Committee recommended an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

BAP Comment:	□ Concur □ Non-concur Additional Comments and Dissentions:

IV. SEDATIVE HYPNOTICS (SED-2s)

P&T Comments

A. Relative Clinical Effectiveness*:*

1) Efficacy

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

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

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

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

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

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

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

2) Safety / Tolerability

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

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

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

Conclusion – The older sedative hypnotic drugs still play a role in the treatment of insomnia and pre-operative sedation, although they have been largely replaced by newer agents in clinical practice. It is widely accepted that the five hypnotic benzodiazepines are therapeutically interchangeable, although temazepam (Restoril, generics) has the most favorable half-life and safety profile. The

barbiturates and chloral hydrate are used infrequently and primarily for special patient populations. There are no clinical reasons to justify designating any of these eight drugs as non-formulary.

***COMMITTEE ACTION**:* The P&T Committee voted to accept the overall clinical effectiveness conclusions stated above.

B. Relative Cost Effectiveness: 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.

Conclusion – The P&T Committee concluded that:

1) Secobarbital (Seconal, generics), chloral hydrate (generics), temazepam (Restoril, generics) 15 and 30 mg, estazolam (Prosom, generics), and triazolam (Halcion, generics) have similar relative cost-effectiveness.
2) 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 would achieve little savings due to current and projected low utilization.

COMMITTEE ACTION: P&T Committee voted to accept the cost effectiveness conclusions stated above.

C. Uniform Formulary Recommendation: 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 to recommend that butabarbital (Butisol), secobarbital (Seconal, generics), chloral hydrate (generics), quazepam (Doral), temazepam (Restoril), estazolam (Prosom, generics), and triazolam (Halcion, generics) be maintained as formulary on the Uniform Formulary and that no agents be classified as non-formulary.

D.* Implementation Plan*: Since no agents were recommended for non-formulary status, establishment of an implementation plan is not applicable.

V. SEDATIVE HYPNOTICS (SED-2s) (cont.)

BAP Comments

A. **Uniform Formulary Recommendation:** The P&T Committee, based upon its collective professional judgment, voted to recommend that butabarbital (Butisol), secobarbital (Seconal, generics), chloral hydrate (generics), quazepam (Doral), temazepam (Restoril), estazolam (Prosom, generics), and triazolam (Halcion, generics) be maintained as formulary on the UF and that no agents be classified as non-formulary.

BAP Comment:	□ Concur □ Non-concur Additional Comments and Dissentions:

VI. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR MODIFINIL

A. Clinical And Cost Background:

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

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

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

The P&T Committee identified five off-label indications, in addition to the three FDA-approved indications, as supportable based on published clinical evidence or recommendations from nationally recognized expert organizations, based on guidelines from the TRICARE Policy Manual 6010.54 (August 2002) chapter 1 section 2.1 regarding coverage of unproven drugs, devices, medical treatments and procedures. With respect to the off-label uses, clinical evidence supports use of

modafinil (Provigil) for augmentation of treatment for major depression, fatigue associated with multiple sclerosis (MS), augmentation of primary cognitive-behavioral therapy in acute rehabilitation of cocaine dependence, fatigue associated with myotonic dystrophy, and fatigue associated with idiopathic hypersomnia. Other off-label uses (e.g., in chronic fatigue syndrome, stroke rehabilitation, appetite suppression, Parkinson's disease and others) are supported only by case reports, uncontrolled trials, single-blinded trials, or chart reviews, which constitute insufficient evidence to establish efficacy and safety per TRICARE regulations.

COMMITTEE ACTION – Based on its increasing use for off-label indications not well established by the medical literature, the P&T Committee recommended that a PA be required for modafinil (Provigil)

VII. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR MODIFINIL (CONT.)

BAP COMMENTS

A. Implementation plan: 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.

BAP Comment:	□ Concur □ Non-concur Additional Comments and Dissentions:

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

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

BAP Comment:	□ Concur □ Non-concur Additional Comments and Dissentions:

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

Clinical Background: 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.

IX. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR FENTANYL PATCHES (DURAGESIC, GENERICS) –CONT

BAP COMMENTS:

A. Implementation plan: 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.

BAP Comment:	□ Concur □ Non-concur Additional Comments and Dissentions:

B. PA Criteria:

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.

BAP Comment:	□ Concur □ Non-concur Additional Comments and Dissentions:

X. NEW DRUGS FROM PREVIOUSLY REVIEWED CLASSES – PART 1

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)

A. Relative Clinical Effectiveness:

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

The UF contains multiple monophasic oral contraceptives containing 30 mcg of EE in combination with various progestogens. These products include Yasmin (3 mg drospirenone) and generic equivalents to Desogen (0.15 mg desogestrel); Loestrin 1.5/30, Loestrin Fe 1.5/30 (1.5 mg norethindrone); Lo/Ovral (0.3 mg norgestrel); and Nordette (0.15 mg levonorgestrel). Two of these (Nordette equivalent products and Yasmin) are on the BCF. All of these products are available in conventional 28-day packaging (21 days of active tablets followed by 7 days of placebo tablets).

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

The rationale for providing seven days of 10 mcg EE instead of placebo is to reduce symptoms associated with estrogen withdrawal, including dysmenorrhea, menstrual migraine, and premenstrual syndrome, although this has not been evaluated in a prospective, randomized, controlled trial. One other oral contraceptive product offering low-dose estrogen during the off period is available (Mircette, Kariva, and equivalents; 21 days of 20 mcg

EE/0.15 mg desogestrel followed by 2 days of placebo and 5 days of 10 mcg EE). It is worth noting that utilization of this product, which is included on the UF, is relatively low compared to other 20 mcg EE products. Alternatives to Seasonique in women being treated on an extended cycle basis who are experiencing menstrual-related problems during the four annual off periods include addition of a low-dose conjugated estrogen product (e.g., 0.3 mg Premarin) during the off period, or decreasing the length or number of off periods.

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

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

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

The rationale for a 24- rather than a 21-day regimen is to decrease the number of bleeding days and reduce adverse events associated with estrogen withdrawal. It is also possible that a longer regimen would increase the safety margin for contraceptive effectiveness with low estrogen products; however, there is no supporting clinical evidence. One trial in 938 women compared Loestrin 24 Fe with Loestrin Fe 1/20 and reported a Pearl Index (number of pregnancies per 100 women per year of use) of 1.85 (five pregnancies) with the 24-day regimen vs. 1.79 (two pregnancies) with the 21-day regimen (no statistics provided). There were no differences between the two products in terms of serious adverse events, treatment-related adverse events, and discontinuations due to adverse events.

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

B. **Relative Cost Effectiveness:**

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.

COMMITTEE ACTION: The P&T Committee voted to accept the clinical and cost effectiveness conclusions stated above.

C. Uniform Formulary Recommendation: The P&T Committee, based upon its collective professional judgment, voted to recommend that Seasonique and Loestrin 24 Fe be classified as non-formulary.

D. Implementation Plan: The P&T Committee 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). The Committee recommended a short implementation period because it would avoid patient disruption as utilization of new products increases. If a coordinated implementation cannot be achieved due to timing constraints of the UF process, the P&T Committee recommended 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.

XI. NEW DRUGS FROM PREVIOUSLY REVIEWED CLASSES – PART 1 (CONT)

BAP COMMENTS -- Contraceptive Agents (Seasonique / Loestrin 24 Fe)

A. Uniform Formulary Recommendation: The P&T Committee, based upon its collective professional judgment, voted to recommend that Seasonique and Loestrin 24 Fe be classified as non-formulary.

BAP Comment:	□ Concur □ Non-concur Additional Comments and Dissentions:

B. Implementation Plan: The P&T Committee 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). The Committee recommended a short implementation period because it would avoid patient disruption as utilization of new products increase. If a coordinated implementation cannot be achieved due to timing constraints of the Uniform Formulary process, the P&T Committee recommended 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.

BAP Comment:	□ Concur □ Non-concur Additional Comments and Dissentions:

XII. NEW DRUGS FROM PREVIOUSLY REVIEWED CLASSES – PART 2

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

A. *Relative Clinical Effectiveness*: The topical antifungal agents were reviewed by the P&T Committee in Aug 05. Topical antifungal agents included on the Uniform Formulary 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 are econazole (Spectazole, generics), sertaconazole (Ertaczo), sulconazole (Exelderm), ciclopirox (Loprox, generics), and oxiconazole (Oxistat). Vusion contains 0.25% miconazole along with 15% zinc oxide and 81.35% white petrolatum, and is only available as an ointment. Over-the-counter (OTC) and prescription miconazole products contain a 2% concentration of miconazole, and are available in several formulations (e.g.,

cream, ointment, spray, spray liquid, powder, and solution). The zinc oxide and petrolatum components of Vusion are skin protectants; numerous OTC products (e.g., Balmex, Happy Hiney) contain varying amounts of these two ingredients, which form a physical barrier on the skin.

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

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

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

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

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

The CMA for Vusion compared the weighted cost per treated utilizer across all three points of service to other antifungal agents previously analyzed during the DoD P&T Committee's August 2005 review of topical antifungals. Comparative

antifungals used specifically for diaper rash included clotrimazole (Lotrimin, generics), miconazole (Monistat, generics), and nystatin (Mycostatin, generics). Other topical antifungals compared included cyclopirox (Loprox, generics), sertaconazole (Ertaczo), oxiconazole (Oxistat), naftifine (Naftin), butenafine (Mentax), sulconazole (Exelderm), econazole (Spectazole, generics), and ketoconazole (Nizoral, generics).

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

COMMITTEE ACTION: The P&T Committee to accept the clinical and cost effectiveness conclusions stated above.

C. Uniform Formulary Recommendation: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that Vusion be classified as non-formulary.

D. Implementation Plan: The P&T Committee recommended 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. As of October 2006, a total of 581 Vusion prescriptions have been dispensed at all three points of service. For the six month period between Apr 06 and Oct 06, there have been 426 unique utilizers of Vusion in the MHS.

XIII. NEW DRUGS FROM PREVIOUSLY REVIEWED CLASSES – PART 2 (CONT)

Topical Antifungal Agents (Vusion)

BAP COMMENTS

A. Uniform Formulary Recommendation: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that Vusion be classified as non-formulary.

BAP Comment:	□ Concur □ Non-concur Additional Comments and Dissentions:

B. Implementation Plan: The P&T Committee recommended 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.

BAP Comment:	□ Concur □ Non-concur Additional Comments and Dissentions:

XIV. NEW DRUGS FROM PREVIOUSLY REVIEWED CLASSES – PART 3

Antiemetic Agents (Cesamet)

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

- *The newer antiemetics*
  - 5-hydroxytryptamine-3 [5-HT3] antagonists: ondansetron (Zofran), granisetron (Kytril)
  - Neurokinin-1 (NK-1) antagonist: aprepitant (Emend)
- *The older antiemetics*
  - Cannabinoids: dronabinol (Marinol)
  - Antihistamines: meclizine (Antivert, generics), promethazine (Phenergan, generics); promethazine (Phenergan, generics) 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 (Marinol). 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 (Cesamet) with dronabinol (Marinol). Additionally, there are no trials comparing nabilone with any of the 5-HT3 antagonists—ondansetron (Zofran), granisetron (Kytril), or dolasetron (Anzemet)—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 (Compazine, generics), 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 (Cesamet) relegate it to use as a second-line agent. Nabilone is a DEA (Drug Enforcement Administration) Schedule II drug, compared to dronabinol (Marinol), a Schedule III drug.

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

B. Relative Cost Effectiveness: Based on the information reported from the relative clinical effectiveness evaluation, there was insufficient evidence to suggest that nabilone (Cesamet) 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 (Marinol), which is currently included on the Uniform Formulary.

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

COMMITTEE ACTION *:* The P&T Committee voted to accept the clinical and cost effectiveness conclusions stated above.

C. Uniform Formulary Recommendation– Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee,

based upon its collective professional judgment, voted to recommend that nabilone (Cesamet) be maintained on the Uniform Formulary.

D. Implementation Plan -- Since nabilone (Cesamet) was not recommended for non-formulary status, establishment of an implementation plan is not applicable.

XV. NEW DRUGS FROM PREVIOUSLY REVIEWED CLASSES – PART 3 (CONT)

Antiemetic Agents (Cesamet)

BAP COMMENTS

A. Uniform Formulary Recommendation– Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that nabilone (Cesamet) be maintained on the Uniform Formulary.

BAP Comment:	□ Concur □ Non-concur Additional Comments and Dissentions: