DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

February 2007

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

A. Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF) – The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee was briefed on two new drugs approved by the Food and Drug Administration (FDA) that did not fall under drug classes previously reviewed for UF consideration: sitagliptin phosphate tablets (Januvia) and paliperidone extended release [ER] tablets (Invega). UF consideration was deferred until drug class reviews are completed. No action is required since the P&T Committee did not recommend a quantity limits (QL) or prior authorization (PA) for either of these drugs.

B. Over-the-Counter Omeprazole Magnesium (Prilosec OTC)

The John Warner National Defense Authorization Act for FY 2007 directed that the Secretary of Defense conduct a demonstration project to assess the impact of authorizing TRICARE coverage for over-the-counter (OTC) agents recommended for inclusion on the UF. The DoD P&T Committee must find that the OTC drug is cost effective and therapeutically equivalent to prescription alternatives. The P&T Committee, after consultation with the TRICARE Management Activity (TMA) Pharmacy Program office, selected the proton pump inhibitor (PPI) omeprazole magnesium as the initial OTC product. It is projected to be available at military treatment facilities (MTFs) and the mail order points of service by 1 May 2007.

The P&T Committee previously reviewed the PPIs in February 2005. PPIs on the UF include prescription omeprazole (Prilosec, generics), rabeprazole (Aciphex), lansoprazole (Prevacid), and pantoprazole (Protonix). Esomeprazole (Nexium), the s-isomer of omeprazole, is non-formulary under the UF. The Basic Core Formulary (BCF) selections in this class are prescription omeprazole and rabeprazole.

Relative Clinical Effectiveness – The P&T Committee concluded (13 for, 0 opposed, 2 abstained, 2 absent) that omeprazole magnesium has similar relative clinical effectiveness compared to other PPIs included on the UF. The P&T Committee also concluded that, while FDA-approved indications differ for the OTC and prescription versions of omeprazole, there is no reason to believe that the clinical effect of omeprazole magnesium, when given to the same patients in the same doses, would differ from the anticipated effects of prescription omeprazole.

Relative Cost Effectiveness – The cost analysis showed that omeprazole magnesium has a cost effectiveness profile similar to prescription omeprazole in the mail order and MTF points of service and a more favorable cost effectiveness profile in the retail sector. Omeprazole magnesium is more cost effective than other products in the PPI class (i.e., esomeprazole, lansoprazole, pantoprazole, and rabeprazole) across all three points of service. Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee voted (13 for, 0 opposed, 2 abstained, 2 absent) that omeprazole magnesium is comparable in cost to prescription omeprazole, and more cost effective than the other PPIs included on the UF.

COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 2 abstained, 2 absent) to recommend that omeprazole magnesium be classified as formulary on the UF (see paragraph 5B on pages 20-22 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

6. DRUG CLASS REVIEW – NEWER SEDATIVE HYPNOTICS (SED-1s)

The P&T Committee evaluated the relative clinical effectiveness of the newer sedative hypnotic agents (SED-1s). The SED-1 drug class includes the following agents: zolpidem immediate release [IR] (Ambien), eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), and zolpidem ER (Ambien CR). All SED-1 agents except ramelteon are classified as benzodiazepine receptor agonists; ramelteon acts as an agonist at melatonin receptors (MT_1 and MT_2) in the suprachiasmatic nucleus of the brain, which is responsible for regulation of the 24-hour sleep-wake cycle (circadian rhythm). All are FDA-indicated for the treatment of insomnia, although specific labeling differs.

As of December 2006, about four million Military Health System (MHS) prescriptions for these agents are filled per month. The SED-1 drug class was ranked #15 in terms of expenditures in FY 2006 ($111 million)—up from #18 in FY 2005 ($72 million), and #20 in FY 2004 ($54 million). Across the MHS, zolpidem IR is the most commonly prescribed SED-1, with about twice as many prescriptions compared to the next most commonly prescribed SED-1 agent, zolpidem ER, followed closely by eszopiclone. Usage of zaleplon is low and stable, while usage of the most recently introduced agent, ramelteon, is low but increasing. All of the SED-1 agents are brand-only; zolpidem IR is expected to become generically available in April 2007.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) Based on placebo-controlled trials, all SED-1 agents decrease sleep latency to a similar degree. Data supporting the effect of ramelteon on sleep latency appears to be the least robust, both in terms of the number of published studies and the amount of improvement demonstrated versus placebo. Zolpidem IR and eszopiclone have evidence indicating consistent and similar increases in sleep

duration. Zaleplon and ramelteon do not appear to consistently increase sleep duration.

2) Based on three comparative trials, zaleplon appears to decrease sleep latency more than zolpidem IR, but zolpidem IR appears to increase total sleep time more than zaleplon. In one comparative trial, very similar results were reported for eszopiclone versus zolpidem IR with respect to measures of sleep latency and sleep duration.

3) Based on comparative trials, SED-1 agents appear to be similar in efficacy and short-term adverse events, compared to benzodiazepines; benzodiazepines may cause more rebound insomnia. Zolpidem IR appears to be similar in efficacy to the sedating antidepressant trazodone (Desyrel, generics), based on one comparative trial in non-depressed patients; trazodone may result in greater daytime somnolence.

4) There are no consistent data to demonstrate that SED-1 agents have beneficial effects on sleep architecture, compared to placebo.

5) There is insufficient evidence to conclude that SED-1 agents have a major beneficial effect on quality of life, although limited data show improvement in certain domains of the SF-36. There are insufficient comparative data to draw conclusions about individual agents.

6) The SED-1 agents appear to have similar adverse effect profiles and to result in similar rates of discontinuation due to adverse events in clinical trials. Eszopiclone is associated with an unpleasant taste. There do not appear to be any major disadvantages for any one agent with respect to drug-drug interactions. Ramelteon may be less effective in smokers.

7) Daytime sleepiness, impairments in psychomotor function and cognitive function, adverse effects on driving safety, and increased risk for falls may occur with any of the benzodiazepine receptor agonists; there are little or no data for the melatonin receptor agonist ramelteon. Agents with longer half-lives tend to pose a greater risk for these effects. The SED-1 agent with the longest half-life is eszopiclone, 6 hours (up to 9 hours in elderly patients); followed by zolpidem (Ambien, Ambien CR), 2.5-2.8 hours; ramelteon, 1-2.6 hours; and zaleplon, 1 hour. Lower starting doses of all SED-1 agents except ramelteon are recommended in elderly patients.

8) The applicability of driving safety studies reporting impaired performance and increased risk of accidents with a 7.5 mg dose of zopiclone (eszopiclone's racemic parent drug) is unclear, since recommended doses of eszopiclone would be equivalent to zopiclone doses lower than 7.5 mg. There was no reported difference between eszopiclone and zolpidem IR on subjective measures of next day effects based on results of an unpublished trial reported in the FDA statistical review of eszopiclone.

9) Because of its very short half-life, zaleplon may be taken in the middle of the night after a patient has had difficulty falling asleep without demonstrating adverse effects on driving performance the next morning. It may have an

advantage in elderly patients, since risk of falls and hip fracture tends overall to increase with increasing half-life (although the relationship between falls and half-life is not straightforward and prescribers must take into account patient activity patterns).

10) No SED-1 agent appears preferable in other special patient populations (hepatic or renal dysfunction, pregnancy, pediatrics); there is some concern about use of ramelteon in pediatric patients due to possible endocrine effects.

11) Rebound insomnia has been reported in clinical trials with all SED-1 agents except ramelteon; more rebound insomnia was noted with zolpidem IR than with zaleplon during comparative trials.

12) All SED-1 agents, with the exception of ramelteon, probably have a small but significant potential for abuse. Ramelteon appears to lack significant abuse potential and may be preferable in patients at high risk for substance abuse. Ramelteon is the only SED-1 agent that is not a Drug Enforcement Agency (DEA) scheduled substance.

13) It is likely that at least two SED-1 agents are needed for adequate clinical coverage, based on provider responses regarding prescribing practices and likely patient response.

Relative Cost Effectiveness Conclusion: Based on the results of the cost minimization analysis (CMA) and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) Eszopiclone was the most cost effective agent until zolpidem IR becomes generically available with competitive pricing.

2) Ramelteon, zaleplon, and zolpidem ER were more costly than eszopiclone and provided no meaningful clinical therapeutic advantage compared to eszopiclone or zolpidem IR.

3) The UF scenario utilizing a prior authorization requiring a trial of zolpidem IR by new SED-1 patients was more cost effective relative to UF scenarios not requiring a trial of zolpidem IR by new SED-1 patients.

A. ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the SED-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 2 abstained, 1 absent) to recommend that: 1) eszopiclone and zolpidem IR be maintained as formulary on the UF with a PA requiring a trial of zolpidem IR for new patients and 2) that ramelteon, zaleplon, and zolpidem ER be classified as non-formulary under the UF, with a PA requiring a trial of zolpidem IR for new patients (see paragraphs 6A, 6B, and 6C on pages 23-31 and Appendix D on page 79 of the P&T Committee minutes).

The Committee agreed that the following PA criteria should apply to SED-1 agents other than zolpidem IR. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:

The patient has received a prescription for any SED-1 agent (including zolpidem IR) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2) PA criteria if automated criteria are not met:

The patient has tried zolpidem IR and had an inadequate response or was unable to tolerate it due to adverse effects.

Treatment with zolpidem IR is contraindicated.

In order for a patient to receive a non-formulary SED-1 agent at the formulary cost-share, both the PA and medical necessity (MN) criteria must be met. If the PA criteria are met without an approved MN determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved PA for ramelteon, zaleplon, or zolpidem ER would NOT automatically receive it at the formulary cost-share.

The P&T Committee also noted that the PA is not intended to apply where there are existing policies or protocols in place for operational/readiness situations and that MTFs should make necessary allowances for such use.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for ramelteon, zaleplon, and zolpidem ER, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) MN criteria for ramelteon, zaleplon, and zolpidem ER (see paragraph 6D on page 31 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 2 abstained, 1 absent) to recommend an effective date of the greater of 1) the first Wednesday following a 90 day implementation period, or 2) the time necessary to complete logistical arrangements to implement the automated PA. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 6E on pages 31-32 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (13 for, 0 opposed, 3 abstained, 1 absent) to recommend adding zolpidem IR as the BCF selection in this class (see paragraph 6F on page 32 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

7. DRUG CLASS REVIEW – NARCOTIC ANALGESICS

The drugs in this class comprise all narcotic analgesics (also referred to as opioids or opiate agonists) used for the treatment of pain on an outpatient basis, including combinations with acetaminophen (APAP), aspirin (ASA), and other non-opioids. Not included in this drug class review are narcotic analgesics given primarily by intravenous injection or infusion, over-the-counter products, products requiring administration by a medical professional, products in which the narcotic component is primarily used as an antitussive, and products indicated solely for the treatment of opioid dependence.

For review purposes, the narcotic analgesics were divided into four categories, based on their potency. Most of these agents are now generically available.

The narcotic analgesics accounted for approximately $153 million dollars in MHS expenditures in FY 2006 and are ranked #8 in terms of total expenditures during that time period. Approximately 437,000 DoD beneficiaries received one or more prescriptions for a narcotic analgesic during FY 2006.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) There is insufficient evidence to support efficacy differences between narcotic analgesics, including high potency long-acting agents for the treatment of chronic cancer or non-cancer pain, high potency IR agents for the treatment of break-through pain, or narcotic analgesics in general for the treatment of neuropathic pain.
2) Strong narcotic analgesics appear to be more effective than non-opioid analgesics (non-steroidal anti-inflammatory drugs [NSAIDs], tricyclic antidepressants [TCAs]) in chronic non-cancer pain.
3) There is no evidence suggesting efficacy differences between long-acting and short-acting formulations of the same agents; however, long-acting products offer greater convenience and may be associated with fewer episodes of breakthrough pain.
4) There is insufficient evidence to support efficacy differences between the 12-hour ER morphine products (e.g., MS Contin and generics) and the 24-hour ER morphine products (Avinza, Kadian), or between the two 24-hour products (Avinza versus Kadian). Avinza is restricted to a maximum dose of 1600 mg daily and cannot be taken with alcohol (including alcohol-containing medications). Kadian has a much longer time to achieve maximum serum levels

(~9.5 hours) compared to Avinza (~0.5 hour) or to 12-hour ER morphine (2-3 hours). Both can be opened and sprinkled on food; Kadian granules can be given via gastrostomy tube.

5) There is insufficient evidence to support efficacy differences between high potency IR agents for the treatment of breakthrough pain in patients with chronic cancer or non-cancer pain, including the newer IR fentanyl products (oral transmucosal lozenges [Actiq, generic] and buccal tablets [Fentora]). Buccal fentanyl is more bioavailable and may offer more consistent dosing; it is also sugar-free. The lack of a 1:1 conversion between the two IR fentanyl products may offer significant potential for medication errors.

6) Narcotic analgesics are rarely considered first line agents for the treatment of neuropathic pain. There is insufficient evidence to support efficacy differences between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.

7) There is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen. The VA/DoD guideline recommends avoiding meperidine for the treatment of postoperative pain.

8) Narcotic analgesics are associated with multiple adverse effects, including nausea, vomiting, constipation, mood changes, somnolence, urinary retention, pruritis, and oral/dental problems. Respiratory depression is uncommon but potentially serious; the risk is generally small when narcotic analgesics are appropriately titrated, as tolerance rapidly develops.

9) A decrease in seizure threshold occurs with the use of all narcotics, but is of particular concern with meperidine (which has a neurotoxic metabolite and should not be used for more than two days in patients with renal impairment, sickle-cell disease, central nervous system [CNS] disease, or in children); propoxyphene (which also has CNS-excitatory metabolites and can cause seizure in high doses, especially in patients with renal disease); and tramadol (which is associated with an increased risk of seizure at higher than recommended doses [300-400 mg daily] or in patients taking other medications or with conditions that increase seizure risk).

10) Propoxyphene is not considered appropriate in elderly patients due to CNS adverse effects, including sedation, confusion, and increased likelihood of falls and fall-related fractures. The consumer watchdog group Public Citizen has petitioned the FDA to phase out propoxyphene from the U.S. market due to the association of excessive doses of propoxyphene with drug-related deaths. Many DoD providers surveyed cited concerns over safety with the use of meperidine and propoxyphene, although others pointed out that they were useful and could be used safely if limited to short-term use in the correct patients.

11) While there are clearly differences among narcotic analgesics with regard to likelihood for abuse (e.g., onset of action and potency), there are no data

supporting differences in potential for abuse among like medications (e.g., high potency long-acting agents) that the P&T Committee considered useful for making any formulary recommendation.

12) In general, drug interactions are relatively similar for all of the drugs in this class and it does not appear that any particular medication offers a substantially higher potential for drug interactions. Two unique considerations are tramadol and meperidine. Because of its dual mechanism of action, tramadol has potential interactions with other medications that increase serotonin and/or norepinephrine levels (e.g., monoamine oxidase inhibitors [MAOIs] and selective serotonin reuptake inhibitors [SSRIs]); meperidine is contraindicated with MAOIs due to the potential for a lethal hyperpyrexic syndrome.

13) There are differences among narcotic analgesics with regard to clinical evidence, extent of clinical experience, and labeling for use in special patient populations (including pediatric and elderly patients, patients who are pregnant or breast-feeding, and patients with renal or hepatic dysfunction). However, the P&T Committee overall did not find sufficient evidence of a unique advantage or disadvantage for specific products that it considered useful for formulary decision-making.

14) Patients with swallowing difficulties may require liquid formulations or products that can be sprinkled on food or administered via a non-oral route. The available narcotic analgesics offer various formulations that meet these needs.

15) Providers surveyed in general emphasized that they require a broad array of narcotic analgesics in their practice to treat their patients and that excessive formulary restrictions would be detrimental to their ability to adequately treat various clinical presentations. They favored ER narcotic analgesics, including the fentanyl transdermal patch, as well as a broad array of strengths of opioid/ acetaminophen combination products. Many pharmacists indicated that centralized contracting for "pre-packed" products in commonly dispensed quantities would facilitate inventory and dispensing at their facilities.

16) Clinical coverage considerations support a broad array of formulary agents and formulations.

Relative Cost Effectiveness Conclusion: Based on the results of the CMAs and other clinical and cost considerations, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 1 absent) that:

1) *High potency long-acting single analgesic agents* – Although the 24-hour ER products (Kadian and Avinza); fentanyl transdermal patch (Duragesic, generics), oxycodone ER (Oxycontin), and oxymorphone (Opana ER) were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin and generics), they possess unique clinical advantages and should be maintained on the UF in order to sufficiently meet the clinical needs of the DoD population.

2) *High potency short-acting single analgesic agents* – Even though fentanyl citrate buccal tablets and fentanyl citrate transmucosal lozenges were more than 40-fold the cost of the two most cost effective agents (morphine sulfate IR and oxycodone

IR), the fentanyl citrate products provide an additional therapeutic alternative for breakthrough pain with novel routes of administration. There was no substantial difference in cost effectiveness between the two fentanyl citrate products.

3) *Low potency single analgesic agents* – Tramadol ER (Ultram ER) was not cost effective relative to other formulations of tramadol (tramadol; tramadol/APAP), which are generically available. All other products in this subclass were cost effective.

4) *Combination agents* – The products within this generic-dominated subclass were all determined to be cost effective relative to their comparators.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the narcotic analgesic drug class, and other relevant factors, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) that tramadol ER be designated non-formulary under the UF, with all other narcotic analgesic agents designated as formulary on the UF. Additionally, the P&T Committee voted to recommend (14 for, 0 opposed, 1 abstained, 1 absent) a QL of 112 tablets/28 days for fentanyl buccal tablets, consistent with established QLs for fentanyl transmucosal lozenges, recommendations in Fentora package labeling recommending a maximum of four tablets per day, and current DoD prescribing patterns for Fentora buccal tablets (see paragraphs 7A, 7B, and 7C on pages 35-51 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for tramadol ER, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) MN criteria for tramadol ER (see paragraph 7D on page 51 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 7E on pages 51-52 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend designating the following medications as the BCF selections in this class: morphine sulfate ER (MS Contin, generics) 15 mg, 30 mg, 60 mg; morphine sulfate IR 15 mg and 30 mg; oxycodone/ APAP 5/325 mg; hydrocodone/APAP 5/500 mg; codeine/APAP 30/300 mg; codeine/ APAP elixir 12/120 mg/5 mL; and tramadol IR 50 mg (see paragraph 7F on page 52 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

8. DRUG CLASS REVIEW – OPHTHALMIC GLAUCOMA AGENTS

The P&T Committee evaluated the relative clinical effectiveness of the ophthalmic glaucoma agents available in the U.S. Based on chemical structure and mechanism of action, the drug class was divided into seven subgroups: ophthalmic prostaglandin analogs; beta blockers; carbonic anhydrase inhibitors and combinations with beta blockers; alpha 2 adrenergic drugs; adrenergics; cholinergics; and cholinesterase inhibitors. The ophthalmic glaucoma agent drug class accounted for $51.1 million in MHS expenditures for the period October 2005 to September 2006, and is ranked #34 in terms of total expenditures during that time period.

Relative Clinical Effectiveness Conclusion – The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) *Prostaglandin analogs* – Bimatoprost (Lumigan), latanoprost (Xalatan), and travoprost (Travatan, Travatan Z) all decrease intraocular pressure (IOP) from baseline by 28% to 33%. A prospectively designed trial assessing efficacy of bimatoprost and travoprost found no difference in efficacy in African Americans; a sub-group analysis from a different trial reported decreased efficacy of latanoprost when compared to travoprost in African Americans versus non-African Americans. Latanoprost has the most favorable ocular adverse event profile of the three prostaglandin analogs, but requires refrigeration prior to opening. The non-benzalkonium (BAK) preservative found in the Travatan Z formulation of travoprost has not shown a major advantage in terms of ocular side effects, compared to the BAK-containing product Travatan.

2) *Beta blockers* – The IOP lowering effects of timolol maleate (Timoptic, generics; Timoptic XE, generics), timolol hemihydrate (Betimol), levobunolol (Betagan, generics), metipranolol (Optipranolol, generics) and carteolol (Ocupress, generics) appear similar based on several head-to-head studies. Timolol maleate solution (Timoptic, generics) and gel-forming solution (Timoptic XE, generics) reduce IOP by 20-35%. The Timoptic XE gel-forming solution has the advantage of once daily dosing, but is associated with transient blurred vision due to the consistency of the gel. There is no evidence that the timolol maleate product Istalol or the timolol hemihydrate product Betimol have additional clinical benefits over other timolol maleate products in IOP lowering or safety profiles.

Betaxolol (Betoptic, generics; Betoptic-S) decreases IOP to a lesser extent than timolol maleate; however, the β1 selectivity of betaxolol may be an advantage in patients with cardiac or pulmonary co-morbidities.

3) *Carbonic anhydrase inhibitors* – The IOP lowering effects of brinzolamide (Azopt) and dorzolamide (Trusopt) appear similar. Dorzolamide/timolol (Cosopt) is the only combination product for glaucoma and offers a convenience to patients. Dorzolamide causes more local ocular irritation than brinzolamide; however the burning and stinging upon instillation lasts less than ten seconds, diminish over time, and has not translated into a higher discontinuation rate due to adverse events.

4) *Alpha 2 adrenergics* – Apraclonidine (Iopidine) is used primarily short-term following ocular surgery, while brimonidine is used chronically for glaucoma. Both apraclonidine and brimonidine lower IOP to similar extent. For brimonidine, changing the BAK preservative (generic) to a purite preservative (Alphagan P) and reducing the concentration from 0.2% to 0.15% or 0.1% does not appear to affect efficacy. There are conflicting data as to whether brimonidine purite 0.15% (Alphagan P) causes less ocular irritation than brimonidine BAK 0.2% (generic). In an unpublished trial, brimonidine purite 0.1% (Alphagan P) demonstrated an improved safety and tolerability profile compared to brimonidine BAK 0.2% (generic).

5) *Adrenergics, cholinergics, and cholinesterase inhibitors* – The cholinergic pilocarpine (Pilocar, generics; Pilopine HS gel) is used for acute angle closure glaucoma and as a miotic agent during ocular surgery. Although not routinely used today, the adrenergic drug dipivefrin (Propine), the cholinergics acetyl-choline (Miochol-E) and carbachol (Isopto Carbachol) and the cholinesterase inhibitor echothiophate (Phospholine Iodide) serve unique niches in therapy.

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

Relative Cost Effectiveness Conclusion: Based on the results of several CMAs, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) that:

1) The CMAs compared the weighted average cost per day of treatment for each drug product. For the prostaglandin analogs: a) travoprost (Travatan, Travatan Z) was most cost effective under a scenario where it was the sole agent on the uniform formulary; b) latanoprost and bimatoprost were most cost effective under a scenario where only two prostaglandin products were placed in the UF; and c) an all-on scenario (i.e., all three prostaglandin products were included on the UF) was less cost effective than a scenario where at least one prostaglandin was designated non-formulary.

2) For the other ophthalmic glaucoma agents, only two products were identified as not cost effective in the beta-blocker subclass. Timolol hemihydrate (Betimol) and timolol maleate (Istalol) were both shown to be significantly more costly and no more effective than other agents in the subclass. Similarly, a comparison of the topical carbonic anhydrase inhibitors showed that brinzolamide was not cost

effective compared to dorzolamide. All other medications in the remaining subclasses were determined to be cost effective relative to their comparators.

A. ***COMMITTEE ACTION: UF RECOMMENDATION*** – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ophthalmic glaucoma agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that latanoprost, bimatoprost, levobunolol, betaxolol, carteolol, timolol maleate (Timoptic, generics), timolol maleate gel-forming solution, brimonidine, apraclonidine, dorzolamide, dorzolamide/timolol, dipivefrin, acetylcholine, carbachol, pilocarpine, echothiophate be maintained as formulary on the UF and that travoprost (Travatan, Travatan Z), timolol hemihydrate, timolol maleate (Istalol) and brinzolamide be classified as non-formulary under the UF (see paragraphs 8A, 8B and 8C on pages 52-64 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation for travoprost, timolol hemihydrate, timolol maleate (Istalol) and brinzolamide, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for travoprost, timolol hemihydrate, timolol maleate (Istalol) and brinzolamide (see paragraph 8D on pages 64-65 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 8E on page 65 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. ***COMMITTEE ACTION: BCF RECOMMENDATION*** – The P&T Committee considered the BCF status of the ophthalmic glaucoma agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend that the BCF include latanoprost; brimonidine, excluding the 0.1% strength; timolol maleate (Timoptic, generics) 0.25% and 0.5%; timolol maleate gel-forming solution 0.25% and 0.5% (Timoptic XE, generics); and pilocarpine (see paragraph 8F on page 65 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

9. DRUG CLASS REVIEW – MAOI ANTIDEPRESSANTS

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the MAOI antidepressants marketed in the U.S. The drugs in the MAOI antidepressant class include three oral agents, isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate, generics); and one transdermal patch, selegiline (Emsam). Tranylcypromine is the only drug in the MAOI antidepressant class available in a generic formulation. All of the drugs are available in oral dosage forms; however, oral selegiline capsules are excluded from the review, since they are indicated for use in Parkinson's Disease and not depression. The three oral MAOI antidepressants were first introduced to the market in the early 1960s, while transdermal selegiline was launched in 2006. The MAOI antidepressants accounted for approximately $283,000 dollars in expenditures in FY 2006, which comprises less than 1% of total MHS expenditures for all antidepressant drug classes.

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

1) The oral MAOI antidepressants isocarboxazid, phenelzine, and tranylcypromine have been marketed for several decades, but have been replaced by newer drug classes (e.g., SSRIs) with more favorable adverse event profiles.
2) Transdermal selegiline is the newest MAOI antidepressant marketed. The non-oral formulation was developed to reduce the risk of hypertensive crisis from dietary tyramine.
3) There do not appear to be major differences in clinical efficacy between the three oral MAOIs when used for depression, based on the results of one meta-analysis showing response rates ranging between 53% to 61%, and one inpatient clinical trial.
4) Response rates ranging from 27% to 30% were reported with transdermal selegiline in three placebo controlled trials. There are no clinical trials directly comparing the oral MAOI antidepressants with transdermal selegiline. However, there are no data to suggest that treatment with transdermal selegiline would result in improved response rates compared to the oral MAOI antidepressants.
5) The MAOI antidepressants have a safety profile that is well recognized in terms of drug-drug and drug-food interactions, and these adverse events also apply to transdermal selegiline. Local application site reactions are common with transdermal selegiline.
6) The purported benefits of transdermal selegiline in terms of loosened dietary tyramine restrictions have only been shown clinically with the lowest dose (6 mg/24 hour). Dietary precautions are required with oral MAOIs and with the 9 mg/24 hr and 12 mg/24 hr dosages of transdermal selegiline.

7) Off-label usage of transdermal selegiline is anticipated for treating patients with Parkinson's Disease.

8) The primary advantage of transdermal selegiline is for patients unable to swallow oral medications and require a once-daily dosage formulation.

9) There is insufficient evidence to determine whether transdermal selegiline represents a therapeutic advance over isocarboxazid, phenelzine and tranylcypromine.

10) Based on clinical issues alone, there are no reasons to designate any of the MAOI antidepressants (phenelzine, isocarboxazid, or tranylcypromine, and transdermal selegiline) as non-formulary on the UF.

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

1) The oral MAOIs demonstrate similar relative cost effectiveness, with phenelzine as the most cost effective agent.

2) Transdermal selegiline is not cost effective relative to the other agents in the class in the treatment of depression and provides no clinically meaningful therapeutic advantage to justify the increased cost.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the MAOI antidepressants, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that isocarboxazid, phenelzine and tranylcypromine be maintained as formulary on the UF, and that transdermal selegiline be classified as non-formulary under the UF (see paragraphs 9A, 9B, and 9C on pages 66-71 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for MN criteria for transdermal selegiline, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for transdermal selegiline (see paragraph 9D on page 71 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation

period will begin immediately following approval by the Director, TMA (see paragraph 9E on pages 71-72 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. ***COMMITTEE ACTION: EXTENDED CORE FORMULARY (ECF) RECOMMENDATION*** – The P&T Committee had previously determined at the November 2006 meeting that one MAOI antidepressant should be added to the ECF based on the clinical and cost effectiveness review. The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that phenelzine be classified as the ECF agent (see paragraph 9F on pages 71-72 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Appendix A – TABLE 1. Implementation Status of UF Recommendations/Decisions
Appendix B – TABLE 2. Newly Approved Drugs
Appendix C – TABLE 3. Abbreviations
Appendix D – FIGURE 1. PA Process for SED-1 Agents Other than Zolpidem IR

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

MG Elder Granger, USA, MC
Deputy Director, TMA
for S. Ward Casscells, M.D.
Date: 5/24/07

Department of Defense
Pharmacy and Therapeutics Committee Minutes
February 2007

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 13-14 February 2007 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

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

B. Voting Members Absent

LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Maj Chang Chinran, NC, USAF	Health Plans Operations, TMA
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CPT Alvin Blackmon, MSC, USA	Defense Supply Center Philadelphia
Mr. Lynn T. Burleson	Assistant General Counsel, TMA
LT Thomas Jenkins, MSC, USN	TMOP/TRRx COR

D. Non-Voting Members Absent

None	

E. Others Present

Col Nancy Misel, BSC, USAF	IMA DoD Pharmacoeconomic Center
CAPT Don Nichols, MC, USN	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
LCDR Joe Lawrence, MSC, USN	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Shana Trice, Pharm.D.	DoD Pharmacoeconomic Center
David Bretzke, Pharm.D.	DoD Pharmacoeconomic Center
Angela Allerman, Pharm.D.	DoD Pharmacoeconomic Center
Eugene Moore, Pharm.D.	DoD Pharmacoeconomic Center
Julie Liss, Pharm.D.	DoD Pharmacoeconomic Center
Elizabeth Hearin, Pharm.D.	DoD Pharmacoeconomic Center
David Meade, Pharm.D.	DoD Pharmacoeconomic Center
Harsha Mistry, Pharm.D.	DoD Pharmacoeconomic Center
Mark Geraci, Pharm.D.	VAPBM
Capt Jeremy King, MC, USAF	WHMC

3. REVIEW MINUTES OF LAST MEETING

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

B. Approval of November Minutes - Dr. William Winkenwerder, Jr., M.D., approved the minutes of the November 2006 DoD P&T Committee meeting on 17 January 2007.

4. ITEMS FOR INFORMATION

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

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

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

C. **Status of Exenatide (Byetta) Prior Authorization (PA)** – The PEC briefed the members of the P&T Committee on preliminary results of implementing the PA for exenatide, which went into effect 31 January 2007. The exenatide PA represents the first use of the new automated profile review capability in the Pharmacy Data Transaction Service (PDTS), which enables PA criteria to be automated based on a "look-back" at patient profiles during a given period. The percent of patients automatically approved through the automated process during the first few days the exenatide PA was in place was consistent with previous estimates; the process appears to be functioning as designed.

D. **Administrative Action: PA Criteria for Exenatide** – The PEC notified the P&T Committee of a December 2006 change in Food and Drug Administration (FDA)-approved labeling for exenatide. The new labeling states that exenatide is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, *a thiazolidinedione*, a combination of metformin and a sulfonylurea, *or a combination of metformin and a thiazolidine-dione*, but have not achieved adequate glycemic control. Italicized text indicates changes in labeling. The P&T Committee ratified the corresponding changes to exenatide PA criteria made under the auspices of the Executive Council, which were accomplished prior to implementation of the PA on 31 January 2007.

E. **Status of Fentanyl Patch PA** – The P&T Committee discussed implementation of the PA for fentanyl patch recommended at the November 2006 meeting and approved by the Director, TMA in January 2007. The Committee clarified the "look-back" period and definition of prior opioid use that will be used by the automated PA review process. The specific automated PA criteria that will be applied to all fentanyl prescriptions will be the following:

   - Patient is likely to be opioid-tolerant based on receiving at least one prescription for one of the following strong opioids (fentanyl patch, morphine, oxycodone (not including combination products), hydromorphone, methadone, or oxymorphone) during the last 60 days.

   The P&T Committee reached this conclusion after reviewing estimates of the number and percent of fentanyl patch patients that would be affected by the PA, including the number of patients who had received fentanyl patch prescriptions during the last 120 days, but not within the last 60 days. The P&T Committee agreed that the best trade-

off between ensuring safety and potentially interrupting therapy for established patients would be to allow pharmacists at retail network pharmacies the ability to override the system warning after determining that the patient could be presumed to be opioid tolerant based on information from the patient or the physician. The retail network pharmacist would also have the option of having Express Scripts, Inc. (ESI) handle the PA by advising patients to have their physicians contact ESI.

F. UF Request Process – The P&T Committee approved a request form to be used by military treatment facility (MTF) healthcare providers requesting consideration of potential changes to the Basic Core Formulary (BCF), Extended Core Formulary (ECF), or UF, including changes to medical necessity (MN) criteria for non-formulary medications, prior authorization criteria, or quantity limits. The three general process points previously agreed upon by the P&T Committee will apply:

- Requests will require review and concurrence by the local MTF P&T Committee.
- Requests will be required to contain adequate supporting evidence, including a fair, balanced, and thorough discussion of the relevant clinical literature, and present a rational argument supporting suggested changes.
- Requestors will be required to explain potential conflicts of interest and certify that the request was not initiated or unduly influenced by pharmaceutical industry representatives.

G. Regulatory Status of Pseudoephedrine (PSE) Products – The PEC briefed the committee on the Methamphetamine Anti-Proliferation Act (MAPA), part of the Children's Health Act of 2000; the Combat Methamphetamine Epidemic Act (CMEA) of 2005; and Oregon House Bill 2485 (2005). These three pieces of legislation were enacted to address the diversion of drug products containing PSE, ephedrine and phenylpropanolamine (PPA) for the illicit production of methamphetamine. (PPA has been removed from the human drug market but remains available for veterinary use.)

The CMEA requires pharmacies and other sellers to place PSE products behind the counter; check the identity of purchasers; maintain a log of each sale that includes the purchaser's name and address, signature of the purchaser, product sold, quantity sold, date, and time; maintain the logbook for at least two years; train employees in the requirements of the law; and certify to the Drug Enforcement Agency (DEA) that the training has occurred. Most states have enacted similar legislation.

The State of Oregon passed Oregon House Bill 2485 (2005), which stipulated that the State Board of Pharmacy designate PSE as a Schedule C-III controlled substance. This designation imposed a limit of 90 days supply for a prescription in the State of Oregon. It also requires that refills be filled within 180 days of prescription origin. The bill does not prohibit over-the-counter (OTC) sales, which continue to be subject to requirements of the CMEA. This bill affected 74 individuals in the TRICARE mail order pharmacy and 800 users in the retail point of service. Oregon patients receiving PSE products by prescription are now required to obtain a new prescription every six months.

As part of the review for this presentation, the PEC contacted eight Army and Navy MTFs to determine the regulatory impact on DoD OTC programs. Air Force policy prohibits OTC programs. Directors of four programs previously removed PSE off the drug list for OTC dispensing. Of facilities supplying PSE, all have QLs, require photo identification, and most require a signature. Navy policy requires entry of any of the drugs obtained from an OTC program into the patient's CHCS profile. Army policy does not require CHCS entries. Entry into the patient's CHCS profile would exceed the CMEA logbook requirement. Neither service has a program in place to meet the training requirements specified in the CMEA.

The P&T Committee agreed that there is little chance that large amounts of PSE could be diverted from MTF pharmacies. Mandatory logbook and training requirements are best addressed by the Pharmacy Service consultants/specialty leaders.

5. REVIEW OF RECENTLY APPROVED AGENTS

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

The P&T Committee was briefed on two new drugs, sitagliptin (Januvia) and paliperidone extended release [ER] tablets (Invega), which were approved by the FDA (see Appendix B). The P&T Committee determined that these two new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed.

B. Over-the-Counter Omeprazole Magnesium (Prilosec OTC)

Section 705 of the John Warner National Defense Authorization Act for Fiscal Year 2007 directs the Secretary of Defense to conduct a demonstration project under section 1092 of title 10, U.S. Code, to allow particular OTC drugs to be included on the UF under section 1074g of such title. For an OTC drug to be included as part of the OTC Demonstration Project, the P&T Committee must find that the OTC drug is cost effective and therapeutically equivalent to a prescription drug. Beneficiaries will be required to have a prescription for the OTC product.

OTC drugs provided under the demonstration project shall be made available through MTFs and the TRICARE mail order pharmacy. The demonstration will begin no later than 1 May 2007, and will last for a time period at least as long as the current contract, but no longer than five years.

Omeprazole magnesium is the first medication proposed for inclusion in the OTC Demonstration Project. Since this is the first opportunity for omeprazole magnesium to be considered for inclusion on the UF, it was reviewed as a new drug in a class already reviewed.

The P&T Committee previously reviewed the proton pump inhibitors (PPIs) in February 2005. These medications suppress secretion of gastric acid by irreversibly inhibiting H+, K+ ATPase (the proton pump) in gastric parietal cells. PPIs on the UF include prescription omeprazole (Prilosec, generics), rabeprazole (Aciphex), lansoprazole (Prevacid), and pantoprazole (Protonix). Esomeprazole (Nexium), the s-

isomer of omeprazole, is non-formulary under the UF. The BCF selections in this class are prescription omeprazole and rabeprazole.

1) *Relative Clinical Effectiveness* – Prescription omeprazole, first approved in 1987, is indicated for short-term treatment of active duodenal ulcer, benign gastric ulcer, and endoscopically-diagnosed erosive esophagitis; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease; maintenance of healing of erosive esophagitis; long-term treatment of pathological hypersecretory conditions such as Zollinger-Ellison Syndrome; and for eradication of *H. pylori* infection (in combination with clarithromycin). Recommended doses range from 20 mg to 60 mg per day. It is available in 10-, 20-, and 40-mg delayed release capsules.

   Omeprazole magnesium was approved as an OTC medication in June 2002 based on placebo-controlled trials that found it to be effective in the treatment of recurring heartburn. It is labeled as a 14-day once-daily course of treatment for frequent heartburn (occurring two or more times per week), which may be repeated every four months. Each 20.6 mg delayed release tablet of omeprazole magnesium is equivalent to 20 mg of omeprazole. There is no reason to believe that the pharmacology or pharmacokinetics of omeprazole magnesium differ from prescription omeprazole.

   Common adverse events reported with the use of omeprazole magnesium include headache, diarrhea, and elevations in liver enzymes. Rare but severe adverse events include liver injury, bone marrow suppression, Stevens-Johnson syndrome, and hypersensitivity. Omeprazole magnesium is Pregnancy Category C. It is not recommended for patients under 18 years of age.

   Conclusion: The P&T Committee concluded that omeprazole magnesium has similar relative clinical effectiveness compared to other PPIs included on the UF. The P&T Committee also concluded that, while Food and Drug Administration (FDA)-approved indications differ for the OTC and prescription versions of omeprazole, there is no reason to believe that the clinical effect of omeprazole magnesium, when given to the same patients in the same doses, would differ from the anticipated effects of prescription omeprazole.

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

   Based on the information reported from the relative clinical effectiveness evaluation, there was evidence to suggest that omeprazole magnesium has similar efficacy, safety, tolerability, and clinical outcomes compared to the existing drugs in the PPI class.

   The cost review for omeprazole magnesium compared the cost per unit across all three points of service to the other PPIs.

Conclusion: The results of the cost review showed that omeprazole magnesium is cost effective on a per unit basis when compared to generic prescription omeprazole in the mail order and MTF points of service. Omeprazole magnesium is more cost effective when compared to generic prescription omeprazole in the retail point of service. Omeprazole magnesium is more cost effective when compared to other products in the PPI class (i.e., esomeprazole, lansoprazole, pantoprazole, and rabeprazole) across all three points of service.

3) *Clinical and Cost effectiveness Conclusions* – The P&T Committee voted (13 for, 0 opposed, 2 abstained, 2 absent) to accept the clinical and cost effectiveness conclusions stated above.

   COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 2 abstained, 2 absent) to recommend that omeprazole magnesium be classified as formulary under the UF.

4) *MN Criteria* – Since omeprazole magnesium was not recommended for nonformulary status under the UF, establishment of MN criteria is not applicable.

5) *UF Implementation Period* – Since omeprazole magnesium was not recommended for nonformulary status under the UF, establishment of an implementation plan is not applicable.

6. DRUG CLASS REVIEW – NEWER SEDATIVE HYPNOTICS (SED-1s)

The P&T Committee evaluated the relative clinical effectiveness of the newer sedative hypnotic agents (SED-1s). The SED-1 drug class includes the following agents: zolpidem immediate release [IR] (Ambien), eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), and zolpidem ER (Ambien CR).

All SED-1 agents except ramelteon are classified as benzodiazepine receptor agonists; they bind to benzodiazepine gamma-aminobutyric acid (GABA) receptors in the brain, but at a different site than the benzodiazepines. Ramelteon is mechanistically different; it acts as an agonist at melatonin receptors (MT_1 and MT_2) in the suprachiasmatic nucleus of the brain, which is responsible for regulation of the 24-hour sleep-wake cycle (circadian rhythm). All are FDA-indicated for the treatment of insomnia, although specific labeling differs.

The newer sedative hypnotics are preferred to benzodiazepines (the second most commonly used drug for insomnia) primarily due to a more favorable adverse effect profile and lower potential for abuse. They are widely used worldwide. Other medications for insomnia include sedating antidepressants such as trazodone, sedating antihistamines such as diphenhydramine, and other rarely used medications (e.g., chloral hydrate).

Utilization of the SED-1 agents is increasing rapidly in DoD. As of Dec 2006, about four million Military Health System (MHS) prescriptions for these agents are filled per month; the drug class was ranked #15 in terms of expenditures in FY 2006 ($111 million) – up from #18 in 2005 ($72 million), and #20 in 2004 ($54 million). Retail network

pharmacies dispense about three times more tablets than do MTFs and approximately five times more than mail order. Across the MHS, zolpidem IR is the most commonly prescribed SED-1, with about twice as many prescriptions compared to the next most commonly prescribed agent, zolpidem ER. Zolpidem ER is followed closely by eszopiclone. Usage of zaleplon is low and stable, while usage of the most recently introduced agent, ramelteon, is low but increasing. All of the SED-1 agents are brand-only; zolpidem IR is expected to become generically available in April 2007.

A. SED-1s – Relative Clinical Effectiveness

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

Insomnia is the most common sleep complaint across all stages of adulthood. Prevalence increases with age, from an estimated 10% of the younger adult population to up to 50% of elderly adults. Treatment includes both pharmacologic and non-pharmacologic approaches; however, non-pharmacologic treatments such as cognitive behavioral therapy are often not available to patients due to the need for extensive clinical contact. Patients should receive instruction on sleep hygiene measures (such as removing distractions from the sleeping area and avoiding stimulants at bedtime).

1) Efficacy

Many clinical trials compare the newer sedative hypnotic agents to placebo; some of these trials include an active comparator (most commonly zolpidem IR in addition to placebo. There are also many published trials comparing these agents to benzodiazepines. Two studies compare zolpidem IR to trazodone (Desyrel, generics), an antidepressant commonly used for insomnia.

In addition to measures of sleep onset and duration, the Committee also reviewed data assessing effect on quality of life, since the ultimate goal of treating insomnia is to improve overall health and well-being, not merely to increase the number of minutes spent asleep.

Based on this information, the P&T Committee came to the following conclusions:

- All SED-1 agents improve sleep latency (the amount of time it takes to fall asleep) compared to placebo, based on both polysomnographic measures (monitoring performed in a sleep lab) and subjective measures (as reported by patients). The amount of improvement compared to placebo appears similar among all of the agents. Data supporting the effect of ramelteon on sleep

latency appear to be the least robust, both in terms of the number of published studies and the amount of improvement demonstrated versus placebo. Published data with zolpidem ER are also limited, with a single published trial, but sleep latency data appear similar to the IR formulation and pharmacokinetic studies show little or no difference in initial drug concentrations.

- Zolpidem IR and eszopiclone appear to consistently improve total sleep time and awake time after sleep onset (or the amount of time spent awake after initially falling asleep) to a similar degree versus placebo. Zaleplon and ramelteon do not consistently demonstrate increases in measures of sleep duration.
- Zolpidem ER is a controlled release version of zolpidem consisting of a two-layer tablet providing an IR phase followed by a prolonged release phase. The formulation is intended to retain the onset and elimination characteristics of zolpidem IR while maintaining plasma concentrations three to six hours post-dose. Time versus concentration curves comparing zolpidem ER to zolpidem IR show comparable initial concentrations followed by higher concentrations of zolpidem ER during this time period. However, it is unclear whether this is associated with a clinically significant increase in sleep duration, as clinical trial data comparing zolpidem IR and ER are not available and reported effects on sleep duration with zolpidem ER do not appear markedly different from results from zolpidem IR trials.
- Trials including two or more SED-1 agents (usually compared to placebo) include three published trials comparing zaleplon and zolpidem IR to placebo and one unpublished trial obtained from the FDA statistical review of eszopiclone that included eszopiclone and zolpidem IR. Based on these trials, zaleplon decreased sleep latency to a greater degree than zolpidem IR (8-24 minutes for zaleplon versus 6-13 minutes for zolpidem IR, but zolpidem IR increased total sleep time more than zaleplon (28-42 minutes for zolpidem IR versus 7-27 minutes for zaleplon). More rebound insomnia was noted with zolpidem IR on the first night after discontinuation. The FDA statistical review for eszopiclone reported very similar results for eszopiclone versus zolpidem IR with respect to sleep latency, total sleep time, and awake time after sleep onset.
- Based on trials comparing zolpidem IR and zopiclone (eszopiclone's racemic parent drug) to benzodiazepines, the newer sedative hypnotics appear to be similar in efficacy to the benzodiazepines. Short-term adverse events appear similar based on published trials; however, there appears to be more rebound insomnia with benzodiazepines than with the newer sedative hypnotics.
- A single comparative trial of zolpidem IR versus trazodone in adult insomnia sufferers without co-morbid depression demonstrated similar efficacy during the two weeks of the study; although trazodone may result in greater daytime somnolence than zolpidem IR.

- In regard to improvement of sleep architecture, there are no consistent data to demonstrate that the newer sedative hypnotics increase the length of time spent in the stages of sleep associated with restorative sleep to a degree that is clinically significant, compared to placebo.
- The most extensive data supporting long-term efficacy and safety are for eszopiclone, which has data from a 6-month randomized controlled trial (RCT) and open label data out to one year. Zolpidem IR has data from RCTs indicating continued efficacy and safety over 35 nights of nightly use and 84 nights of non-nightly use, with open label data out to one year. No long-term data is available for zolpidem ER, which was only tested in short-term trials (three weeks), although it is probably reasonable to expect long-term results similar to zolpidem IR (Ambien). Zaleplon RCT data are limited to 4-week trials, although open label data supporting efficacy and safety for up to one year is available in elderly patients. Ramelteon has shown sustained efficacy and safety for up to five weeks in RCTs, with open label data out to one year.
- Improvement in overall quality of life as a function of improved sleep was not usually addressed in either short- or long-term clinical trials. However, a few trials employed quality of life assessment tools, with one of the most useful measures being the standardized short-form 36 (SF-36) questionnaire. Two non-nightly zolpidem IR studies demonstrated a minimal improvement on certain aspects of the SF-36 after treatment, but no difference from placebo on other aspects. Two eszopiclone studies that included pre and post-treatment questionnaires addressing improvement in overall sense of well-being showed no significant improvement versus placebo. The Committee concluded that there is insufficient evidence to conclude that SED-1 agents have a major beneficial effect on quality of life, although there limited are data showing improvement in certain aspects of quality of life. There are insufficient comparative data to draw conclusions about individual agents.

2) Safety / Tolerability

- The SED-1 agents, including both the benzodiazepine receptor agonists and ramelteon, appear to have similar adverse effect profiles, most commonly drowsiness, dizziness, and headache. Rates of discontinuation due to adverse events during clinical trials were similar among the SED-1 agents, ranging from about 2-6% in short-term trials. Adverse effects and discontinuation rates due to adverse events were similar in comparative trials (zolpidem IR versus zaleplon; eszopiclone versus zolpidem IR). An unpleasant taste was consistently reported with eszopiclone during clinical trials, occurring in about 26.1% of patients receiving eszopiclone versus 5.6% with placebo over the course of a 6-month trial.
- Daytime sleepiness, impairments in psychomotor function and cognitive function, adverse effects on driving safety, and increased risk for falls may occur with any of the benzodiazepine receptor agonists; there are little or no data for the melatonin receptor agonist ramelteon. Agents with longer elimination half-lives tend to pose a greater risk for these effects. Particularly

notable is the 6-hour half-life of eszopiclone, which may extend to nine hours in elderly patients, compared to half-lives of about one hour for zaleplon, 1-2.6 hours for ramelteon and 2.5-2.8 hours for zolpidem (Ambien, Ambien CR). Lower starting doses of all SED-1 agents except ramelteon are recommended in elderly patients.

- Driving safety studies report impaired performance and increased risk of accidents with eszopiclone's racemic parent drug zopiclone (widely used outside the U.S.) at a 7.5 mg daily dose. The applicability of these data to eszopiclone is unclear, since the usual younger and elderly adult dosing strengths of eszopiclone (3 and 2 mg, respectively) would be equivalent to zopiclone doses lower than 7.5 mg. Product labeling and marketing for eszopiclone advises against taking the product unless the patient is able to get eight or more hours of sleep; adherence to this warning is advisable. There was no reported difference between eszopiclone and zolpidem IR on subjective measures of next day effects (morning sleepiness, daytime alertness, daytime ability to function), based on results of one unpublished trial reported in the FDA statistical review of eszopiclone.
- Because of its very short half-life, a repeat dose of zaleplon may be taken after the patient has had difficulty falling asleep, as long as the patient is able to sleep for four or more hours. Driving studies with zaleplon 10 and 20 mg showed no significant effects on morning driving even after middle-of-the-night administration. Since the risk of falling and hip fracture tend overall to increase with increasing half-life, zaleplon may have an advantage in elderly patients. However, this is not a simple relationship and prescribers must take into account patient activity patterns; short half-life agents may be more likely to cause falls during the early part of the night.
- In other special patient populations, it is difficult to see major advantages or disadvantages for any one agent. All are hepatically metabolized and carry warnings about use and/or recommendations for dose adjustment in patients with hepatic dysfunction; pharmacokinetic parameters do not appear to be substantially affected by renal dysfunction. All are Pregnancy Category C. Little data is available concerning use in pediatric patients; there is some concern about chronic or chronic intermittent use of ramelteon in pediatric patients due to effects on prolactin and testosterone levels that are not felt to be clinically significant in adults.
- The most prominent withdrawal symptom upon discontinuation of the SED-1 agents is probably rebound insomnia, or worsening of insomnia compared to the patient's pre-treatment baseline; other withdrawal symptoms may also occur. Rebound insomnia typically occurs only in the first night after discontinuation. Occurrence of rebound insomnia has been reported in clinical trials with all of the SED-1 agents except ramelteon. Based on three trials, more rebound insomnia on the first night after discontinuation was noted with zolpidem IR versus zaleplon.

- All of the newer sedative hypnotics, with the exception of ramelteon, probably have a small, but significant potential for abuse, although this is likely to be rare in patients without psychiatric disorders or previous history of substance abuse. Ramelteon appears to lack significant abuse potential and may be preferable in patients with a high risk of substance abuse. Ramelteon is the only agent in this class that is not a DEA scheduled substance.
- No major comparative disadvantages were noted among the agents based on potential for drug-drug interactions. All are affected by potent CYP 3A4 inducers or inhibitors and have predictable additive effects if given with alcohol or other medications that can impair psychomotor performance. Cimetidine (Tagamet, generics) markedly increases levels of zaleplon due to inhibition of two metabolic pathways (CYP 3A4 and aldehyde oxidase); the initial dose of zaleplon should be decreased. The major metabolic route for ramelteon is CYP 1A2; ramelteon is contraindicated with the potent 1A2 inhibitor fluvoxamine (Luvox, generics) and may be less effective in smokers, since smoking is a 1A2 inducer.

3) Other Uses

Based on its effects on the sleep-wake cycle, ramelteon may have a niche in therapy for time zone shifting in travelers, or for phase shifting in shift workers, but data at this point are limited.

4) Provider Opinion

A total of 173 DoD healthcare providers responded to a survey regarding the SED-1 agents; 72% of responders were physicians, 22% pharmacists, 5% physician assistants or advanced practice nurses, and 1% other. The most common specialties were psychiatry (25%), pharmacists (22%), and family practice, internal medicine, or general practice (21%). The vast majority of responders (97%) indicated that they had zolpidem IR on their local formulary, but relatively few indicated that other SED-1 agents were on formulary (zolpidem ER 18%, ramelteon 3%, eszopiclone and zaleplon 0%).

The majority of responders estimated that between 40 and 79% of patients could be successfully treated with their first choice of agents. Most (71%) would treat patients failing the first agent with another SED-1 agent; the majority estimated that between 20 and 59% of patients could be successfully treated with the second agent. The majority of responders estimated that fewer than 20% of patients discontinue therapy due to adverse events.

5) Clinical Effectiveness Conclusion

The P&T Committee concluded that:

a) Based on placebo-controlled trials, all SED-1 agents decrease sleep latency to a similar degree. Data supporting the effect of ramelteon on sleep latency appear to be the least robust, both in terms of the number of published studies and the amount of improvement demonstrated versus placebo. Zolpidem IR and eszopiclone have evidence indicating consistent and similar increases in

sleep duration. Zaleplon and ramelteon do not appear to consistently increase sleep duration.

b) Based on three comparative trials, zaleplon appears to decrease sleep latency more than zolpidem IR, but zolpidem IR appears to increase total sleep time more than zaleplon. In one comparative trial, very similar results were reported for eszopiclone versus zolpidem IR with respect to measures of sleep latency and sleep duration.

c) Based on comparative trials, SED-1 agents appear to be similar in efficacy and short-term adverse events, compared to benzodiazepines; benzodiazepines may cause more rebound insomnia. Zolpidem IR appears to be similar in efficacy to the sedating antidepressant trazodone, based on one comparative trial in non-depressed patients; trazodone may result in greater daytime somnolence.

d) There are no consistent data to demonstrate that SED-1 agents have beneficial effects on sleep architecture, compared to placebo.

e) There is insufficient evidence to conclude that SED-1 agents have a major beneficial effect on quality of life, although limited data show improvement in certain domains of the SF-36. There are insufficient comparative data to draw conclusions about individual agents.

f) The SED-1 agents appear to have similar adverse effect profiles and to result in similar rates of discontinuation due to adverse events in clinical trials. Eszopiclone is associated with an unpleasant taste. There do not appear to be any major disadvantages for any one agent with respect to drug-drug interactions. Ramelteon may be less effective in smokers.

g) Daytime sleepiness, impairments in psychomotor function and cognitive function, adverse effects on driving safety, and increased risk for falls may occur with any of the benzodiazepine receptor agonists; there are little or no data for the melatonin receptor agonist ramelteon. Agents with longer half-lives tend to pose a greater risk for these effects. The SED-1 agent with the longest half-life is eszopiclone, six hours (up to nine hours in elderly patients); followed by zolpidem (Ambien, Ambien CR), 2.5-2.8 hours; ramelteon, 1-2.6 hours; and zaleplon, one hour. Lower starting doses of all SED-1 agents except ramelteon are recommended in elderly patients.

h) The applicability of driving safety studies reporting impaired performance and increased risk of accidents with a 7.5 mg dose of zopiclone (eszopiclone's racemic parent drug) is unclear, since recommended doses of eszopiclone would be equivalent to zopiclone doses lower than 7.5 mg. There was no reported difference between eszopiclone and zolpidem IR on subjective measures of next day effects based on results of an unpublished trial reported in the FDA statistical review of eszopiclone.

i) Because of its very short half-life, zaleplon may be taken in the middle of the night after a patient has had difficulty falling asleep without demonstrating adverse effects on driving performance the next morning. It may have an

advantage in elderly patients, since risk of falls and hip fracture tends overall to increase with increasing half-life (although the relationship between falls and half-life is not straightforward and prescribers must take into account patient activity patterns).

j) No SED-1 agent appears preferable in other special patient populations (hepatic or renal dysfunction, pregnancy, pediatrics); there is some concern about use of ramelteon in pediatric patients due to possible endocrine effects.

k) Rebound insomnia has been reported in clinical trials with all SED-1 agents except ramelteon; more rebound insomnia was noted with zolpidem IR than with zaleplon during comparative trials.

l) All SED-1 agents, with the exception of ramelteon, probably have a small but significant potential for abuse. Ramelteon appears to lack significant abuse potential and may be preferable in patients at high risk for substance abuse. Ramelteon is the only SED-1 agent that is not a DEA scheduled substance.

m) It is likely that at least two SED-1 agents are needed for adequate clinical coverage, based on provider responses regarding prescribing practices and likely patient response.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

B. SED-1s – Relative Cost Effectiveness

In considering the relative cost effectiveness of agents within this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2). Given the overall clinical conclusion that the agents within the SED-1 class have similar relative clinical effectiveness, a cost-minimization analysis (CMA) was employed to assess the relative cost effectiveness of the agents within this therapeutic class. The agents were evaluated on their weighted average cost per day of therapy across all three points of service.

The CMA for the SED-1 class revealed the following cost effectiveness rank-order (from most to least cost effective): 1) eszopiclone; 2) ramelteon; 3) zaleplon; 4) zolpidem IR; and 5) zolpidem ER. Although zolpidem IR was not as cost effective as eszopiclone in this CMA, the P&T Committee noted that zolpidem IR is scheduled to become generically available on 21 April 2007 and will likely become the most cost effective agent within the class shortly thereafter.

A budget impact analysis (BIA) of various UF formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, and non-formulary cost-shares). The goal of the BIA was to aid the P&T Committee in determining which group of SED-1 agents best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS.

The BIA also considered the cost effectiveness of implementing a prior authorization (PA) that requires a trial of zolpidem IR for patients starting treatment with a SED-1 agent. This PA would incorporate the automated PA capability in PDTS in order to "look-back" at the patient's profile during the last 180 days. Based on this automated review, TRICARE would cover prescriptions for a SED-1 agent other than zolpidem IR if the patient had received a prescription for any SED-1 agent (including zolpidem IR) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during this previous 180 days. Patients who had not received a SED-1 agent prescription during the last 180 days would be required to meet PA criteria for any SED-1 agent other than zolpidem IR (Ambien). (See Appendix D.)

Cost Effectiveness Conclusion

The P&T Committee concluded that:

1) Eszopiclone was the most cost effective agent until zolpidem IR becomes generically available with competitive pricing.
2) Ramelteon, zaleplon, and zolpidem ER were more costly than eszopiclone and provided no meaningful clinical therapeutic advantage compared to eszopiclone or zolpidem IR.
3) The UF scenario utilizing a prior authorization requiring a trial of zolpidem IR by new SED-1 patients was more cost effective relative to UF scenarios not requiring a trial of zolpidem IR by new SED-1 patients.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to accept the cost effectiveness conclusion stated above.

C. SED-1s – UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the SED-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 2 abstained, 1 absent) to recommend that: 1) zolpidem IR and eszopiclone be maintained as formulary on the UF with a prior authorization requiring a trial of zolpidem IR for new patients and 2) that ramelteon, zaleplon, and zolpidem ER be classified as non-formulary under the UF with a PA requiring a trial of zolpidem IR for new patients.

The P&T Committee agreed that the following PA criteria should apply to SED-1 agents other than zolpidem IR. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:

   The patient has received a prescription for any SED-1 agent (including zolpidem IR) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2) PA criteria if automated criteria are not met:

   The patient has tried zolpidem IR and had an inadequate response or was unable to tolerate it due to adverse effects.

Treatment with zolpidem IR is contraindicated.

The P&T Committee noted that in order for a patient to receive a non formulary SED-1 agent at the formulary cost-share, both the PA and MN criteria must be met. If the PA criteria are met without an approved MN determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved PA for ramelteon, zaleplon, or zolpidem ER would NOT automatically receive it at the formulary cost-share.

The P&T Committee also noted that the PA is not intended to apply where there are existing policies and protocols in place for operational/readiness situations and that MTFs should make necessary allowances for such use.

D. SED-1s – MN Criteria

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

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Use of formulary alternatives has resulted in therapeutic failure.

The P&T Committee noted that while zolpidem IR and eszopiclone would both be considered formulary alternatives, a trial of zolpidem IR would be required for patients who had not received a SED-1 prescription in the last 180 days at an MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order).

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

E. SED-1s – UF Implementation Period

Approximately 40,447 patients (21% of all SED-1 patients) would be affected by the recommended non-formulary selections in this drug class. This figure includes both patients who have previously received SED-1 agents, as well as new users starting on SED-1 agents. Based on the number of new users and the current percentage of new users receiving SED-1 agents other than zolpidem IR in retail (50%) and mail (40%), the prior authorization for SED-1 agents other than zolpidem IR would affect approximately 12,500 users per quarter, or 50,000 annually.

The P&T Committee noted that this would be the first time a PA including the newly available automated review process had been established in a class also including non-formulary agents and that many operational details of the process had yet to be worked out. Accordingly, the P&T Committee voted to recommend an implementation period of the greater of 1) the first Wednesday following a 90-day implementation period or 2) the time necessary to complete logistical arrangements to implement the automated PA.

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

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 2 abstained, 1 absent) to recommend an implementation period of the greater of 1) the first Wednesday following 90 day implementation period or 2) the time necessary to complete logistical arrangements to implement the automated PA.

F. SED-1s – BCF Review and Recommendations

The P&T Committee considered the BCF status of the SED-1 Agents. Currently there are no SED-1 agents on the BCF; the P&T Committee had previously determined at the August 2006 meeting that at least one SED-1 agent would be placed on the BCF. Zolpidem IR is widely used at MTFs, has clinical data supporting efficacy both for decreasing sleep latency and increasing sleep duration, is clinically similar to other SED-1 agents with respect to safety and tolerability, and is expected to become the most cost effective SED-1 agent after it becomes generically available (anticipated date: 21 April 2007). The P&T Committee agreed that zolpidem IR should be placed on the BCF.

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 3 abstained, 1 absent) to recommend adding zolpidem IR as the BCF selection in this class.

7. DRUG CLASS REVIEW – NARCOTIC ANALGESICS

The drugs in this class comprise all narcotic analgesics (also referred to as opioids or opiate agonists) used for the treatment of pain on an outpatient basis, including combinations with acetaminophen (APAP), aspirin (ASA), and other non-opioids. Not included in this drug class review are narcotic analgesics given primarily by intravenous injection or infusion, over-the-counter products, products requiring administration by a medical professional, products in which the narcotic component is primarily used as an antitussive, and products indicated solely for the treatment of opioid dependence.

For review purposes, the narcotic analgesics were divided into the following categories, based on their potency (as reflected by their DEA status) and whether or not they are combined with a non-opioid analgesic, as outlined in Table 1. These categories do not take into account all differences among agents, but serve to reduce the large number of available agents into manageable categories. Most of these agents are now generically available.

The narcotic analgesics accounted for approximately $153 million dollars in MHS expenditures in FY 2006 and are ranked #8 in terms of total expenditures during that time period. Approximately 437,000 DoD beneficiaries received one or more prescriptions for a narcotic analgesic during FY 2006.

By category, the majority of MHS narcotic analgesic prescriptions during FY 2006 (59%) were for the lower potency opioid combinations, which are widely prescribed following

Table 1: Narcotic Analgesic Categories & BCF Listings as of Feb 2007

Category	Medications	BCF Agents (Feb 07)
High potency Opioids (Schedule II Agents) – Single Analgesic Ingredient	▪ Codeine* - tablets, solution, injection ▪ **Fentanyl** – transdermal (Duragesic), transmucosal lozenges (Actiq), buccal tablets (Fentora) ▪ Hydromorphone – injection, tablets, liquid ▪ Levorphanol – tablets, injection ▪ Meperidine – tablets, solution, injection ▪ Meperidine / promethazine – capsules ▪ Methadone – oral concentrate, solution, tablet, injection ▪ **Morphine** – IR tablets, 12-hr ER tablets (MS Contin, generics; Oramorph SR), 24-hr ER capsules (Avinza, Kadian), solution, suppositories, injection ▪ Opium - tincture; opium / belladonna alkaloids – suppositories ▪ **Oxycodone** – IR capsules, oral concentrate, solution, 12-hr ER tablets (Oxycontin), IR tablets ▪ Oxymorphone – IR tablets (Opana); 12-hr ER tablets (Opana ER)	Morphine sulfate 15 mg, 30 mg and 60 mg 12-hour extended release tablets (MS Contin, generics; excludes 100 and 200 mg strengths)
High potency (Strong) Opioids (Schedule II Agents) – Analgesic Combos	▪ **Oxycodone/** APAP – tablets, capsules, solution ▪ Oxycodone / ASA – tablets	Oxycodone 5 mg/APAP 325 mg and/or 500 mg oral
Lower-Potency (Mild) Opioids (Schedule III, IV, V & Non-Controlled Agents) – Single Analgesic Ingredient Agents	▪ Buprenorphine – injection (sublingual tablets not included in class) ▪ Butorphanol – nasal spray, injection ▪ Pentazocine / naloxone – tablets ▪ Propoxyphene – capsules, tablets ▪ Nalbuphine (not controlled) – injection ▪ **Tramadol** (not controlled) – IR tablet, 24-hr ER tablets (Ultram ER)	None
Lower-Potency (Mild) Opioids (Schedule III, IV, V & Non-Controlled Agents) – Analgesic Combos	▪ **Codeine / APAP** – tablets, elixir, oral suspension ▪ Codeine / ASA – tablets ▪ Codeine / ASA / carisoprodol - tablets ▪ Codeine / caffeine / butalbital / APAP – capsules ▪ Codeine / caffeine / butalbital / ASA – capsules ▪ Dihydrocodeine / caffeine / APAP – capsules, tablets ▪ Dihydrocodeine / caffeine / ASA – capsules ▪ **Hydrocodone / APAP** – capsules, solution, tablets ▪ Pentazocine / APAP – tablets ▪ **Propoxyphene / APAP** – tablets ▪ Propoxyphene / ASA / caffeine – capsule ▪ **Tramadol / APAP** (not controlled) – tablets	Codeine/APAP oral

* Pharmacologically and therapeutically, codeine is usually referred to as a weak opioid; however, single ingredient codeine formulations are classified by the DEA as Schedule II medications (C-IIs) and are so classified in this table. The most commonly used medications are bolded.
APAP = acetaminophen; ASA = aspirin; ER = extended release; IR = immediate release

injuries or medical / dental procedures; followed by high potency opioid combos (19%); high potency single analgesic products (13%); and lower potency opioid single analgesic products (9%). The majority of expenditures during this time period, however, were for the high potency single analgesic products (67%), followed by the lower-potency opioid combinations (20%), the high potency opioid combinations (8%), and the lower-potency single analgesic products (5%). This reflects the relatively higher cost and more intensive treatment regimens associated with the high potency single analgesic products used for chronic treatment of pain, some of which are still brand-only medications.

Pharmacologically, the narcotic analgesics act at opioid receptors (mu, kappa, and delta), inhibiting excitatory neurotransmission of substance P, acetylcholine, norepinephrine, dopamine, and GABA by blocking voltage-dependent calcium channels. Analgesia is mediated through changes in the perception of pain at the spinal cord (mu_2, delta, kappa receptors) and higher levels in the central nervous system (CNS) (mu_1 and kappa

receptors). Narcotic analgesics also have effects on the endocrine and immune systems. Stimulation at the mu receptor produces euphoria, respiratory depression, and physical dependence. In addition to acting at mu receptors, tramadol is also a weak inhibitor of norepinephrine and serotonin reuptake, resulting in inhibition of pain transmission in the spinal cord (similar to monoamine oxidase inhibitors [MAOIs] or tricyclic antidepressants [TCAs]).

Narcotic analgesics are primarily indicated for the treatment of mild, moderate and severe pain. Use correlates with potency, with the higher potency agents (e.g., morphine, oxycodone, fentanyl) used in more severe pain and lower potency agents and combinations with non-opioids used for less severe pain. Some narcotic analgesics have specific clinical niches:

- Opium is used in combination with the anticholinergic belladonna for the treatment of pain caused by ureteral spasm; more effective and/or safer agents have largely replaced the use of opium tincture for diarrhea.
- Use of meperidine, a short-acting narcotic analgesic primarily given parenterally due to poor oral absorption, is limited to acute pain situations due to a neurotoxic metabolite that can cause anxiety, tremors, myoclonus, and generalized seizures with repetitive dosing.
- Methadone is used for detoxification and maintenance treatment of narcotic addiction, but also for chronic pain.
- The nasal formulation of butorphanol is used primarily for migraine headache; this product was initially released as a non-scheduled product, but was subsequently scheduled as a C-IV controlled substance following multiple reports of abuse.
- Tramadol has a lower potential for abuse or respiratory depression than other narcotic analgesics, lacks significant cardiac effects, and is not associated with peptic ulcer disease, making it an alternative in patients who cannot tolerate non-steroidal anti-inflammatory drugs (NSAIDs). Due to its dual mechanism of action, tramadol may have a more prominent place in the treatment of neuropathic pain than other narcotic analgesics.

The majority of the narcotic analgesics are IR and/or short-acting medications most commonly used on an every four to six hour basis. Longer duration products include fentanyl transdermal patches (Duragesic, generics), which are applied every 72 hours; morphine, which is available in 12-hour (MS Contin, generics; Oramorph SR) and 24-hour ER formulations (Avinza, Kadian); oxycodone, which is available in a 12-hour ER formulation (Oxycontin); oxymorphone, which was recently approved as a 12-hour ER formulation (Opana ER), tramadol, which is available in a once daily ER formulation (Ultram ER), and methadone, which may be dosed less frequently when given chronically, due to a depot effect. Levorphanol has a long half-life and an extended duration of action (four to eight hours), but its use is limited by sedation and concerns about drug accumulation.

Pure opiate agonists may be categorized by their chemical structure as phenanthrenes (codeine, hydromorphone, morphine, and oxycodone; phenylpiperidines (fentanyl, meperidine); or diphenylheptanes (methadone, propoxyphene). They are therapeutically

classified as either strong opiates (hydromorphone, morphine, methadone, and oxycodone) or weak opiates (codeine, hydrocodone, and propoxyphene). Use of mixed agonist antagonists (e.g., buprenorphine, nalbuphine, butorphanol, and pentazocine) is limited by ceiling analgesia effects and the risk of inducing withdrawal symptoms and recurrence of pain in patients taking chronic opioids.

Tolerance to the adverse effects of narcotic analgesics, including respiratory depression, occurs with chronic use. Tolerance to therapeutic effects requiring dose escalation also occurs; some patients may require very large doses of narcotic analgesics to control their pain. Patients often require changes in chronic opioid therapy to address adverse effects or lack of efficacy; switching or rotating different opioids (opioid rotation) has been proposed as a strategy to obtain optimal pain control with minimum adverse effects.

Combination products including both a narcotic analgesic and non-opioid analgesic (most commonly acetaminophen) provide additive analgesic effects, but also limit the possible dose of the narcotic analgesic due to potential toxicity and dosing limits associated with the non-opioid component (e.g., no more than 4 grams of acetaminophen daily). They are not well suited for the treatment of chronic pain.

Standard tables of equianalgesic doses are available to assist clinicians in safely switching between long-acting opioids, typically by converting the total 24-hour dose to an equivalent amount of morphine and from there to the appropriate 24-hour dose of the new opioid. This process is complicated by wide intra-patient variability in response and incomplete cross-tolerance among opioids; for this reason, recommended conversions are usually conservative and titration of the new opioid is likely to be required. Disparate methodologies in calculating equianalgesic doses for transdermal fentanyl, levorphanol and methadone exist; these agents may be more difficult to titrate than other narcotic analgesics.

A. Narcotic Analgesics – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the narcotic analgesics class. Narcotic analgesics were divided into the categories outlined in Table 1, based on DEA schedule, potency, and whether or not the analgesic is a combination agent. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

The clinical efficacy review was divided into two major areas: chronic pain (cancer, non-cancer, or neuropathic) and acute pain (post-operative or non-specific). Because ample information is available for most of these agents, the review focused primarily on published meta-analyses, systematic reviews, and well-accepted tertiary literature sources, including clinical practice guidelines. A more detailed review of the literature was performed for specific issues affecting potential formulary decisions.

No single systematic review, meta-analysis, or clinical practice guideline addresses the use of narcotic analgesics to treat all types of chronic and acute pain. Sources included:

- *Chronic cancer pain* – Available cancer pain studies are in general too heterogeneous to conduct systematic reviews. The review included applicable conclusions from a 2001 Agency for Healthcare Research and Quality (AHRQ) technical report, a meta-analysis of four evaluable trials comparing long-acting oxycodone to morphine and hydromorphone [Reid *et al*, 2006], and head-to-head trials and data analyses comparing two or more narcotic analgesics published since the AHRQ report. Sources of clinical practice guidelines for the treatment of cancer pain include the World Health Organization, the American Pain Society, and the University of Texas MD Anderson Cancer Center.
- *Chronic non-cancer pain* – The most useful reference for the treatment of chronic non-cancer pain was the Drug Effectiveness Review Project (DERP) review of long-acting opioid analgesics for non-cancer pain, last updated July 2006 [Chou *et al*, 2006]. This review included all drugs reviewed here except for hydrocodone, levorphanol, and the agonist-antagonist agents. In addition, the review included a meta-analysis [Furlan *et al*, 2006] comparing "weak" opioids (tramadol, propoxyphene, codeine) and "strong" opioids (morphine, oxycodone) to other agents in chronic pain patients primarily suffering from chronic non-cancer pain (osteoarthritis, rheumatoid arthritis, or low back pain), as well as clinical trials assessing the efficacy of the two available fentanyl formulations for breakthrough pain (buccal tablets and transmucosal lozenges). Sources of clinical practice guidelines for the treatment of chronic non-cancer pain included the American Society of Interventional Pain and VA/DoD.
- *Chronic neuropathic pain* – Clinical evidence specifically addressing the use of narcotic analgesics in chronic neuropathic pain is limited; the most useful review was considered to be the one conducted by Finnerup *et al* (2005) in an attempt to construct an evidence-based algorithm for the treatment of neuropathic pain. The review also included a meta-analysis of trials assessing the efficacy of morphine, methadone, and oxycodone for neuropathic pain and published treatment recommendations from an expert panel group.
- *Acute pain* – There is little literature addressing the use of narcotic analgesics for non-specific acute pain. Consensus statements from the American Pain Society and the American Society for Pain Management Nursing support the appropriate use of "as needed" dosage range orders for narcotic analgesics in the treatment of acute pain. With respect to postoperative pain, the review relied heavily on the Bandolier Oxford League Table of Analgesic Efficacy, which is based on data compiled from single-dose studies in patients with moderate to severe pain. The review also provided clinical trial data or the results of Cochrane reviews for agents not included in the League table and recommendations from the VA/DoD Clinical Practice Guideline for the Management of Postoperative Pain.

1) Efficacy

a) Chronic pain

The clinical review divided chronic pain into three types, based on etiology: cancer pain, non-cancer pain, and neuropathic pain (considered separately from other causes of non-cancer chronic pain).

Treatment algorithms for chronic cancer pain typically start with non-opioids (e.g., NSAIDs, acetaminophen); progress to weak opioids such as codeine or hydrocodone, normally in combination with the non-opioid (some algorithms skip this step depending on pain severity); and then progress to around-the-clock treatment with long-acting high potency single analgesic agents plus IR opioids for breakthrough pain.

There is less consensus about the use of chronic opioids in patients with non-cancer pain (e.g., low back pain, rheumatoid arthritis, osteoarthritis), although various professional organizations have endorsed judicious use of opioids in patients with refractory chronic non-cancer pain. Recommended treatment algorithms are similar to chronic cancer pain.

The categories of drugs most pertinent to treatment of chronic pain are likely the high potency long-acting agents used on an around-the-clock basis for the treatment of constant pain, and the high potency IR agents, which are used for the treatment of breakthrough pain occurring despite treatment with long-acting agents. The most commonly used medications are long-acting and IR formulations of morphine, oxycodone, and fentanyl.

The placement of narcotic analgesics in treatment guidelines for neuropathic pain appears controversial; discussion of the topic is complicated by the fact that some authors consider tramadol to be an opioid and some do not. In general, narcotic analgesics are regarded as third-line agents after TCAs and gabapentin/pregabalin, although at least one set of treatment recommendations lists them among other agents as potential first-line choices.

iii) Clinical evidence in constant cancer pain

Available cancer pain studies are in general too heterogeneous to conduct systematic reviews and many are small and of poor quality. The 2001 AHRQ technical report provided an extensive review of cancer pain literature that served to highlight the limited data available. Out of nine trials, one reported oxycodone to be less effective than morphine, but equally or more often preferred by patients; one reported tramadol to be similar to morphine in efficacy and patient preference (nurses thought pain control was better with morphine but tramadol more tolerable); two reported methadone to be as effective as morphine; one reported buprenorphine as effective as morphine; and one reported propoxyphene to be more effective than low-dose morphine. Eight studies comparing sustained (12-hour formulations) and IR morphine found no difference in efficacy.

Head-to-head comparative trials, one meta-analysis, and a pooled analysis of transdermal fentanyl data published since the AHRQ report add little additional information. A meta-analysis of four randomized double-blind controlled trials found no differences in mean pain scores between oxycodone and either morphine or hydromorphone. An open-label trial comparing transdermal fentanyl to sustained release (every 12-hour) morphine found no differences in efficacy; the percentage of patients reporting constipation and withdrawals due to adverse effects favored transdermal fentanyl. A pooled analysis of transdermal fentanyl data reported similar results, with withdrawals due to adverse effects of 16% with transdermal fentanyl versus 23% with morphine ($p<0.001$). A 4-week trial comparing methadone and morphine reported similar efficacy, but a higher withdrawal rate with methadone (22% versus 6%, $p=0.019$). Two open-label crossover trials involving oxymorphone (Opana ER) versus morphine or oxycodone sustained release reported similar efficacy and concluded that patients could safely be switched from these medications to ER oxymorphone.

The 24-hour ER morphine products (Avinza and Kadian) are purported to have distinct advantages compared to 12-hour ER morphine products, including continuous pain relief, reduced sleep disturbance, ease of use, and fewer reported side effects. These benefits have not been shown to be statistically or clinically significant based on head-to-head trials with 12-hour ER morphine. Trials comparing Kadian or Avinza to 12-hour ER morphine have demonstrated bioequivalence (i.e., 12-hour ER morphine given as 45 mg every 12 hours = 90 mg of Avinza every 24 hours). There are no published trials directly comparing the two 24-hour ER products.

The two products do have some differences. Avinza is a capsule containing both IR and ER beads of morphine sulfate. Therapeutic serum levels are achieved rapidly (~0.5 hour) and then maintained for 24 hours. At steady state, plasma concentrations remain constant (no peak-trough phenomenon). Avinza is restricted to a maximum dose of 1600 mg daily, since it contains fumarate and can cause renal toxicity. Alcohol, including alcohol-containing medications, cannot be taken with Avinza, since this can lead to a rapid dissolution of the ER granules and premature release of morphine.

Kadian capsules contain polymer-coated ER pellets of morphine sulfate, which release morphine slowly within the gastrointestinal tract. The time to achieve maximum serum levels (~9.5 hours) is much longer than with 12-hour ER morphine (2-3 hours) or Avinza (~0.5 hours).

Both products can be opened and sprinkled onto applesauce for patients who have trouble swallowing pills. Kadian granules can also be suspended in water and administered down a large bore (≥16 French) gastrostomy tube, which is not possible with 12-hour ER morphine or oxycodone products.

iv) Clinical evidence in constant non-cancer pain

The DERP report on long-acting narcotic analgesics for non-cancer pain included products requiring dosing three or fewer times per day, including transdermal fentanyl and oral oxycodone, morphine, methadone, levorphanol, codeine, dihydrocodeine, and oxymorphone.

- Based on direct evidence from head-to-head studies, the report found no differences between agents overall. Evidence included three RCTs comparing transdermal fentanyl and long-acting morphine (two fair-quality trials showed similar efficacy, one poor quality trial showed greater efficacy for transdermal fentanyl); one RCT showing similar efficacy for long-acting morphine once-daily versus twice daily; and one RCT showing equal efficacy between long-acting oxymorphone and long-acting oxycodone.
- Reviewers found no useful indirect evidence concerning comparative efficacy based on 20 clinical trials comparing narcotic analgesics to other agents or placebo; withdrawal rates did not suggest tolerability advantages for any one product.
- Reviewers further found no evidence to suggest greater efficacy for long-acting versus short-acting opioids, based on seven fair-quality trials. Based on three of these trials, they concluded that there was fair evidence that long- and short-acting oxycodone were equally effective for pain control.

A 2006 systematic review [Furlan *et al*, 2006] included data from 41 trials of opioids (codeine, morphine, oxycodone, tramadol, or propoxyphene) for the treatment of chronic non-cancer pain. Results from a meta-analysis of 28 placebo-controlled trials favored opioids. A meta-analysis of eight trials comparing opioids to other agents (NSAIDs, TCAs) found no significant difference overall, although strong opioids (oxycodone, morphine) were significantly more effective than other agents. The review outlined adverse effect rates with opioids but did not provide useful detail regarding comparison of different agents.

A systematic review of eight trials [Devulder *et al*, 2005] assessing functional and quality of life outcomes in patients with chronic non-cancer pain in general reported favorable results with opioids, but studies were too heterogeneous to allow comparison of agents.

v) Clinical evidence in breakthrough pain

Historically, the standard practice has been to use the same opioid for treatment of baseline and breakthrough pain (e.g., sustained release and IR morphine), although fentanyl patches are commonly used along with morphine IR for breakthrough pain. Narcotic analgesics offering both a long-acting formulation and a short-acting formulation include morphine, oxycodone, fentanyl, and oxymorphone.

Recent trials primarily focus on the newer fentanyl products: oral transmucosal lozenges (Actiq, generic) and buccal tablets (Fentora). There is insufficient comparative evidence to directly compare the two formulations. Buccal fentanyl is more bioavailable and may therefore offer more consistent dosing; it is also sugar-free, unlike the transmucosal lozenges. The two products cannot be switched at a 1:1 conversion due to the difference in bioavailability (for example, patients receiving 200 to 400 mcg of Actiq should start on 100 mcg of Fentora). A specific regimen is provided in Fentora labeling for converting from Actiq to Fentora (but not vice versa). From a safety standpoint, there is probably a significant potential for medication errors related to this conversion.

vi) Clinical evidence in neuropathic pain

Authors of a systematic review of double-blinded, placebo-controlled trials in neuropathic pain conditions [Finnerup *et al*, 2005] attempted to use numbers-needed-to-treat (NNTs) to achieve one patient with 50% pain relief and numbers-needed-to-harm (NNHs) for one patient to drop out due to adverse effects to construct a treatment algorithm for neuropathic pain. The systematic review included 11 trials comparing opioids (morphine, oxycodone, methadone, or tramadol) to placebo. These trials showed evidence of efficacy for morphine in post-herpetic neuralgia and mixed neuropathic pain; oxycodone and tramadol in post-herpetic neuralgia and polyneuropathy, and methadone in post-herpetic neuralgia.

Authors concluded that if the proposed algorithm was based solely on NNTs for pain relief, it should place TCAs first, followed by opioids or gabapentin/pregabalin. However, taking into account quality of life measures and NNHs, the authors proposed an algorithm placing opioids as third-line therapy, following TCAs and gabapentin/pregabalin. A 2005 meta-analysis [Eisenberg *et al*, 2005] that included most of the same trials but excluded tramadol found overall efficacy for opioids in neuropathic pain, compared to placebo.

Overall, while there is evidence that opioids are effective for neuropathic pain, there is insufficient evidence to conclude that there are differences in efficacy between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.

b) *Acute pain*

The clinical review divided acute pain into two types, based on etiology: non-specific pain (e.g., low back, neck, shoulder, arm, or extremity pain) and post-operative pain.

Data in acute pain consist primarily of a plethora of very small, short-term (including single-dose) trials, most commonly in patients with post-op pain, and meta-analyses of these trials. There is little clinical evidence specifically addressing non-specific acute pain.

The most coherent approach to making sense of the available data appears to be the Oxford League Table of Analgesic Efficacy, a resource maintained by the evidence-based medicine journal/site Bandolier. The "League Table" aggregates data from randomized, double-blind, single-dose studies in patients with moderate to severe pain, using the NNT to achieve at least 50% pain relief over 4 to 6 hours as a common measure. Despite reliability issues (confidence intervals are broad for agents with relatively small datasets and probably unreliable for datasets representing fewer than 250 patients), some tentative conclusions can be drawn:

- For the combination agents, the League table generally supports the common perception of relative efficacy (oxycodone/APAP > hydrocodone/APAP > codeine or propoxyphene/APAP).
- Overall, both opioid combination agents and tramadol compare relatively poorly with NSAIDs.

Sources addressing agents not included in the League table did not add substantially to available data. One double-blind RCT [White *et al*, 1997] found similar efficacy with hydrocodone 7.5 mg/APAP 750 mg and ketorolac 10 mg given every 6 hours for up to 3 days following tubal ligation (although neither agent was regarded by authors as very effective). Ketorolac appeared to be more tolerable. A Cochrane review of 16 poor quality studies [Elbourne and Wiseman, 2006] comparing IM meperidine to tramadol or pentazocine concluded there was insufficient evidence to evaluate comparable efficacy and safety. More vomiting and drowsiness was noted with meperidine.

The VA/DoD guideline for postoperative pain draws few specific conclusions, but does advise against use of meperidine.

Overall, there is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain, although the League table does give an overall impression of relative potency. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen.

c) *Efficacy conclusion*

The DoD P&T Committee concluded that:

a) All of the reviewed narcotic analgesics appear to be effective at providing analgesia when used in equipotent dosing. There is insufficient evidence to conclude that there are differences in efficacy between narcotic analgesics, including high potency long-acting agents for the treatment of chronic cancer or non-cancer pain, high potency IR agents for the treatment of breakthrough pain, or narcotic analgesics in general for the treatment of neuropathic pain.

b) Strong narcotic analgesics appear to be more effective than non-opioid analgesics (NSAIDs, TCAs) in chronic non-cancer pain.

c) There is no evidence suggesting efficacy differences between long-acting and short-acting formulations of the same agents; however, long-acting products offer greater convenience and may be associated with fewer episodes of breakthrough pain.

d) There is insufficient evidence to support efficacy differences between the 12-hour ER morphine products (e.g., MS Contin and generics) and the 24-hour ER morphine products (Avinza, Kadian), or between the two 24-hour products (Avinza versus Kadian). Avinza is restricted to a maximum dose of 1600 mg daily and cannot be taken with alcohol (including alcohol-containing medications). Kadian has a much longer time to achieve maximum serum levels (~9.5 hours) compared to Avinza (~0.5 hour) or to 12-hour ER morphine (2-3 hours). Both Avinza and Kadian capsules can be opened and sprinkled on food; Kadian granules can be given via gastrostomy tube.

e) Historically, the standard practice has been to use the same opioid for treatment of baseline and breakthrough pain (e.g., sustained release and IR morphine), although fentanyl patches are commonly used along with morphine IR for breakthrough pain. There is insufficient evidence to conclude that there are differences in efficacy between IR agents for the treatment of breakthrough pain in patients with chronic cancer or non-cancer pain. Trials focusing on the newer IR fentanyl products—oral transmucosal lozenges and buccal tablets—do not supply sufficient evidence to directly compare efficacy. Buccal fentanyl is more bioavailable and may therefore offer more consistent dosing; it is also sugar-free, unlike the transmucosal lozenges. The lack of a 1:1 conversion between the two formulations may offer significant potential for medication errors.

f) Narcotic analgesics are rarely considered first-line treatment for the treatment of neuropathic pain. There is insufficient evidence to conclude that there are differences in efficacy between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.

g) There is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain, although the League table does give an overall impression of relative potency. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen.

2) Safety and Tolerability

a) General adverse effects

Narcotic analgesics are associated with an increased risk of nausea, vomiting and constipation. Other prominent adverse effects include mood changes (dysphoria, euphoria), somnolence, urinary retention (associated with increased sphincter tone), and urticaria/pruritis (associated with histamine

release). Respiratory depression is uncommon but potentially serious. Death secondary to opiate overdose is nearly always due to respiratory depression. When these agents are appropriately titrated, the risk of severe respiratory depression is generally small, as tolerance rapidly develops to this effect.

A decrease in seizure threshold occurs with the use of all narcotics and is of particular concern when these medications are given with other agents that lower seizure threshold or used in patients predisposed to seizure.

Codeine is often associated with gastrointestinal intolerance, which some patients incorrectly identify as an allergic reaction. True allergy to opiate agonists is uncommon. Narcotic analgesics may also decrease or inhibit salivary flow, contributing to oral/dental problems.

b) *Drug-specific adverse effects*

Meperidine – Neurotoxicity (anxiety, tremors, myoclonus, and generalized seizures) has been observed with repeated use of meperidine due to accumulation of a metabolite, normeperidine, which functions as a CNS excitotoxin. Patients using meperidine for more than two days, with pre-existing renal impairment, sickle-cell disease, or CNS disease, or receiving meperidine doses greater than 600 mg/24 hours are at particularly high risk for normeperidine toxicity. Use in children is not recommended.

Propoxyphene – Like meperidine, propoxyphene has CNS-excitatory metabolites and can cause CNS disturbances including seizure when administered in high doses, especially in patients with renal disease. Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants (including alcohol), are a major cause of drug-related deaths (many of them in patients with histories of emotional disturbance, suicidal ideation or attempts, or misuse of tranquilizers, alcohol, and other CNS-active drugs). The consumer watchdog group Public Citizen petitioned the FDA in February 2006 to phase out propoxyphene from the U.S. market. Propoxyphene overdoses can be more difficult to reverse than with other opioids. Propoxyphene is not considered appropriate in elderly patients due to CNS adverse effects, including sedation, confusion, and increased likelihood of falls and fall-related fractures. It is one-half to two-thirds as potent an analgesic as codeine.

Many DoD providers surveyed cited concerns for safety with the use of meperidine and propoxyphene, although others pointed out that they were useful and could be used safely if limited to short-term use in the correct patients.

Tramadol – Doses of tramadol are limited by its association with an increased risk of seizure at higher than recommended doses. Per labeling, total dose should not exceed 300 mg of tramadol per day for the ER tablets (Ultram ER) and tramadol/APAP combination (Ultracet, generics), or 400 mg per day for tramadol IR tablets (Ultram, generics). Tramadol may increase seizure risk in

patients with a history of seizures, conditions with a recognized risk of seizure, or taking other medications that increase seizure risk.

Oral transmucosal and buccal fentanyl citrate are IR, high potency products indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and tolerant of opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who have been taking morphine 60 mg/day or more, transdermal fentanyl 50 mcg/h, or an equianalgesic dose of another opioid for a week or longer. These products should not be used in opioid non-tolerant patients because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates. They are contraindicated in the management of acute or postoperative pain. Patients requiring more than four doses per day should have their maintenance analgesic reevaluated; use of round-the-clock oral transmucosal or buccal fentanyl citrate is not recommended.

Transdermal fentanyl is indicated for management of persistent, moderate to severe chronic pain requiring continuous, around-the-clock administration for an extended period of time, that cannot be managed by other means, and ONLY in patients who are already receiving opioids, have demonstrated opioid tolerance, and require a total daily dose at least equivalent to fentanyl 25 mcg/hr. It should not be used for management of acute pain or short periods of opioid analgesia; post-op pain, including outpatient/day surgeries; mild pain; or intermittent pain. The DoD P&T Committee agreed in November 2006 that a PA was needed for transdermal fentanyl; the recommendation was approved by the Director, TMA in January 2007. Please see the November 2006 DoD P&T minutes for more information.

c) *Potential for abuse*

Numerous factors determine how and whether a drug is abused. It is generally accepted that rapidly acting medications (or ER dosage systems that can be compromised to cause drug to become rapidly available) are more prone to abuse than slow-acting or ER medications. Factors such as availability, local market conditions, drug popularity, and drug abuse culture may very greatly among geographic areas. Prescriptions for C-III to C-V controlled medications can generally be phoned in to pharmacies, written with refills, and are not tracked in statewide databases. This makes them easier to obtain through fraudulent activity (e.g., forging prescriptions). Prescriptions for C-II controlled medications, which have restrictions on telephone orders, cannot be refilled, and are usually tracked at the state level, are more difficult to obtain but are also more desirable to addicts due to their higher potency. Clearly there are differences among narcotic analgesics with regard to these factors; however, there were no data supporting differences in potential for abuse among like medications (for example, comparing the various long-acting high potency formulations) that the P&T Committee considered useful for making formulary recommendations.

d) Drug interactions

A large number of medications may interact with the narcotic analgesics. In general, these drug interactions are relatively similar for all of the drugs in this class and do not suggest that any particular medication offers a substantially higher potential for drug interactions. One unique consideration arises due to the dual mechanism of action of tramadol, leading to potential interactions (including increased risk of seizures or serotonin syndrome) with other medications that increase levels of serotonin and/or norepinephrine (e.g., MAOIs and selective serotonin reuptake inhibitors [SSRIs]). Another is the potential for a lethal hyperpyrexic syndrome with delirium if meperidine is administered to patients receiving MAOIs; this combination is contraindicated.

e) Special populations

There are differences among narcotic analgesics with regard to clinical evidence, extent of clinical experience, and labeling for use in special patient populations (including pediatric and elderly patients, patients who are pregnant or breast-feeding, and patients with renal or hepatic dysfunction). However, the P&T Committee overall did not find sufficient evidence of a unique advantage or disadvantage for specific products that it considered useful for formulary decision-making.

Patients with swallowing difficulties may require liquid formulations or products that can be sprinkled on food or administered via a non-oral route (e.g., as a transdermal patch, nasal spray, buccal tablet, transmucosal lozenge, or rectal suppository). The available narcotic analgesics offer various formulations that meet these needs (see Table 1).

3) Provider Opinion

The P&T Committee reviewed survey responses from 342 MHS healthcare providers with experience in prescribing narcotic analgesics for the treatment of pain. Responders represented more than 40 specialties (including a number of dental specialties), reflecting the ubiquity of use of the narcotic analgesics in clinical practice; however, the majority of responders were from Family Practice, Internal Medicine, and General Surgery. Overall, providers emphasized that they require a broad array of narcotic analgesics in their practice to treat their patients and that excessive formulary restrictions would be detrimental to their ability to adequately treat various clinical presentations. They favored ER narcotic analgesics, including the fentanyl transdermal patch, as well as a broad array of strengths of opioid/acetaminophen combination products.

The P&T Committee also reviewed comments from MTF pharmacists regarding the ability of their facilities to accommodate additional controlled substances if placed on the BCF, which would require additional vault space and increase administrative burden (i.e., performing narcotic counts) for MTFs that did not already have the additional medications on formulary. Many pharmacists indicated that centralized contracting for "pre-packed" products in commonly-

dispensed quantities would facilitate inventory and dispensing requirements at their facilities.

4) Clinical Coverage Considerations

The issue of clinical coverage, or "how many agents do we need on formulary to meet the majority of patients' needs," is dependent on multiple factors, including the efficacy, safety, and tolerability of individual agents for the treatment of conditions in which they are used, the needs of specific subpopulations, how interchangeable the medications are, the degree of intra-patient variability, and whether or not patients failing one agent (due to lack of efficacy, adverse effects, or hypersensitivity) typically respond to or tolerate another. In the case of the narcotic analgesics, several factors support availability of multiple agents and formulations.

- There is evidence that patients failing one narcotic analgesic due to lack of efficacy may respond better to another.
- Patients allergic to medications in one chemical class may be able to tolerate another without cross-sensitivity (i.e., may be able to take a phenylheptane [e.g., methadone] if allergic to a phenanthrene [e.g., morphine]).
- As with other pain medications, there is substantial intra-patient variability in response. Rotation of different narcotic analgesics has been proposed as a strategy to increase efficacy and decrease adverse effects, although clinical data are limited.
- Alternative formulations (e.g., liquids, suppositories, or patches) are needed in some patient populations. Long-acting products may be desirable not only for convenience, but to provide more blood concentrations and reduce the number of episodes of breakthrough pain.
- Utilization of these agents spreads across the entire population and touches virtually every disease state and professional specialty. Differences in clinical practice exist both locally and by specialty (e.g., products typically used in dental practice).

5) Narcotic Analgesics – Overall Clinical Effectiveness Conclusion

The P&T Committee concluded that:

a) There is insufficient evidence to support efficacy differences between narcotic analgesics, including high potency long-acting agents for the treatment of chronic cancer or non-cancer pain, high potency IR agents for the treatment of breakthrough pain, or narcotic analgesics in general for the treatment of neuropathic pain.

b) Strong narcotic analgesics appear to be more effective than non-opioid analgesics (NSAIDs, TCAs) in chronic non-cancer pain.

c) There is no evidence suggesting efficacy differences between long-acting and short-acting formulations of the same agents; however, long-acting products

offer greater convenience and may be associated with fewer episodes of breakthrough pain.

d) There is insufficient evidence to support efficacy differences between 12-hour (e.g., MS Contin and generics) and 24-hour ER morphine products (Avinza, Kadian), or between the two 24-hour products (Avinza versus Kadian). Avinza is restricted to a maximum dose of 1600 mg daily and cannot be taken with alcohol (including alcohol-containing medications). Kadian has a much longer time to achieve maximum serum levels (~9.5 hours) compared to Avinza (~0.5 hour) or to 12-hour ER morphine (2-3 hours). Both can be opened and sprinkled on food; Kadian granules can be given via gastrostomy tube.

e) There is insufficient evidence to support efficacy differences between IR agents for the treatment of breakthrough pain in patients with chronic cancer or non-cancer pain, including the newer IR fentanyl products (oral transmucosal lozenges and buccal tablets). Buccal fentanyl is more bioavailable and may offer more consistent dosing; it is also sugar-free. The lack of a 1:1 conversion between the two IR fentanyl products may offer significant potential for medication errors.

f) Narcotic analgesics are rarely considered first line agents for the treatment of neuropathic pain. There is insufficient evidence to support efficacy differences between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.

g) There is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen. The VA/DoD guideline recommends avoiding meperidine for the treatment of postoperative pain.

h) Narcotic analgesics are associated with multiple adverse effects, including nausea, vomiting, constipation, mood changes, somnolence, urinary retention, pruritis, and oral/dental problems. Respiratory depression is uncommon but potentially serious; the risk is generally small when narcotic analgesics are appropriately titrated, as tolerance rapidly develops.

i) A decrease in seizure threshold occurs with the use of all narcotics, but is of particular concern with meperidine (which has a neurotoxic metabolite and should not be used for more than two days, in patients with renal impairment, sickle-cell disease, or CNS disease, or in children); propoxyphene (which also has CNS-excitatory metabolites and can cause seizure in high doses, especially in patients with renal disease); and tramadol (which is associated with an increased risk of seizure at higher than recommended doses [300-400 mg daily] or in patients taking other medications or with conditions that increase seizure risk).

j) Propoxyphene is not considered appropriate in elderly patients due to CNS adverse effects, including sedation, confusion, and increased likelihood of

falls and fall-related fractures. The consumer watchdog group Public Citizen has petitioned the FDA to phase out propoxyphene from the U.S. market due to the association of excessive doses of propoxyphene with drug-related deaths. Many DoD providers surveyed cited concerns for safety with the use of meperidine and propoxyphene, although others pointed out that they were useful and could be used safely if limited to short-term use in the correct patients.

k) While there are clearly differences among narcotic analgesics with regard to likelihood for abuse (e.g., onset of action and potency), there are no data supporting differences in potential for abuse among like medications (e.g., high potency, long-acting agents) that the P&T Committee considered useful for making any formulary recommendation.

l) In general, drug interactions are relatively similar for all of the drugs in this class and it does not appear that any particular medication offers a substantially higher potential for drug interactions. Two unique considerations are tramadol and meperidine. Because of its dual mechanism of action, tramadol has potential interactions with other medications that increase serotonin and/or norepinephrine levels (e.g., MAOIs, SSRIs); meperidine is contraindicated with MAOIs due to the potential for a lethal hyperpyrexic syndrome.

m) There are differences among narcotic analgesics with regard to clinical evidence, extent of clinical experience, and labeling for use in special patient populations (including pediatric and elderly patients, patients who are pregnant or breast-feeding, and patients with renal or hepatic dysfunction). However, the P&T Committee overall did not find sufficient evidence of a unique advantage or disadvantage for specific products that it considered useful for formulary decision-making.

n) Patients with swallowing difficulties may require liquid formulations or products that can be sprinkled on food or administered via a non-oral route. The available narcotic analgesics offer various formulations that meet these needs.

o) Providers surveyed in general emphasized that they require a broad array of narcotic analgesics in their practice to treat their patients and that excessive formulary restrictions would be detrimental to their ability to adequately treat various clinical presentations. They favored ER narcotic analgesics, including the fentanyl transdermal patch, as well as a broad array of strengths of opioid/ acetaminophen combination products. Many pharmacists indicated that centralized contracting for "pre-packed" products in commonly-dispensed quantities would facilitate inventory and dispensing requirements at their facilities.

p) Clinical coverage considerations support a broad array of formulary agents and formulations.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to accept the clinical effectiveness conclusions stated above.

B. Narcotic Analgesics – Relative Cost Effectiveness

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

Cost minimization analyses (CMAs) were conducted for four subclasses of the narcotic analgesics, which differed slightly from the categories used during the clinical review: (1) long-acting high potency single analgesic agents; (2) short-acting high potency single analgesic agents; (3) low potency single analgesic agents; and (4) combination products. The conclusion of the relative clinical effectiveness evaluation was that there was insufficient evidence to suggest that the narcotic analgesics differed within the defined subclasses (long-acting high potency agents, short-acting high potency agents, low potency agents, and combination products) in regards to efficacy, safety, tolerability, or clinical outcomes in the treatment of pain. As a result, several CMAs were performed to determine the relative cost effectiveness of the agents within each subclass. The CMAs compared the agents based on their weighted average cost per equianalgesic dose.

The results of the CMA for the high potency long-acting single analgesic agents showed that the 12-hour morphine sulfate ER product (MS Contin, generics) was the most cost effective agent. This result was anticipated since this product is generically available at a significantly discounted cost relative to brand name MS Contin. The other long-acting high potency single analgesic agents—the 24-hour ER morphine products (Kadian, Avinza), fentanyl patch, oxycodone ER, and oxymorphone ER—were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin, generics). Two of these products, fentanyl patch and oxycodone ER only recently became generically available. The cost of these generics is only slightly lower than their respective brand name products. The other three long-acting high potency single analgesic agents—the 24-hour ER morphine products (Kadian, Avinza) and oxymorphone ER—are brand-only products. There was no substantial difference in cost effectiveness between Kadian and Avinza.

The results of the CMA for the high potency short-acting single analgesic agents showed that morphine sulfate IR and oxycodone IR had similar relative cost effectiveness and were the most cost effective agents. Once again, this result was anticipated since morphine sulfate IR and oxycodone IR are now generically available at a significantly discounted cost relative to the their respective brand name products. The other two agents, fentanyl citrate buccal tablets and fentanyl citrate transmucosal lozenges, were 40-fold the cost of the two most cost effective agents. Fentanyl citrate transmucosal lozenges only recently became generically available. There was no substantial difference in cost effectiveness between the two fentanyl citrate products (Fentora versus Actiq or its generic equivalent).

The results of the CMA for the low potency single analgesic agents showed that tramadol ER was not cost effective relative to other formulations of tramadol (tramadol; tramadol/APAP), which are generically available.

The CMA for the combination agents showed that the agents within this generic-dominated class were all similar in terms of relative cost effectiveness.

The P&T Committee's discussion primarily focused on the relative clinical and cost effectiveness of the high potency long-acting and high potency short-acting single analgesic agents. The general consensus of the P&T Committee was that the UF should provide a broad array of these agents sufficient to meet the clinical needs of the DoD population. The P&T Committee made the following conclusions for each of these two subclasses:

1) *High potency long-acting single analgesic agents* – Although the 24-hour ER products (Kadian and Avinza); fentanyl transdermal patch, oxycodone ER, and oxymorphone ER were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin and generics), these agents should be maintained on the UF in order to sufficiently meet the clinical needs of the DoD population. This conclusion was based on the following factors:

    a. The 24-hour ER morphine products (Kadian and Avinza) provide more consistent levels of medication throughout a 24-hour period, which may reduce the number and/or severity of breakthrough pain episodes. Both products can be sprinkled on food to ease administration for patients who cannot swallow oral solid dosage forms. There was no substantial difference in cost effectiveness between Kadian and Avinza.

    b. Oxycodone ER provides an alternative for patients who cannot tolerate morphine sulfate.

    c. Transdermal fentanyl provides a unique dosage form for patients who are unable to swallow.

    d. Oxymorphone ER provides an additional long-acting oral alternative for patients who cannot tolerate morphine sulfate or oxycodone. The place of oxymorphone in therapy relative to other long-acting narcotic analgesics with much longer periods of clinical experience is not yet clear.

2) *High potency short-acting single analgesic agents* – Even though fentanyl citrate buccal tablets and fentanyl citrate transmucosal lozenges were more than 40-fold the cost of the two most cost effective agents, morphine sulfate IR and oxycodone IR, the fentanyl citrate products provide an additional therapeutic alternative for breakthrough pain with novel routes of administration. There was no substantial difference in cost effectiveness between the two fentanyl citrate products.

Cost Effectiveness Conclusion

1) *High potency long-acting single analgesic agents* – Although the 24-hour ER products (Kadian and Avinza); fentanyl transdermal patch, oxycodone ER, and oxymorphone ER were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin and generics), they have unique clinical

advantages and should be maintained on the UF in order to sufficiently meet the clinical needs of the DoD population.

2) *High potency short-acting single analgesic agents* – Even though fentanyl citrate buccal tablets and fentanyl citrate transmucosal lozenges were more than 40-fold the cost of the two most cost effective agents, morphine sulfate IR and oxycodone IR, the fentanyl citrate products provide an additional therapeutic alternative for breakthrough pain with novel routes of administration. There was no substantial difference in cost effectiveness between the two fentanyl citrate products.

3) *Low potency single analgesic agents* – Tramadol ER was not cost effective relative to other formulations of tramadol (tramadol; tramadol/APAP), which are generically available. All other products in this subclass were cost effective.

4) *Combination agents* – The products within this generic-dominated subclass were all determined to be cost effective relative to their comparators.

The P&T Committee agreed (14 for, 0 opposed, 1 abstained, 2 absent) with the relative cost effectiveness analysis of the narcotic analgesic agents.

C. Narcotic Analgesics – UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the narcotic analgesic drug class, and other relevant factors, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) that tramadol ER tablets be designated non-formulary under the UF, with all other narcotic analgesic agents designated as formulary on the UF. Additionally, the P&T Committee voted to recommend (14 for, 0 opposed, 1 abstained, 1 absent) a QL of 112 tablets/28 days for fentanyl buccal tablets, consistent with established quantity limits for fentanyl transmucosal lozenges, recommendations in Fentora package labeling, and current DoD prescribing patterns for Fentora buccal tablets.

D. Narcotic Analgesics – MN Criteria

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

1) Use of formulary alternatives is contraindicated.

2) The patient previously responded to tramadol ER and changing to a formulary alternative would incur unacceptable clinical risk.

The P&T Committee did not agree that other MN criteria were likely to apply, given the UF status of tramadol IR.

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to approve the MN criteria outlined above.

E. Narcotic Analgesics – UF Implementation Period

Because of the small number of unique utilizers affected (approximately 6500 patients [~1.5%] out of approximately 437,000 unique utilizers at all three points of

service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

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

COMMITTEE ACTION: The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. Narcotic Analgesics – BCF Review and Recommendation

The P&T Committee considered the BCF status of the narcotic analgesics. Currently the only narcotic analgesic agents on the BCF are the 15 mg, 30 mg, and 60 mg strengths of morphine sulfate ER (MS Contin, generics); codeine/APAP oral (formulations not specified), and oxycodone/APAP 5/325 mg or 5/500 mg tablets. In addition to the medications already on the BCF, the P&T Committee agreed that morphine sulfate IR 15 and 30 mg and tramadol IR 50 mg should be added to the BCF and that the listings for hydrocodone/APAP and codeine/APAP should be clarified to specify the most commonly used and clinically necessary formulations and strengths (hydrocodone / APAP 5/500 mg; codeine/APAP 30/300 mg, and codeine/APAP elixir 12/120 mg per 5 mL). All of these drugs are cost effective, widely used agents in the MTF setting.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend the following agents be designated as the BCF selections in this class: morphine sulfate ER 15 mg, 30 mg, 60 mg; morphine sulfate IR 15 mg and 30 mg; oxycodone/APAP 5/325 mg; hydrocodone/ APAP 5/500 mg; codeine/APAP 30/300 mg; codeine/APAP elixir 12/120 mg per 5 mL; and tramadol IR 50 mg.

8. DRUG CLASS REVIEW – OPHTHALMIC GLAUCOMA AGENTS

The P&T Committee evaluated the relative clinical effectiveness of the ophthalmic glaucoma agents. Based on chemical structure and mechanism of action, the drug class was divided into seven categories as outlined in Table 2. The seven categories include ophthalmic prostaglandin analogs; beta blockers; carbonic anhydrase inhibitors; alpha 2 adrenergics; adrenergics; cholinergics; and cholinesterase inhibitors. The glaucoma drug class accounted for $51.1 million in MHS expenditures in FY 2006, and is ranked #34 in terms of total expenditures during that time period.

A. Ophthalmic Glaucoma Agents – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the ophthalmic glaucoma agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical

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

Table 2: Ophthalmic Glaucoma Agents Available in the U.S.

Subclass	Generic Name	Brand Name
Prostaglandin Analogs	Bimatoprost Latanoprost Travoprost	Lumigan Xalatan Travatan; Travatan Z
Beta Blockers	Betaxolol Carteolol Levobunolol Metipranolol Timolol maleate solution Timolol maleate gel-forming solution Timolol maleate with potassium sorbate Timolol hemihydrate	Betoptic, generics; Betoptic-S Ocupress, generics Betagan, generics Optipranolol, generics Timoptic, generics Timoptic XE, generics Istalol Betimol
Carbonic Anhydrase Inhibitor; Combination Drug	Brinzolamide Dorzolamide Dorzolamide / timolol	Azopt Trusopt Cosopt
Alpha 2 adrenergics	Brimonidine BAK 0.2% Brimonidine Purite 0.15%/ 0.1% Apraclonidine	Generic (Alphagan brand discontinued) Alphagan P Iopidine
Adrenergics	Dipivefrin	Propine, generics
Cholinergics (miotics)	Acetylcholine Carbachol Pilocarpine	Miochol-E Isopto Carbachol Pilocar, generics; Pilopine HS gel
Cholinesterase Inhibitors	Echothiophate	Phospholine iodide

1) Efficacy Measures

The primary outcome measure used to assess efficacy of the glaucoma drugs is the change in intraocular pressure (IOP) as compared to baseline, expressed as an absolute value in mm Hg or as a relative percentage change from baseline.

2) Efficacy

a) Prostaglandin analogs

i) Products – The prostaglandins available on the market include bimatoprost (Lumigan), latanoprost (Xalatan), and travoprost (Travatan). These three products contain benzalkonium chloride (BAK) as a preservative, which has been associated with local ocular irritation. Travoprost is also available with a non-BAK preservative under the trade name of Travatan Z. None of the products are available in generic formulations.

ii) Meta-analyses – The efficacy of the ophthalmic prostaglandin analogs was evaluated in two meta-analyses. At peak levels, the mean differences from baseline IOP were similar; -33% (95% CI -29% to -27%) with bimatoprost,

-28% (95% CI -30% to -26%) with latanoprost, and -29% (95% CI -32% to -25%) with travoprost [Van der Valk *et al*, 2005].

Ni Li *et al* in 2006 found no difference in the IOP lowering effects when travoprost was compared to bimatoprost (weighted mean difference 0.08, 95% CI -0.62 to 0.79; p=0.8), or to latanoprost (weighted mean difference 0.57, 95% CI -1.18 to 0.04; p = 0.07). The IOP lowering efficacy of bimatoprost was not directly compared to latanoprost.

iii) Head-to-head trials – Two RCTs that evaluated the prostaglandin analogs in a head-to-head manner did not find significant differences in the efficacy of the drugs. Parrish *et al* in 2003 found no difference among all comparison groups (p = 0.128), while Orzalesi *et al* in 2006 reported that the performance of all three drugs was statistically identical within the 1.5 mmHg power of the trial.

iii) Racial differences in efficacy – Travoprost was more effective than latanoprost at lowering IOP in African Americans than non-African Americans in one sub-analysis [Netland *et al*, 2001]. The difference of up to 1.5 mm Hg was statistically significant (p = 0.04) in favor of travoprost. However, this was a post-hoc analysis that was not prospectively designed to evaluate racial differences in efficacy.

No significant differences between bimatoprost and travoprost in mean IOP-lowering were found in one prospectively designed trial involving ninety-four African American patients [Noecker *et al*, 2006]. Both drugs resulted in a statistically significant reduction from baseline IOP at all study visits ($p < 0.001$). There were no statistically significant between-group differences in IOP-lowering ($p \geq 0.130$).

b) Beta blockers

i) Products – Six ophthalmic beta blockers are included in the class; one β1 selective product, betaxolol (Betoptic-S, Betoptic); and five non-selective products, levobunolol (Betagan), metipranolol (OptiPranolol), timolol hemihydrate (Betimol), timolol maleate (Timoptic, Istalol, Timoptic Ocudose and Timoptic XE, a gel-forming solution), and carteolol (Ocupress).

ii) Generics – Several beta blockers are available in generic formulations, with the exception of betaxolol suspension 0.25% (Betoptic-S), timolol hemihydrate (Betimol), the branded timolol maleate product Istalol, and preservative free unit dose timolol maleate (Timoptic Ocudose).

iii) Timolol – Timolol was the first beta blocker marketed and is the gold standard to which other ophthalmic glaucoma agents are compared. On average, timolol reduces IOP by 20% to 35%. Several different formulations and salts are available:

- *Timolol maleate solution (Timoptic, generics) versus timolol maleate gel-forming solution* – Timolol maleate solution requires twice daily

dosing. Timolol maleate gel-forming solution is dosed once daily, and potentially has increased ocular penetration and duration of action compared to the solution, but causes transient blurred vision. One study comparing the solution with the gel-forming solution found no difference in IOP-lowering from baseline; both products lowered IOP by 30% to 31%.

- *Timolol hemihydrate* – The timolol hemihydrate salt theoretically enhances ocular drug availability, due to increased solubility compared to timolol maleate. The hemihydrate formulation is dosed twice daily, as is timolol maleate. Two comparative studies of timolol hemihydrate with timolol maleate solution or timolol maleate gel-forming solution showed similar reductions in IOP from baseline by about 22%. One study [Mundorf *et al*, 1998] found there was no change in IOP after three months when patients previously receiving timolol maleate solution were switched to timolol hemihydrate.
- *Timolol maleate (Istalol)* – The timolol maleate branded product Istalol is dosed once daily. Potassium sorbate is incorporated into the formulation, which purportedly enhances ocular penetration into the eye. However, a clinical trial comparing Istalol to timolol maleate (Timoptic, generics) dosed twice daily demonstrated no efficacy differences between the products, both drugs reduced IOP by 23% to 24% [Mundorf *et al*, 2004].

iv) Levobunolol, metipranolol, carteolol – Comparative trials with the non-selective beta blockers levobunolol, metipranolol, and carteolol each with timolol maleate (Timoptic, generics) show similar reductions in IOP.

vi) Betaxolol – Betaxolol is the sole β_1 selective ophthalmic beta blocker. It is available in two strengths, a 0.25% suspension (Betoptic-S) that is not available in a generic formulation, and a 0.5% solution (Betoptic, generics). Clinical trial data suggest that timolol maleate may decrease IOP to a greater extent than betaxolol. Due to betaxolol's β_1 selectivity, patients with respiratory or reactive airway diseases may not experience adverse pulmonary effects seen with non-selective beta blockers. However, there is only one published study enrolling nine subjects demonstrating a lack of adverse effect on pulmonary function tests.

c) Carbonic anhydrase inhibitors; combinations with beta blockers

i) Products – The ophthalmic carbonic anhydrase inhibitors include brinzolamide (Azopt), and dorzolamide (Trusopt). The branded product Cosopt consists of dorzolamide and timolol maleate and is the only combination glaucoma product marketed. Generic formulations of the three products are not available. The carbonic anhydrase inhibitors are used in patients with contraindications to other glaucoma drugs, and can be used concomitantly with other drugs that lower IOP. Brinzolamide and dorzolamide both decrease intraocular pressure by 15%-26%.

ii) *Meta-analysis* – One meta-analysis included an indirect comparison of brinzolamide and dorzolamide. Both drugs significantly reduced IOP, compared with placebo. At trough levels, the mean differences from baseline IOP were similar; -17% (95% CI -19% to -15%) for both drugs [Van der Valk *et al*, 2005].

Head-to-head trials – One randomized trial reported similar reductions in IOP with brinzolamideand dorzolamide (-17% to -20% for both), compared to increases in IOP of 8% to 19% with placebo [Sall *et al*, 2000]. When brinzolamide and dorzolamide were given with timolol maleate, similar IOP reductions were also seen (-14% to -21% for both) [Michaud *et al*, 2001]. Similar absolute reductions in IOP of 0.1 to 0.3 mm Hg were reported with brinzolamide and dorzolamide when the carbonic anhydrase inhibitor was added on to a regimen of latanoprost and timolol (Timoptic, generics) [Tsukamoto *et al*, 2005].

iii) *Dorzolamide/timolol (Cosopt)* – Clinical trials sponsored by the manufacturer lasting 3 to 15 months found the combination of dorzolamide with timolol produced similar reductions in IOP as the two separate components administered together. The net effect of administering the Cosopt combination is an absolute IOP reduction of 3-4 mm Hg below that seen with timolol (Timoptic, generics).

d) *Alpha 2 adrenergics*

i) *Products* – The alpha 2 adrenergic agents include the parent compounds of apraclonidine (Iopidine) and brimonidine. Brimonidine is available in three formulations: a 0.2% concentration with BAK as a preservative (available only as a generic, as the proprietary product has been discontinued); a 0.15% solution with purite as a preservative (Alphagan P), and a 0.1% solution with purite as a preservative (also called Alphagan P). Apraclonidine and brimonidine reduce intraocular pressure by 18% to 27% two to five hours after dosing and by 10% at 8 to 12 hours after administration.

ii) *FDA Indications* – There are differences in the FDA-approved indications for apraclonidine and brimonidine. All formulations of brimonidine BAK 0.2% (generic) and brimonidine purite 0.15% and 0.1% (Alphagan P) are indicated to reduce IOP in patients with glaucoma. Apraclonidine is approved for use following laser procedures to control post-surgical IOP elevations (1% concentration), or for short-term use in patients receiving maximally tolerated medical therapy who require additional IOP reductions prior to surgery (0.5% concentration).

iii) *Apraclonidine* – Apraclonidine is primarily used short-term, as it is associated with tachyphylaxis and diminished intraocular pressure lowering effect over time. DoD utilization of apraclonidine represents a small percentage of overall alpha 2 adrenergic drug use (0.5%).

iv) *Apraclonidine versus brimonidine 0.2% BAK* – Head-to-head studies of brimonidine BAK 0.2% and apraclonidine demonstrated similar intraocular

pressure lowering effects, both in patients with glaucoma, and in laser surgery. Both agents lower intraocular pressure by 17 to 26% in this setting.

v) *Brimonidine* – One meta-analysis reported that brimonidine reduced intraocular pressure by 25% at peak and 18% at trough, but to a lesser extent than the prostaglandins (25% to 35%) [Van der Valk *et al*, 2005].

Brimonidine formulations – Two head-to-head trials comparing brimonidine BAK 0.2% formulation (generic) with brimonidine purite 0.15% (Alphagan P) did not show differences in IOP lowering [Katz *et al*, 2002; Mundorf *et al*, 2003]. One comparative trial with brimonidine purite 0.1% (Alphagan P) reported similar efficacy with brimonidine BAK 0.2% (generic), but few details were provided [package insert]. Product labeling states that the brimonidine purite 0.15% (Alphagan P) and brimonidine purite 0.1% (Alphagan P) both lower IOP by 2-6 mmHg; no corresponding percentage reduction in intraocular pressure was provided.

e) *Adrenergics, cholinergics, and cholinesterase inhibitors*

i) *Products* – Dipivefrin (Propine, generic) is the only ophthalmic adrenergic, and echothiophate (Phospholine iodide) is the only ophthalmic cholinesterase inhibitor. The cholinergics include acetylcholine (Miochol-E), carbachol (Isopto Carbachol), and pilocarpine gel (Pilopine HS) and pilocarpine solution (Pilocar, generics). The adrenergics, cholinergics, and cholinesterase inhibitors were introduced in the early 1980s, and were the first agents used to treat glaucoma, but have been replaced by newer therapies, due to adverse effects. They are now third-line treatments for glaucoma, but do fulfill unique niches in therapy.

ii) *Dipivefrin* – Dipivefrin is a pro-drug that has improved lipophilicity and enhanced corneal penetration compared to the parent compound epinephrine. IOP reduction with dipivefrin ranges from 15% to 25%.

iii) *Cholinergics* – The direct-acting cholinergics or miotics are used for glaucoma to decrease IOP via increased aqueous outflow, or are used to induce miosis during surgery. Acetylcholine, carbachol and pilocarpine solution are all dosed four times daily; only pilocarpine solution is available generically.

Acetylcholine – Acetylcholine is used intraocularly to constrict the pupil during cataract surgery, or after placement of the intraocular lens following cataract removal.

Carbachol – Carbachol has two mechanisms to decrease IOP; it directly stimulates muscarinic receptors in the eye, and indirectly inhibits acetylcholinesterase.

Pilocarpine – Pilocarpine lowers IOP by 22% to 30%. It is dosed four times daily in the treatment of open-angle glaucoma. In acute angle closure glaucoma, pilocarpine is used as monotherapy or in combination with other cholinergic agents or with a carbonic anhydrase inhibitor to relieve IOP prior to ocular surgery. Pilocarpine gel is a sustained release formulation

that is applied at bedtime to provide 24-hour control of IOP; pilocarpine gel reduces the adverse effects of myopia.

iv) Echothiophate – Echothiophate is dosed twice daily for glaucoma. It has a role for the treatment of aphakia or pseudophakia (patients with their lens replaced by artificial lens). The drug is poorly absorbed due to its quaternary structure, but has similar IOP reductions as pilocarpine.

3) Safety / tolerability

a) Prostaglandin analogs

i) Serious adverse events – Overall the ophthalmic prostaglandins have a low incidence of systemic adverse effects, which has contributed to their use as first-line therapy for glaucoma.

ii) Minor adverse events

- *Hyperemia* is the most common minor adverse event reported with the ophthalmic prostaglandins. A comparison of package insert data shows a higher incidence of hyperemia with bimatoprost (15-45%) and travoprost (30-50%), as compared to latanoprost (5-15%). In one head-to-head trial, hyperemia occurred in 69% of patients receiving bimatoprost, 58% of travoprost-treated patients, and 47% of latanoprost-treated patients [Parrish *et al*, 2003]. Significantly fewer patients experienced an ocular adverse event with latanoprost in this trial. Hyperemia appears to be more of a cosmetic issue and is noted to generally be mild in severity and transient in nature.
- *Increased pigmentation* occurs more frequently with latanoprost (5-15%) than either bimatoprost (1-3%) or travoprost (1-4%). The pigmentation changes may be permanent.
- *Preservatives (Travatan versus Travatan Z)* – Products with preservatives that do not contain BAK are purported to have a favorable adverse event profile over products with BAK-based preservatives. A randomized trial in 700 patients evaluated the adverse events of the BAK-containing travoprost product (Travatan) with the non-BAK preservative formulation (Travatan Z). Hyperemia occurred in 9% of patients receiving Travatan, compared to 6.4% with Travatan Z (no p value provided) [Lewis 2007]. The adverse events in this trial were not serious and did not interrupt treatment.

iii) Drug discontinuations due to adverse effects

The prostaglandins are well tolerated. Discontinuation rates noted in package labeling due to conjunctival hyperemia were 3% for both travoprost and bimatoprost, and <1% for latanoprost. The discontinuation rates due to adverse events in one head to head trial were 0.7% with travoprost, 1.4% with bimatoprost, and zero with latanoprost [Parrish *et al*, 2003].

b) *Beta blockers*

i) *Serious adverse events* – As a class, the ophthalmic beta blockers are associated with systemic adverse effects that limit their use for glaucoma, including bradycardia, arrhythmia, cardiac block, congestive heart failure, and bronchospasm. Betaxolol is the only β1 selective ophthalmic beta blocker; however bronchospasm has occurred in patients with asthma and chronic obstructive pulmonary disease. Both selective and non-selective beta blockers are contraindicated for use in patients with severe cardiovascular disease including sinus bradycardia, second and third degree heart block, cardiogenic shock, or patients with overt cardiac failure.

ii) *Minor adverse events* – Local adverse events of the beta blockers include stinging, itching, redness and blurred vision, which may be due to the preservative and pH of the solutions. Overall, stinging is most commonly associated with betaxolol and metipranolol. Timoptic maleate gel-forming solution is associated with transient blurry vision due to its thick consistency upon instillation.

Timolol maleate (Istalol) – A higher incidence of burning and stinging was associated with the once daily branded formulation of timolol maleate (Istalol) compared to timolol maleate (Timoptic, generics) in one trial (41.6% versus 22.9%) [Mundorf *et al*, 2004].

c) *Carbonic anhydrase inhibitors; and combinations with beta blockers*

i) *Serious adverse events* – Brinzolamide and dorzolamide both have similar contraindications (hypersensitivity to the individual components). Brinzolamide/timolol (Cosopt) contains precautions regarding pulmonary and cardiovascular function seen with other ophthalmic beta blockers, due to the timolol component. Rare effects with dorzolamide include altered cornea endothelial cell function, renal calculi, and thrombocytopenia.

ii) *Minor adverse effects* – The most common adverse effects of the ophthalmic carbonic anhydrase inhibitors include local burning and stinging upon drug instillation, and taste perversion. In head-to-head-trials comparing brinzolamide with dorzolamide, dorzolamide was associated with a higher incidence of burning/stinging (12-16% versus 2-3%). The higher incidence of ocular discomfort with dorzolamide may be due to the acidic pH of the product (5.6) versus the more physiologic pH of brinzolamide (7.5). However, the ocular discomfort with dorzolamide appears transient, lasts about 10 seconds, is characterized as mild and diminishes with continued therapy [Stewart *et al*, 2004]. The incidence of taste perversion appears similar between the two products, based on head-to-head clinical trials.

iii) *Discontinuations due to adverse effects* – It is difficult to determine differences in tolerability between brinzolamideand dorzolamide, as only a few patients discontinued therapy due to adverse events in the head-to-head clinical trials.

d) *Alpha 2 adrenergics*

i) *Serious adverse effects* – Both apraclonidine and brimonidine are contraindicated in patients with hypersensitivity to the individual agents, patients taking clonidine, and patients taking MAOIs. The alpha 2 adrenergics as a class may reduce pulse and blood pressure. Apraclonidine penetrates the blood brain barrier to a lesser extent than brimonidine, and is less likely to reduce heart rate and blood pressure.

ii) *Minor adverse effects* – Overall, the alpha 2 adrenergics are associated with a relatively high incidence of minor adverse events, including fatigue and local allergic reactions, compared to other glaucoma drug classes. As a class, the alpha 2 adrenergic agents can cause ocular intolerance (allergy leading to conjunctival erythema and potential periorbital infection) in 13% to 36% of patients. Apraclonidine can cause dry nose and mouth and upper eyelid retraction, and follicular conjunctivitis has occurred frequently. Brimonidine has a higher incidence of dry mouth (33%) than apraclonidine, but is associated with less frequent ocular side effects.

iii) *Brimonidine formulations* –There are three concentrations of brimonidine marketed; a 0.2% concentration with BAK as a preservative, and two products (0.15% and 0.1%) containing a purite preservative. There is only limited data comparing the safety differences between the three products. There are conflicting data as to whether brimonidine purite 0.15% (Alphagan P) causes less ocular irritation than brimonidine BAK 0.2%. A statistically significant 41% reduction in reports of allergic conjunctivitis, oral dryness, conjunctival hyperemia, and eye discharge with brimonidine purite 0.15% compared to brimonidine BAK 0.2% was found in one head-to-head trial, [Katz *et al*, 2002], while another study noted no significant differences between the two drugs in the overall incidence of adverse events [Mundorf *et al*, 2003)]. Indirect comparison of the trials does not suggest any difference in the incidence of discontinuation due to adverse drug reactions between the two agents.

Data from an unpublished study cited in product labeling found a significantly lower frequency of treatment-related adverse events with brimonidine purite 0.1% (Alphagan P) versus brimonidine BAK 0.2%. More patients (34%) discontinued treatment due to adverse events with brimonidine BAK 0.2% than with brimonidine purite 0.1% (21%).

e) *Adrenergics, cholinergics, and cholinesterase inhibitors*

i) *Dipivefrin* – Today dipivefrin is rarely used due to adverse effects such as conjunctival hyperemia, hypersensitivity and ocular irritation. It is contra-indicated in patients with narrow-angle glaucoma, since any dilation of the pupil may predispose the patient to an exacerbation of closed-angle glaucoma.

ii) *Cholinergics* – Retinal detachment and tearing may occur if the cholinergic drugs are used in patients with pre-existing retinal disease. Miotics may

also cause angle closure in patients with narrow angle glaucoma due to increased resistance to aqueous flow from the posterior to the anterior eye chamber.

Acetylcholine – Safety concerns with acetylcholine include infrequent corneal edema, corneal clouding, and corneal decompensation. Major adverse events are rare, but include bradycardia, hypotension, flushing, breathing difficulties, and sweating.

Carbachol – Carbachol is more potent than pilocarpine, and can induce significant adverse effects. Transient stinging and burning, in addition to corneal clouding have been reported. Brow ache is the most frequent patient-reported adverse effect, due to stimulation of the ciliary muscle, which exerts a physical pull on the trabecular mesh network. Older patients with cataracts often complain of dimmed vision caused by miosis. Severe but rare systemic effects include headache, sweating, epigastric distress, nausea, vomiting, and diarrhea.

Pilocarpine – Pilocarpine is associated with miosis or accommodative spasm, which may cause blurred vision and night blindness. Long-term use is limited by loss of visual field, due to the decreased amount of light entering the eye. Systemic adverse effects include atrioventricular block and other cardiovascular effects.

iii) Echothiophate – Echothiophate frequently causes blurred vision, brow ache, eyelid fasisculation, and watery eyes. Rarely, burning or stinging has been reported. Rare but serious adverse effects are similar to those of the miotics, but also include punctul stenosis of the nasolacrimal system. Organophosphate pesticides should be used with caution, as echothiophate activity may increase, raising the potential for adverse effects.

4) Other Factors

a) Prostaglandin analogs

Storage and stability – Latanoprost requires refrigeration prior to opening, to maintain a 36-month shelf life; it does not require refrigeration once opened. Bimatoprost and travoprost (Travatan, Travatan Z) do not require refrigeration.

Special populations – There are no differences between the prostaglandin analogs in their pregnancy category rating (all are pregnancy category C) or labeling for pediatric use (none are FDA-approved).

b) Beta blockers

Special populations – The ophthalmic beta blockers are rated a pregnancy category C. Timolol crosses into breast milk, so it should be avoided in lactating women. Safety and efficacy of ophthalmic beta-blockers have not been established in pediatrics. The majority of published information in children has been with timolol maleate. Topical application of timolol 0.5% can cause cardiac blockade in infants younger than 2 years of age.

Frequency of dosing – Patient convenience is an advantage of once daily ophthalmic beta blockers, particularly if multiple ophthalmic drugs are required. The branded timolol maleate product Istalol, and timolol maleate gel-forming solution are dosed once daily.

c) *Carbonic anhydrase inhibitors; combinations with beta blockers*

Dosing dispenser – The dosing dispenser of dorzolamide is specifically designed to deliver a controlled pre-measured drop, and will not operate unless the instructions are followed correctly.

Patient convenience – The primary advantage of the combination of dorzolamide with timolol (Cosopt) is patient convenience in reducing the number of bottles and daily ophthalmic drops required, potentially improving compliance.

d) *Adrenergics, cholinergics, and cholinesterase inhibitors*

i) *Dipivefrin* – The adrenergic dipivefrin still has a place in therapy as adjunctive therapy to beta blockers, pilocarpine and carbachol.

ii) *Cholinergics* – The cholinergics are usually reserved for patients who have not responded to other topical glaucoma treatments.

Pilocarpine – Pilocarpine is used to treat acute angle closure glaucoma and as a miotic during ocular surgery.

iii) *Echothiophate* – The cholinesterase inhibitor echothiophate has fallen out of favor, due to four times daily dosing, compared to newer agents.

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

1) *Prostaglandin analogs* – Bimatoprost, latanoprost, and travoprost all decrease IOP from baseline by 28% to 33%. A prospectively designed trial assessing efficacy of bimatoprost and travoprost found no difference in efficacy in African Americans; a sub-group analysis from a different trial reported decreased efficacy of latanoprost when compared to travoprost in African Americans versus non-African Americans. Latanoprost has the most favorable ocular adverse event profile of the three prostaglandin analogs, but requires refrigeration prior to opening. The non-BAK preservative found in the Travatan Z formulation of travoprost has not shown a major advantage in terms of ocular side effects, compared to the BAK-containing product Travatan.

2) *Beta blockers* – The IOP-lowering effects of timolol maleate (Timoptic, generics; Timoptic XE, generics), timolol hemihydrate, levobunolol, metipranolol and carteolol appear similar, based on several head-to-head studies. Timolol maleate solution (Timoptic, generics) and gel-forming solution reduce IOP by 20-35%. The Timoptic XE gel-forming solution has the advantage of once daily dosing, but is associated with transient blurred vision due to the consistency of the gel. There is no evidence that the timolol maleate product Istalol or the timolol hemihydrate product Betimol have additional clinical benefits over other timolol maleate products in IOP lowering or safety profiles. Betaxolol decreases IOP to a lesser

extent than timolol maleate; however, the β1 selectivity of betaxolol may be an advantage in patients with cardiac or pulmonary co-morbidities.

3) *Carbonic anhydrase inhibitors* – The IOP lowering effects of brinzolamideand dorzolamide appear similar. Dorzolamide/timolol (Cosopt) is the only combination product for glaucoma and offers a convenience to patients. Dorzolamide causes more local ocular irritation than brinzolamide; however, burning and stinging upon instillation last 10 seconds, diminish over time, and have not translated into a higher discontinuation rate due to adverse events.

4) *Alpha 2 adrenergics* – Apraclonidine is used primarily short-term following ocular surgery, while brimonidine is used chronically for glaucoma. Both apraclonidine and brimonidine lower IOP to a similar extent. For brimonidine, changing the BAK preservative (generic) to a purite preservative (Alphagan P) and reducing the concentration from 0.2% to 0.15% or 0.1% does not appear to affect efficacy. There are conflicting data as to whether brimonidine purite 0.15% (Alphagan P) causes less ocular irritation than brimonidine BAK 0.2% (generic). Brimonidine purite 0.1% (Alphagan P) may have an improved safety and tolerability profile compared to brimonidine BAK 0.1% (generic), but the one supportive study has not been published in a peer-reviewed journal.

5) *Adrenergics, cholinergics, and cholinesterase inhibitors* – The cholinergic pilocarpine is used for acute angle closure glaucoma and as a miotic agent during ocular surgery. Although not routinely used today, the adrenergic drug dipivefrin, the cholinergics acetylcholine and carbachol and the cholinesterase inhibitor echothiophate serve unique niches in therapy.

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

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to accept the clinical effectiveness conclusions state above.

B. Ophthalmic Glaucoma Agents – Relative Cost Effectiveness

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

The ophthalmic glaucoma agents were classified and compared within subgroups based on mechanism of action. The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the glaucoma medications differed within subclasses in regards to efficacy, safety, tolerability, or clinical outcomes in the treatment of glaucoma. As a result, several CMAs were performed to determine the relative cost effectiveness of the agents within each subclass. The CMAs compared the weighted average cost per day of treatment for each drug product.

Results from the CMA of the prostaglandin subclass included three key findings: (1) travoprost (Travatan, Travatan Z) was most cost effective under a scenario where it was the sole agent on the uniform formulary; (2) Latanoprost and bimatoprost were most cost effective under a scenario where only two prostaglandin products were placed in the UF; and (3) an all on scenario (i.e., all three prostaglandin products included on the UF) was less cost effective than a scenario where at least one prostaglandin was designated non-formulary.

The results from the CMA of the topical beta-blockers showed that the majority of these products were cost effective. Only two products were identified as not cost effective in the beta-blocker subclass. Timolol hemihydrate and timolol maleate (Istalol) were both shown to be significantly more costly and no more effective than other agents in the subclass. Similarly, a comparison of the topical carbonic anhydrase inhibitors showed that brinzolamide was not cost effective compared to dorzolamide. All other medications in the remaining subclasses were determined to be cost effective relative to their comparators.

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

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to accept the cost effectiveness conclusions stated above.

C. Ophthalmic Glaucoma Agents – UF Recommendations

COMMITTEE ACTION: In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ophthalmic glaucoma agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend that latanoprost, bimatoprost, levobunolol, betaxolol (Betoptic, generics; Betoptic-S), carteolol, metipranolol, timolol maleate (Timoptic, generics), timolol maleate gel-forming solution (Timoptic XE, generics), brimonidine (generics; Alphagan P), apraclonidine, dorzolamide, dorzolamide/timolol (Cosopt), dipivefrin (Propine), acetylcholine (Miochol-E), carbachol (Isopto Carbachol), pilocarpine (Pilopine HS gel; Pilocar, generics), echothiophate (Phospholine Iodide) be maintained as formulary on the UF and that travoprost (Travatan, Travatan Z), timolol hemihydrate (Betimol), timolol maleate (Istalol) and brinzolamidebe classified as non-formulary under the UF.

D. Ophthalmic Glaucoma Agents – MN Criteria

Based on the clinical evaluation for travoprost (Travatan, Travatan Z), timolol hemihydrate, timolol maleate (Istalol) and brinzolamide, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T

Committee recommended the following general MN criteria for travoprost (Travatan, Travatan Z), timolol hemihydrate, timolol maleate (Istalol) and brinzolamide:

1) Formulary alternatives are contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Use of formulary alternatives has resulted in therapeutic failure.

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

E. Ophthalmic Glaucoma Agents – UF Implementation Period

Because of the small number of unique utilizers affected (approximately 17,000 patients [15%] of approximately 111,000 unique utilizers at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

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

COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. Ophthalmic Glaucoma Agents – BCF Review and Recommendations – The P&T Committee considered the BCF status of the ophthalmic glaucoma agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that the BCF include latanoprost; brimonidine, excluding the 0.1% strength; timolol maleate (Timoptic, generics) 0.25% and 0.5%; timolol maleate gel-forming solution 0.25% and 0.5%; and pilocarpine.

9. DRUG CLASS REVIEW – MAOI ANTIDEPRESSANTS

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the MAOI antidepressants marketed in the U.S. The drugs in the MAOI antidepressant class include three oral agents, isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate, generics); and one transdermal patch, selegiline (Emsam). Tranylcypromine is the only drug in the MAOI antidepressant class available in a generic formulation. All of the drugs are available in oral dosage forms; however, oral selegiline capsules are excluded from the review, since they are indicated for use in Parkinson's disease and not depression. The three oral MAOI antidepressants were first introduced to

the market in the early 1960s, while transdermal selegiline was launched in 2006. The MAOI antidepressants accounted for approximately $283,000 dollars spent in FY 2006 wresp, which amounts to less than 1% of total MHS expenditures for all antidepressant drug classes.

A. MAOI Antidepressants – Relative Clinical Effectiveness

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

1) Pharmacology

There are two MAOI enzymes. Inhibition of MAO-B enzyme in the CNS leads to decreased metabolism of norepinephrine, dopamine and serotonin. Inhibition of MAO-A enzyme in the gastrointestinal tract results in decreased catabolism of tyramine, which can increase blood pressure. Patients taking MAOI anti-depressants who do not restrict dietary sources of tyramine can potentially develop hypertensive crisis. Theoretically, administering an MAOI anti-depressant via the transdermal route would obviate the need for strict dietary precautions.

2) Efficacy for Atypical Depression and Major Depressive Disorder (MDD)

a) FDA-approved indications

The three oral MAOI antidepressants, isocarboxazid, phenelzine, and tranylcypromine, are FDA-approved to treat either atypical depression or MDD. The selegiline transdermal patch is indicated only for treatment of MDD.

b) Efficacy measures

The Hamilton Rating Scale for Depression (HAM-D) is the most widely used observer-rated scale that assesses the symptoms and severity of depression. In efficacy trials for the MAOI antidepressants, a 50% reduction in the HAM-D from baseline was considered a response to treatment. Remission refers to reduction in the HAM-D score below a specific cut-off score.

c) Efficacy of oral MAOI antidepressants

i) Meta-analysis – One meta-analysis [Thase *et al*, 1995] evaluated 55 RCTs (published from 1959 through 1992) that focused on depressive disorders in adults in the outpatient setting. The trials evaluated the efficacy of isocarboxazid, phenelzine, and tranylcypromine.

There were no apparent differences in the overall efficacy between isocarboxazid (60% ± 7%), phenelzine (58% ± 4%), and tranylcypromine (53% ± 12%). Limitations to the meta-analysis included differences in trial methodologies and patient populations between trials and the fact that evaluated studies were from approximately 30 years ago.

ii) Head-to-head clinical trial – One head-to-head trial compared the efficacy of phenelzine and tranylcypromine in 77 inpatients with antidepressant-refractory depression [Birkenhager *et al*, 2004]. A response to therapy occurred in 44% (17/39) of the patients receiving tranylcypromine, and 47 % (18/38) of the patients randomized to phenelzine (p=0.82). Only 18% (7/39) of the tranylcypromine-treated patients and 11% (4/38) of the phenelzine-treated patients met criteria for remission (p=0.52). This trial had limited power to detect a difference between the two drugs and was conducted in the inpatient setting.

d) Efficacy of transdermal selegiline

Three published placebo-controlled trials lasting six to eight weeks and one open-label trial lasting 52 weeks evaluate the efficacy of the transdermal selegiline formulation. There are no comparative trials evaluating efficacy differences between transdermal selegiline and any of the three oral MAOI antidepressant or other antidepressants (e.g., TCAs, SSRIs).

i) Placebo-controlled trials – In the first trial, a response to therapy occurred in 38% of patients receiving transdermal selegiline 6 mg/24 hr, compared to 23% receiving placebo (p=0.01); remission occurred in 23% of the patients treated with the patch compared to 11 % with placebo (p=0.05) [Bodkin *et al*, 2002]. In the second trial, response rates ranged from 32% to 33% with transdermal selegiline 6 mg/24 hr, versus 21% to 30% with placebo [Amsterdam *et al*, 2003]. In the third trial [Fieger *et al*, 2006], the response rate was 40% with transdermal selegiline (flexible dosing up to 12 mg/24 hr) versus 30% with placebo (p value not significant)

ii) Open label extension trial – In an open label extension trial enrolling 600 patients who had previously responded to transdermal selegiline, 17% of patients randomized to the patch relapsed after one year, compared to 31% of placebo-treated patients (p=0.003).

e) Clinical efficacy conclusion

A meta-analysis comparing the three oral MAOIs reported similar overall efficacy rates of 58% with phenelzine, 60% with isocarboxazid, and 53% with tranylcypromine in the outpatient setting. One trial conducted in an inpatient population found no statistically significant difference between phenelzine and tranylcypromine in response or remission rates. For transdermal selegiline, three placebo controlled trials are available. The response rates with transdermal selegiline ranged from 30% to 40%, compared to 21% to 30% with placebo.

3) Safety and Tolerability

a) *Minor adverse events* – The most common adverse effects of the oral MAOI antidepressants are orthostatic hypotension, dizziness, edema, tremor, insomnia, mydriasis, and anorgasmia. There are no data to suggest that one oral MAOI antidepressant is more likely than another to be associated with minor adverse effects.

Mild to moderate local irritation at the application site occurred in 15% to 36% of patients receiving transdermal selegiline in the placebo controlled trials. As with the oral MAOI antidepressants, insomnia and orthostatic hypotension are also concerns, with higher incidences reported with the 9 mg/24 hr and 12 mg/24 hr strengths.

b) *Serious adverse events* – As a class, the MAOI antidepressants have the potential for causing serotonin syndrome when administered with other serotonergic drugs or when dietary precautions are not followed. Deaths have been reported with the oral MAOI antidepressants due to both drug-drug and drug-food interactions. The MAOI antidepressants are considered third-line agents due to their adverse effect profile. To date there have been no deaths or other life-threatening events including hypertensive crisis attributed to transdermal selegiline in the controlled setting of the clinical trials.

c) *Drug-food interactions* – Consumption of tyramine-containing foods (e.g., aged meats, aged cheeses) and beverages (e.g., non-pasteurized beers) while taking any MAOI may result in hypertensive crisis. The lowest dosage strength of transdermal selegiline (6 mg/24 hr) is the only dosage where dietary tyramine restrictions are not required in the product labeling. A tyramine-restricted diet is required with all oral MAOIs and with the 9 mg/24 hr and 12 mg/24 hr strengths of transdermal selegiline. Most patients are likely to require the higher strengths of transdermal selegiline for MDD.

d) *Drug-drug interactions* – As a class, the oral MAOI antidepressants are associated with several well known and clinically important drug-drug interactions. The same extensive list of drug-drug interactions also applies to transdermal selegiline. Concomitant use of any MAOI antidepressant, including transdermal selegiline, is contraindicated with meperidine, tramadol, methadone, propoxyphene, dextromethorphan, cyclobenzaprine, carbamazepine, other MAOIs, SSRIs, and amphetamine derivatives.

e) *Withdrawal due to adverse events* – Differences in tolerability profiles between the three oral MAOI antidepressants are difficult to determine, as the available clinical trials used less rigorous study design than is standard today.

In the three short-term (6- to 8-week) placebo controlled trials evaluating transdermal selegiline, 6% (23/370) of patients randomized to the patch discontinued therapy due to an adverse event, compared to 4% (16/373) of subjects in the placebo groups. Application site reactions were the most common reason for discontinuation. In the 52-week open label trial,

discontinuation rates due to application site reactions were 15% with transdermal selegiline versus 4% with placebo.

f) Safety and tolerability conclusion – The MAOI antidepressants as a class are associated with several serious adverse events. Hypertensive crisis and risk of death due to dietary and drug-drug interactions are well-publicized. In the placebo controlled trials with transdermal selegiline, a high incidence of local patch irritation was reported. Dietary restrictions are required with all oral MAOIs and with the 9 mg/24 hr and 12 mg/24 hr strengths of transdermal selegiline. There are no head-to-head trials comparing the safety and tolerability profiles of transdermal selegiline versus the oral MAOIs.

4) Other factors

a) Available dosage formulations – Transdermal selegiline is the only MAOI antidepressant available in a non-oral dosage formulation. Transdermal selegiline would be preferred over the oral MAOI antidepressants in patients with dysphagia.

b) Dosing frequency – Transdermal selegiline and tranylcypromine are the only MAOI antidepressants that are dosed once daily. Isocarboxazid and phenelzine require dosing twice to three times daily.

c) Potential for off-label uses – The oral MAOI antidepressants have many off-label uses other than depression, including panic disorder and social anxiety disorder. Oral selegiline is currently used in conjunction with carbidopa-levodopa in Parkinson's Disease. Transdermal selegiline is currently undergoing Phase II trials to evaluate efficacy for depression in patients with Parkinson's Disease, but no peer-reviewed studies have been published.

d) Pregnancy – The oral MAOI antidepressants and transdermal selegiline are contraindicated for use during pregnancy; however, there are published reports of the use of phenelzine and tranylcypromine in pregnant patients with severe depression.

e) Pediatrics – The three oral MAOI antidepressants and transdermal selegiline are not approved for use in children younger than 16 years of age.

f) Other factors conclusion – There are only minor differences in other factors for the MAOIs, including dosing frequency, availability of non-oral dosage formulations, and potential for off-label uses.

MAOI Antidepressant Overall Clinical Effectiveness Conclusion – The P&T Committee concluded that:

1) The oral MAOI antidepressants isocarboxazid, phenelzine, and tranylcypromine have been marketed for several decades, but have been replaced by newer drug classes (e.g., SSRIs) with more favorable adverse event profiles.

2) Transdermal selegiline is the newest MAOI antidepressant marketed. The non-oral formulation was developed to reduce the risk of hypertensive crisis from tyramine.

3) There do not appear to be major differences in clinical efficacy between the three oral MAOIs when used for depression, based on the results of one meta-analysis showing response rates ranging between 53% to 61%, and one inpatient clinical trial.

4) Overall, response rates ranging from 27% to 30% were reported with transdermal selegiline in three placebo controlled trials. There are no clinical trials directly comparing the oral MAOI antidepressants with transdermal selegiline However, there are no data to suggest that treatment with transdermal selegiline would result in improved response rates compared to the oral MAOI antidepressants.

5) The MAOI antidepressants have a safety profile that is well recognized in terms of drug-drug and drug-food interactions, and these adverse events also apply to transdermal selegiline. Local application site reactions are common with transdermal selegiline.

6) The purported benefits of transdermal selegiline in terms of loosened dietary tyramine restrictions have only been shown clinically with the lowest dose (6 mg/24 hr). Dietary precautions are required with oral MAOIs and with the 9 mg/24 hr and 12 mg/24 hr dosages of transdermal selegiline.

7) Off-label usage of transdermal selegiline is anticipated for treating patients with Parkinson's Disease.

8) The primary advantage of transdermal selegiline is for patients unable to swallow oral medications and require a once-daily dosage formulation.

9) There is insufficient evidence to determine whether transdermal selegiline represents a therapeutic advance over isocarboxazid, phenelzine and tranylcypromine.

10) Based on clinical issues alone, there are no reasons to designate any of the MAOIs (phenelzine, isocarboxazid, or tranylcypromine, and transdermal selegiline) as non-formulary on the Uniform Formulary.

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

B. MAOI Antidepressants – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the MAOI antidepressants in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e) (2). Given the overall clinical conclusion that the agents within the MAOI class have similar relative clinical effectiveness, a CMA was employed to assess the relative cost effectiveness of the agents within this therapeutic class. The agents were evaluated on their weighted average cost per day of therapy across all three points of service.

Results of the CMA for the MAOI class showed that:

1) Among the oral agents, phenelzine was the most cost effective agent, followed closely by tranylcypromine and isocarboxazid.

2) Transdermal selegiline was the least cost effective MAOI for the treatment of depression. The weighted average cost per day of treatment with transdermal selegiline was four-fold higher than the most costly oral MAOI, isocarboxazid.

Cost Effectiveness Conclusion

1) The oral MAOIs demonstrate similar relative cost effectiveness, with phenelzine as the most cost effective agent.

2) Transdermal selegiline is not cost effective relative to the other agents in the class in the treatment of depression and provides no clinically meaningful therapeutic advantage to justify the increased cost.

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

C. MAOI Antidepressants – UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the MAOIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that phenelzine, tranylcypromine and isocarboxazid be maintained as formulary on the UF and that transdermal selegiline be classified as non-formulary under the UF.

D. MAOI Antidepressants – MN Criteria

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

1) Use of formulary alternatives is contraindicated.

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

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

4) The patient previously responded to a nonformulary pharmaceutical agent and changing to a formulary pharmaceutical agent would incur an unacceptable clinical risk.

5) No formulary alternative is available.

The P&T Committee noted that criterion #5 would only apply to patients unable to take oral medications.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. MAOI Antidepressants – UF Implementation Period

Because of the small number of unique utilizers affected (approximately 135 patients per quarter at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The

implementation period will begin immediately following approval by the Director, TMA.

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

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. MAOI Antidepressant – ECF Review and Recommendations

The P&T Committee had previously determined at the November 2006 P&T Committee meeting that one MAOI antidepressant should be added to the ECF based on the clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that phenelzine be classified as the ECF agent. Phenelzine was determined to be the most cost effective MAOI and currently has the greatest utilization across the MHS.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend phenelzine be classified as the ECF agent.

10. CLASS OVERVIEWS

Portions of the clinical reviews for the ophthalmic non-steroidal anti-inflammatory agents (Ophthalmic NSAIDs) and erythropoiesis stimulating agents (ESAs) were presented to the P&T Committee.

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

11. ADJOURNMENT

The second day of the meeting adjourned at 1430 hours on 14 February 2007. The next meeting will be 13-15 May 2007.

Patricia Buss

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

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

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem)	BCF	▪ zolpidem IR (Ambien)	Pending approval	Pending approval
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	Pending approval	Pending approval
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	Pending approval	Pending approval
Feb 07	MAOI Antidepressants	▪ transdermal selegiline (Emsam)	ECF	▪ phenelzine (Nardil)	Pending approval	Pending approval
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	NA
Nov 06	ADHD	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR	17 Jan 07	18 Apr 07 (90 days)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
May 06 (updated for new drugs Nov 06)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospironone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	24 Jan 07 (to coincide with May 06 meeting decision)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide / Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated for new drugs Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
		Recommended Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			17 Jan 07	21 Feb 07 (30 days)

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

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

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

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

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

Appendix B – Table 2. Newly Approved Drugs. February 2007 DoD P&T Committee Meeting

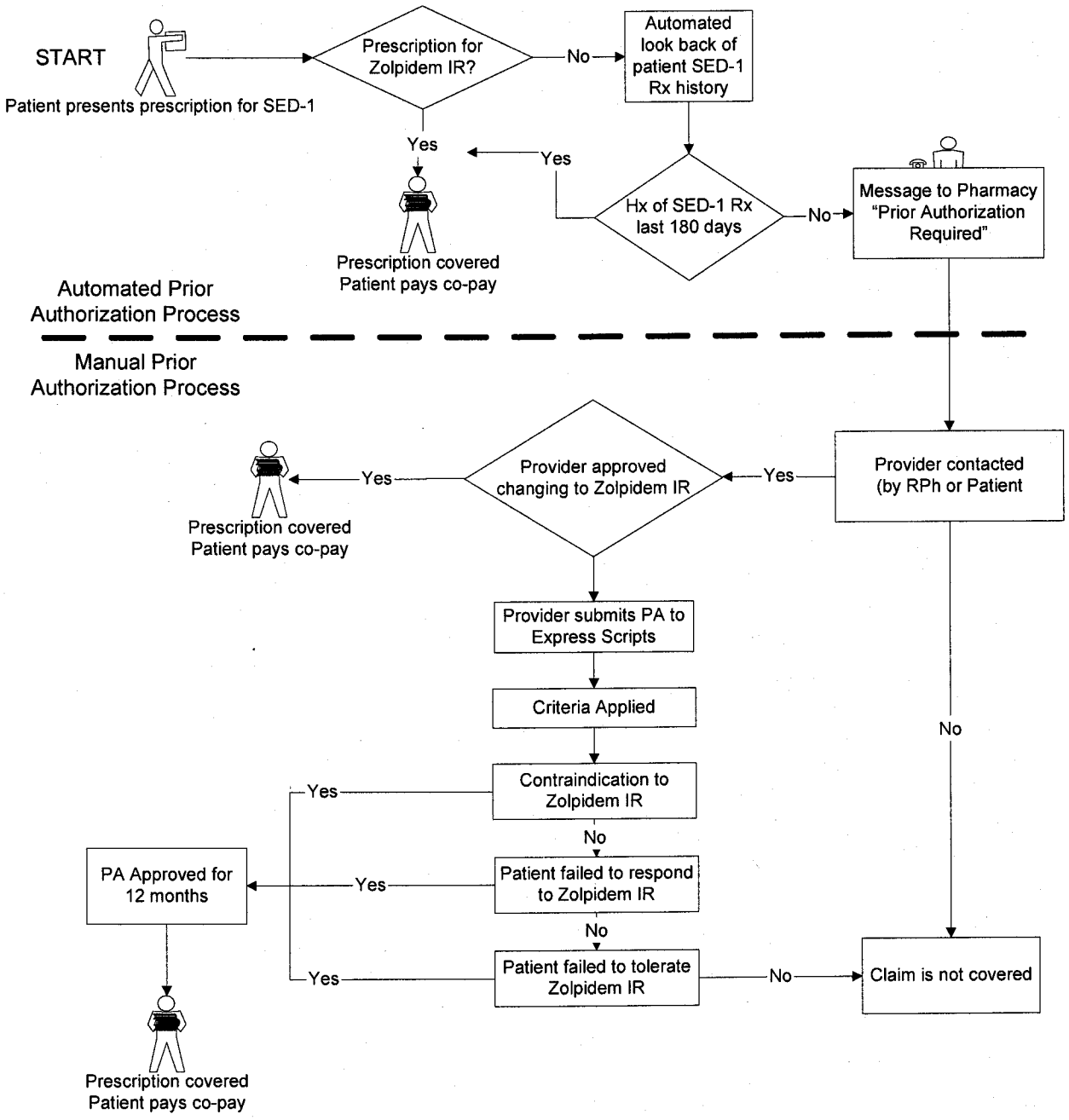
Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Sitagliptin phosphate tablets (Januvia ;Merck) Oral hypoglycemic drug (dipeptidyl peptidase IV [DPP4] inhibitor)	Oct 06 (launched Nov 06) ▪ For use as monotherapy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus ▪ For use in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, or a thiazolidinediones when the single agent alone, with diet and exercise, does not provide adequate glycemic control. ▪ Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings	No UF recommendation at this meeting. Consideration of UF status deferred until oral hypoglycemic drugs are reviewed; UF review not anticipated for 12 months.
Paliperidone extended release tablets (Invega; Janssen/ALZA)) Atypical antipsychotic	Dec 06 (launched Jan 07) ▪ Treatment of schizophrenia ▪ Efficacy in acute treatment of schizophrenia established in three 6-week, placebo controlled, fixed-dose trials in subjects with schizophrenia. ▪ Efficacy not evaluated in placebo-controlled trials for longer than six weeks; physicians electing to use paliperidone for extended periods should periodically re-evaluate long-term usefulness	No UF recommendation at this meeting. Consideration of UF status deferred until atypical antipsychotics are reviewed; UF review not anticipated for 12 months.

Appendix C – Table 3. Table of Abbreviations

AHRQ	Agency for Healthcare Research and Quality
APAP	acetaminophen
ASA	aspirin
BAK	benzalkonium chloride
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
CFR	Code of Federal Regulations
CMA	cost minimization analysis
CNS	central nervous system
CYP	cytochrome P450
DEA	Drug Enforcement Agency
DERP	Drug Effectiveness Review Project
DoD	Department of Defense
ECF	Extended Core Formulary
ER	extended release
ESA	erythropoiesis stimulating agents
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FY	fiscal year
GABA	gamma-aminobutyric acid
HAM-D	Hamilton Rating Scale for Depression
IOP	intraocular pressure
IR	immediate release
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MHS	Military Health System
MTF	military treatment facility
NNH	number-needed-to-harm
NNT	number-needed-to-treat
NSAIDs	non-steroidal anti-inflammatory drugs
OTC	over-the-counter
PA	prior authorization
P&T	Pharmacy and Therapeutics
PDTS	Pharmacy Data Transaction Service
PEC	Pharmacoeconomic Center
PPI	proton pump inhibitor
RCT	randomized controlled trial
SED-1s	newer sedative hypnotics
SSRIs	selective serotonin reuptake inhibitors
TCAs	tricyclic antidepressants
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
UF	Uniform Formulary

Appendix D – Figure 1. Prior Authorization Process for SED-1 Agents Other than Zolpidem IR (Ambien)

Figure 1. TRICARE Pharmacy Network Step Therapy Process
Newer Sedative Hypnotics (SED-1)



2 May 2007

Executive Summary

UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL COMMENTS
March 2007

The Uniform Formulary Beneficiary Advisory Panel commented on the recommendations from the DOD Pharmacy & Therapeutics Committee February 2007 meeting.

- For all therapeutic classes, new drugs, and prior authorizations, the Beneficiary Advisory Panel overwhelming supported the recommendations of the Pharmacy & Therapeutics Committee. The Panel commented that much more needs to be done to inform beneficiaries of formulary changes prior to the implementation date.

Director, TMA:

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