DOD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

INFORMATION FOR THE UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL

I. Uniform Formulary Review Process

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

II. NEWER SEDATIVE HYPNOTICS (SED-1s)

P&T Comments

A. Relative Clinical Effectiveness:

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 [Ambien]) in addition to placebo. There are also many published trials comparing these agents to benzodiazepines. Two studies compare zolpidem IR (Ambien) 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 (Rozerem) 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. Published data with zolpidem ER (Ambien CR) 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 (Ambien) and eszopiclone (Lunesta) 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 (Sonata) and ramelteon (Rozerem) 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 (Ambien) while maintaining plasma concentrations 3 to 6 hours post-dose. Time vs. concentration curves comparing zolpidem ER (Ambien CR) to zolpidem IR (Ambien) show comparable initial concentrations followed by higher concentrations of Ambien CR 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 (Ambien) trials.
- Trials including two or more SED-1 agents (usually compared to placebo) include three published trials comparing zaleplon (Sonata) and zolpidem IR (Ambien) to placebo and one unpublished trial obtained from the FDA statistical review of eszopiclone (Lunesta) that included eszopiclone (Lunesta) and zolpidem IR (Ambien). Based on these trials, zaleplon (Sonata) decreased sleep latency to a greater degree than zolpidem IR (Ambien) (8-24 minutes for zaleplon (Sonata) vs. 6-13 minutes for zolpidem IR [Ambien]), but zolpidem IR (Ambien) increased total sleep time more than zaleplon (Sonata) (28-42 minutes for zolpidem IR (Ambien) vs. 7-27 minutes for zaleplon [Sonata}). More rebound insomnia was noted with zolpidem IR (Ambien) on the first night after discontinuation. The FDA statistical review for eszopiclone (Lunesta) reported very similar results for eszopiclone (Lunesta) vs. zolpidem IR (Ambien) with respect to sleep latency, total sleep time, and awake time after sleep onset.
- Based on trials comparing zolpidem IR (Ambien) 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; but there appears to be more rebound insomnia with benzodiazepines than with the newer sedative hypnotics.
- A single comparative trial of zolpidem IR (Ambien) vs. trazodone (Desyrel, generics) in adult insomnia sufferers without co-morbid depression demonstrated similar efficacy during the two weeks of the study; although trazodone (Desyrel, generics) may result in greater daytime somnolence than zolpidem IR (Ambien).
- In regard to improvement of sleep architecture, there is 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 is for eszopiclone (Lunesta), which has data from a 6-month RCT and open label data out to 1 year. Zolpidem IR (Ambien) 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 1 year. No long-term data is available for zolpidem ER (Ambien CR), which was only tested in short-term trials (3 weeks), although it is probably reasonable to expect long-term results similar to zolpidem IR (Ambien). Zaleplon (Sonata) RCT data is limited to 4-week trials, although open label data supporting efficacy and safety for up to 1 year is available in elderly patients. Ramelteon (Rozerem) has shown sustained efficacy and safety for up to 5 weeks in RCTs, with open label data out to 1 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 (Ambien) studies demonstrated a minimal improvement on certain aspects of the SF-36 after treatment, but no difference from placebo on other aspects. Two eszopiclone (Lunesta) studies that included pre and post-treatment questionnaires addressing improvement in overall sense of well-being showed no significant improvement vs. 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 (Rozerem), 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 [Ambien] vs. zaleplon (Sonata); eszopiclone (Lunesta) vs. zolpidem IR [Ambien]). An unpleasant taste was consistently reported with eszopiclone (Lunesta) during clinical trials, occurring in about 26.1% of patients receiving eszopiclone (Lunesta) vs. 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 is little or no data for the melatonin receptor agonist ramelteon (Rozerem). 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 (Lunesta), which may extend to 9 hours in elderly patients, compared to half-lives of about 1 hour for zaleplon (Sonata), 1-2.6 hours for ramelteon (Rozerem) and 2.5-2.8 hours for zolpidem (Ambien, Ambien CR). Lower starting doses of all SED-1 agents except ramelteon (Rozerem) are recommended in elderly patients.

- Driving safety studies report impaired performance and increased risk of accidents with eszopiclone's (Lunesta) racemic parent drug zopiclone (widely used outside the U.S.) at a 7.5 mg daily dose. The applicability of these data to eszopiclone (Lunesta) is unclear, since the usual younger and elderly adult dosing strengths of eszopiclone (Lunesta) (3 and 2 mg, respectively) would be equivalent to zopiclone doses lower than 7.5 mg. Product labeling and marketing for eszopiclone (Lunesta) advises against taking the product unless the patient is able to get 8 or more hours of sleep; adherence to this warning is advisable. There was no reported difference between eszopiclone (Lunesta) and zolpidem IR (Ambien) 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 (Lunesta).
- Because of its very short half-life, a repeat dose of zaleplon (Sonata) may be taken after the patient has had difficulty falling asleep, as long as the patient is able to sleep for 4 or more hours. Driving studies with zaleplon (Sonata) 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 (Rozerem) 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 (Rozerem).

Based on three trials, more rebound insomnia on the first night after discontinuation was noted with zolpidem IR (Ambien) vs. zaleplon (Sonata).

- All of the newer sedative hypnotics, with the exception of ramelteon (Rozerem), 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 (Rozerem) appears to lack significant abuse potential and may be preferable in patients with a high risk of substance abuse. Ramelteon (Rozerem) 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 (Sonata) due to inhibition of two metabolic pathways (CYP 3A4 and aldehyde oxidase); the initial dose of zaleplon (Sonata) should be decreased. The major metabolic route for ramelteon (Rozerem) is CYP 1A2; ramelteon (Rozerem) 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 (Rozerem) 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 (Ambien) on their local formulary, but relatively few indicated that other SED-1 agents were on formulary (Ambien CR 18%, Rozerem 3%, Lunesta and Sonata 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 (Rozerem) 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 (Ambien) and eszopiclone (Lunesta) have evidence indicating consistent and similar increases in sleep duration. Zaleplon (Sonata) and ramelteon (Rozerem) do not appear to consistently increase sleep duration.

b) Based on three comparative trials, zaleplon (Sonata) appears to decrease sleep latency more than zolpidem IR (Ambien), but zolpidem IR appears to increase total sleep time more than zaleplon (Sonata). In one comparative trial, very similar results were reported for eszopiclone (Lunesta) vs. zolpidem IR (Ambien) 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 (Ambien) 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.

d) There is 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 (Lunesta) 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 (Rozerem) 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 is little or no data for the melatonin receptor agonist ramelteon (Rozerem). 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 (Lunesta), 6 hours (up to 9 hours in elderly patients); followed by zolpidem (Ambien, Ambien CR), 2.5-2.8 hours; ramelteon (Rozerem), 1-2.6 hours; and zaleplon (Sonata), 1 hour. Lower starting doses of all SED-1 agents except ramelteon (Rozerem) 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 (Lunesta) would be equivalent to zopiclone doses lower than 7.5 mg. There was no reported difference between eszopiclone (Lunesta) and zolpidem IR

(Ambien) on subjective measures of next day effects based on results of an unpublished trial reported in the FDA statistical review of eszopiclone (Lunesta).

i) Because of its very short half-life, zaleplon (Sonata) 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 (Rozerem) in pediatric patients due to possible endocrine effects.

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

l) All SED-1 agents, with the exception of ramelteon (Rozerem), probably have a small but significant potential for abuse. Ramelteon (Rozerem) appears to lack significant abuse potential and may be preferable in patients at high risk for substance abuse. Ramelteon (Rozerem) 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 to accept the clinical effectiveness conclusions stated above.

B. Relative Cost Effectiveness:

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 (Lunesta); 2) ramelteon (Rozerem); 3) zaleplon (Sonata); 4) zolpidem IR (Ambien); and 5) zolpidem ER (Ambien CR). Although zolpidem IR (Ambien) was not as cost-effective as eszopiclone (Lunesta) in this CMA, the P&T Committee noted that zolpidem IR (Ambien) 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 (Ambien) 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 (Ambien) 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).

Cost Effectiveness Conclusion

The P&T Committee concluded that:

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

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

C. Uniform Formulary Recommendation

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the SED-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that: 1) eszopiclone (Lunesta) and zolpidem IR (Ambien) be maintained as formulary on the UF with a prior authorization requiring a trial of zolpidem IR (Ambien) for new patients and 2) that ramelteon (Rozerem), zaleplon

(Sonata), and zolpidem ER (Ambien CR) be classified as non-formulary under the UF with a prior authorization requiring a trial of zolpidem IR (Ambien) for new patients.

The P&T Committee agreed that the following prior authorization criteria should apply to SED-1 agents other than zolpidem IR (Ambien). 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 [Ambien]) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during this previous 180 days.

2) PA criteria if automated criteria are not met:

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

   Treatment with zolpidem IR (Ambien) 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 medical necessity criteria must be met. If the PA criteria are met without an approved medical necessity determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved prior authorization for ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) 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. Implementation Plan:

The P&T Committee voted 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 prior authorization.

III. NEWER SEDATIVE HYPNOTICS (SED-1s) (cont.)

BAP Comments

A. Uniform Formulary 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 to recommend that: 1) eszopiclone (Lunesta) and zolpidem IR (Ambien) be maintained as formulary on the UF with a prior authorization requiring a trial of zolpidem IR (Ambien) for new patients and 2) that ramelteon (Rozerem), zaleplon (Sonata), and zolpidem ER (Ambien CR) be classified as non-formulary under the UF with a prior authorization requiring a trial of zolpidem IR (Ambien) for new patients.

The P&T Committee agreed that the following prior authorization criteria should apply to SED-1 agents other than zolpidem IR (Ambien). 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 [Ambien]) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during this previous 180 days.

2) PA criteria if automated criteria are not met:

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

   Treatment with zolpidem IR (Ambien) 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 medical necessity criteria must be met. If the PA criteria are met without an approved medical necessity determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved prior authorization for ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) 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.

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

B. Implementation Plan: The P&T Committee voted 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 prior authorization.

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

IV. NARCOTIC ANALGESICS

P&T Comments

A. Relative Clinical Effectiveness*:*

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 immediate release 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 immediate release 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 immediate release 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 immediate release 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 vs. 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% vs. 6%, $p=0.019$). Two open-label crossover trials involving oxymorphone extended release (Opana ER) vs. morphine or oxycodone sustained release reported similar efficacy and concluded that patients could safely be switched from these medications to extended release 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 45mg every 12 hours = 90mg 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 immediate release and extended release 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 extended release granules and premature release of morphine.

Kadian capsules contain polymer-coated extended release 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 Drug Effectiveness Review Project (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 randomized controlled trials (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 vs. 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 vs. 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 8 trials comparing opioids to other agents (NSAIDs, tricyclic antidepressants) 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 8 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 immediate release 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 (Fentora) 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 consists 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 immediate release 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 vs. 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 immediate release 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 immediate release 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 (Actiq, generic) and buccal tablets (Fentora)—do not supply sufficient evidence to directly compare efficacy. Buccal fentanyl (Fentora) 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 (GI) 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 2 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 extended release 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 (Actiq, generic; Fentora) are immediate release, 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 4 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 prior authorization 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 extended release dosage systems that can be compromised to cause drug to become rapidly available) are more prone to abuse than slow-acting or extended release 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 formulary decision-making.

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, 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 extended release 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 Basic Core Formulary, 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).

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 immediate release 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 vs. 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 immediate release agents for the treatment of breakthrough pain in patients with chronic cancer or non-cancer pain, including the newer immediate release fentanyl products (oral transmucosal lozenges [Actiq, generic] and buccal tablets [Fentora])). Buccal fentanyl (Fentora) 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 postop 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 2 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 formulary decision-making.

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 (Ultram, generics; Ultram ER) 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 extended release 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 to accept the clinical effectiveness conclusions stated above.

B. Relative Cost Effectiveness: Cost minimization analyses 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 cost-minimization analyses (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 (Duragesic, generics), oxycodone ER (Oxycontin), and Oxymorphone ER (Opana ER)— were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin, generics). Two of these products, fentanyl patch (Duragesic) and oxycodone extended release (Oxycontin) 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 (Opana 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 (Fentora) and fentanyl citrate transmucosal lozenges (Actiq, generics), were 40-fold the cost of the two most cost-effective agents. Fentanyl citrate transmucosal lozenges (Actiq) only recently became generically available. There was no substantial difference in cost effectiveness between the two fentanyl citrate products (Fentora vs. Actiq or its generic equivalent).

The results of the CMA for the low potency single analgesic agents showed that tramadol extended release (Ultram 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 (Duragesic, generics), oxycodone extended release (Oxycontin), and oxymorphone (Opana 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 (Oxycontin) provides an alternative for patients who cannot tolerate morphine sulfate.

    c. Transdermal fentanyl (Duragesic, generics) provides a unique dosage form for patients who are unable to swallow.

    d. Oxymorphone ER (Opana 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 (Fentora) and fentanyl citrate transmucosal lozenges (Actiq, generics) 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 (Duragesic, generics), oxycodone extended release (Oxycontin), and oxymorphone (Opana 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 (Fentora) and fentanyl citrate transmucosal lozenges (Actiq, generics) 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 extended release (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.

COMMITTEE ACTION: The P&T Committee agreed with the relative cost-effectiveness analysis of the narcotic analgesic agents.

C. Uniform Formulary 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 that tramadol extended release tablets (Ultram ER) be designated non-formulary; with all other narcotic analgesic agents designated as formulary on the Uniform Formulary. Additionally, the P&T Committee voted to recommend a quantity limit of 112 tablets/ 28 days for fentanyl buccal tablets (Fentora), consistent with established quantity limits for fentanyl transmucosal lozenges (Actiq, generics), recommendations in Fentora package labeling, and current DoD prescribing patterns for Fentora buccal tablets.

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

V. NARCOTIC ANALGESICS (cont.)

BAP Comments

***A.* Uniform Formulary 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 that tramadol extended release tablets (Ultram ER) be designated non-formulary; with all other narcotic analgesic agents designated as formulary on the Uniform Formulary. Additionally, the P&T Committee voted to recommend a quantity limit of 112 tablets/ 28 days for fentanyl buccal tablets (Fentora), consistent with established quantity limits for fentanyl transmucosal lozenges (Actiq, generics), recommendations in Fentora package labeling, and current DoD prescribing patterns for Fentora buccal tablets.

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

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

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

VI. DRUG CLASS REVIEW – OPHTHALMIC GLAUCOMA AGENTS

A. Relative Clinical Effectiveness:

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). The three products contain benzalkonium chloride (BAK) as a preservative, which has been associated with local ocular irritation. Travoprost is also available with a non-benzalkonium (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 (Lumigan), -28% (95% CI -30% to -26%) with latanoprost (Xalatan), and -29% (95% CI -32% to -25%) with travoprost (Travatan) [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 randomized controlled trials 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 (Travatan) was more effective than latanoprost (Xalatan) 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 (Lumigan) and travoprost (Travatan) 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) vs. timolol maleate gel - forming solution (Timoptic XE, generics)* – Timolol maleate solution (Timoptic, generics) requires twice daily dosing. Timolol maleate gel forming solution (Timoptic XE, generics) 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 (Betimol)* – 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 (Timoptic, generics) or timolol maleate gel forming solution (Timoptic XE, generics) 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 BID demonstrated no efficacy differences between the products, both drugs reduced IOP by 23% to 24% [Mundorf et al, 2004].

iv) *Levobunolol (Betagan, generics), metipranolol (Optipranolol, generics), carteolol (Ocupress, generics)* – 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 (Betoptic, generics; Betoptic-S)* – 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 (Azopt) and dorzolamide (Trusopt). 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 brinzolamide (Azopt) and dorzolamide (Trusopt) (-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 (Xalatan) 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 (Cosopt) 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 (Iopidine) 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 (Iopidine) – Apraclonidine (Iopidine) 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 (Iopidine) vs. brimonidine 0.2% BAK (generic) – Head-to-head studies of brimonidine BAK 0.2% (generic) and apraclonidine (Iopidine) 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 (Propine, generics)* – 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 (Miochol-E) – Acetylcholine is used intraocularly to constrict the pupil during cataract surgery, or after placement of the intraocular lens following cataract removal.

Carbachol (Isoptocarbachol) – 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 (Pilopine HS) 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 (Phospholine iodide)* – Echothiophate is dosed BID 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 (Lumigan) (15-45%) and travoprost (Travatan) (30-50%), as compared to latanoprost (Xalatan) (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 (Xalatan) (5-15%) than either bimatoprost (Lumigan) (1-3%) or travoprost (Travatan) (1-4%). The pigmentation changes may be permanent.
- *Preservatives (Travatan vs. 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 (Travatan) and bimatoprost (Lumigan), and <1% for latanoprost (Xalatan). 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 (Betoptic, generics; Betoptic-S) is the only β1 selective ophthalmic beta blocker; however bronchospasm has occurred

in patients with asthma and COPD. 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 (Betoptic, generics; Betoptic-S) and metipranolol (Optipranolol, generics). Timoptic maleate gel forming solution (Timoptic XE, generics) 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% vs. 22.9%) [Mundorf et al, 2004].

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

i) *Serious adverse events* – Brinzolamide (Azopt) and dorzolamide (Trusopt) 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 (Azopt) with dorzolamide (Trusopt), dorzolamide was associated with a higher incidence of burning/stinging (12-16% vs. 2-3%). The higher incidence of ocular discomfort with dorzolamide may be due to the acidic pH of the product (5.6) vs. 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 brinzolamide (Azopt) and dorzolamide (Trusopt), 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 (Iopidine) and brimonidine are contraindicated in patients with hypersensitivity to the individual agents, patients taking clonidine, and patients taking monoamine oxidase (MAO) inhibitors. 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 (Iopidine) 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 is conflicting data as to whether brimonidine purite 0.15% (Alphagan P) causes less ocular irritation than brimonidine BAK 0.2% (generic). 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) vs. brimonidine BAK 0.2% (generics). More patients (34%) discontinued treatment due to adverse events with brimonidine BAK 0.2% (generics) than with brimonidine purite 0.1% (21%).

e) *Adrenergics, cholinergics, and cholinesterase inhibitors*

i) *Dipivefrin (Propine, generic)* – Today dipivefrin is rarely used due to adverse effects such as conjunctival hyperemia, hypersensitivity and ocular irritation. It is contraindicated 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 (Miochol-E) – 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 (Isoptocarbachol) - 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 (Phospholine iodide)* – Echothiophate frequently causes blurred vision, brow ache, eyelid fasisculation, and watery eyes. Rarely, burning or stinging have 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 (Xalatan) requires refrigeration prior to opening, to maintain a 36-month shelf life; it does not require refrigeration once opened. Bimatoprost (Lumigan) 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 QD ophthalmic beta blockers, particularly if multiple ophthalmic drugs are required. The branded timolol maleate product Istalol, and timolol maleate gel forming solution (Timoptic XE, generics) are dosed once daily.

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

Dosing dispenser – The dosing dispenser of dorzolamide (Trusopt) 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 (Propine, generic)* – 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 (Phospholine iodide) 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 (Lumigan), latanoprost (Xalatan), and travoprost (Travatan, Travatan Z) 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 vs. 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 (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, 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 (Iopidine) 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 is 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 (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 acetylcholine (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.

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

B. Ophthalmic Glaucoma Agents – Relative Cost Effectiveness

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 cost-minimization analyses (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 (Xalatan) and bimatoprost (Lumigan) were most cost-effective under a scenario where only two prostaglandin products were placed in the Uniform Formulary; and (3) an all on scenario (i.e., all three prostaglandin products included on the Uniform Formulary) 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 (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 (Azopt) was not cost-effective compared to dorzolamide (Trusopt). 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 budget impact analysis (BIA) of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost shares). The goal of the BIA was to aid the P&T Committee in determining which group of ophthalmic glaucoma agents best met 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 to accept the cost-effectiveness conclusions stated above.

C. Uniform Formulary 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 to recommend that latanoprost (Xalatan), bimatoprost (Lumigan), levobunolol (Betagan, generics), betaxolol (Betoptic, generics; Betoptic-S), carteolol (Ocupress, generics), metipranolol (Optipranolol, generics), timolol maleate (Timoptic, generics), timolol maleate gel forming solution (Timoptic XE, generics), brimonidine (generics; Alphagan P), apraclonidine (Iopidine), dorzolamide (Trusopt), 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 brinzolamide (Azopt) be classified as non-formulary.

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

VII. Ophthalmic Glaucoma Agents (cont.)

BAP Comments

A. **Uniform Formulary Recommendation:** The P&T Committee, based upon its collective professional judgment, voted to recommend that latanoprost (Xalatan), bimatoprost (Lumigan), levobunolol (Betagan, generics), betaxolol (Betoptic, generics; Betoptic-S), carteolol (Ocupress, generics), metipranolol (Optipranolol, generics), timolol maleate (Timoptic, generics), timolol maleate gel forming solution (Timoptic XE, generics), brimonidine (generics; Alphagan P), apraclonidine (Iopidine), dorzolamide (Trusopt), 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 brinzolamide (Azopt) be classified as non-formulary.

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

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

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

VIII. DRUG CLASS REVIEW – MONOAMINE OXIDASE INHIBITOR ANTIDEPRESSANTS (MAOIs)

A. MAOI Antidepressants – Relative Clinical Effectiveness

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

1) 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 GI tract results in decreased catabolism of tyramine, which can increase blood pressure. Patients taking MAOI antidepressants who do not restrict dietary sources of tyramine can potentially develop hypertensive crisis. Theoretically, administering an MAOI antidepressant 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 (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate, generics), are FDA-approved to treat either atypical depression or MDD. The selegiline transdermal patch (Emsam) is only indicated 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 randomized controlled trials (published from 1959 through 1992) that focused on depressive disorders in adults in the outpatient setting. The

trials evaluated the efficacy of isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate, generics).

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 (Nardil) and tranylcypromine (Parnate, generics) 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 (Emsam)

Three published placebo-controlled trials lasting 6 to 8 weeks and one open-label trial lasting 52 weeks evaluate the efficacy of the transdermal selegiline formulation (Emsam). 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, vs. 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) vs. 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 (Nardil), 60% with isocarboxazid (Marplan), and 53% with tranylcypromine (Parnate, generics) 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 is 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 vs. 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 vs. the oral MAOI inhibitors.

4) Other factors

a) *Available dosage formulations* – Transdermal selegiline (Emsam) 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 (Parnate, generics) are the only MAOI antidepressants that are dosed once daily. Isocarboxazid (Marplan) and phenelzine (Nardil) 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 (Nardil) and tranylcypromine (Parnate, generics) in pregnant patients with severe depression.

e) *Pediatrics* – The three oral MAOI antidepressants and transdermal selegiline (Emsam) 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 (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate, generics) 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 (Emsam) 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 (Emsam) in three placebo controlled trials. There are no clinical trials directly comparing the oral MAOI antidepressants with transdermal selegiline However, there is 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 (Emsam).

6) The purported benefits of transdermal selegiline (Emsam) 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 who require a once-daily dosage formulation.

9) There is insufficient evidence to determine whether transdermal selegiline (Emsam) represents a therapeutic advance over isocarboxazid (Marplan), phenelzine (Nardil) and tranylcypromine (Parnate, generics).

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 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 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.

Results of the cost minimization analysis for the MAOI class showed that:

1) Among the oral agents, phenelzine (Nardil) was the most cost-effective agent, followed closely by tranylcypromine (Parnate, generics) and isocarboxazid (Marplan).

2) Transdermal selegiline (Emsam) was the least cost-effective MAOI for the treatment of depression. The weighted average cost per day of treatment with transdermal selegiline was 4-fold higher than the most costly oral MAOI, isocarboxazid (Marplan).

Cost Effectiveness Conclusion

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

2) Transdermal selegiline (Emsam) 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 to accept the cost-effectiveness conclusions stated above.

C. Uniform Formulary Recommendations

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 to recommend that phenelzine (Nardil), tranylcypromine (Parnate, generics) and isocarboxazid (Marplan) be maintained as formulary on the UF and that transdermal selegiline (Emsam) be classified as non-formulary.

D. Uniform Formulary Implementation Period

Because of the small number of unique utilizers affected (approximately 135 patients per quarter at all three POS), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

IX. DRUG CLASS REVIEW – MONOAMINE OXIDASE INHIBITOR ANTIDEPRESSANTS (MAOIs)

BAP Comments

A. Uniform Formulary Recommendations. 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 to recommend that phenelzine (Nardil), tranylcypromine (Parnate, generics) and isocarboxazid (Marplan) be maintained as formulary on the UF and that transdermal selegiline (Emsam) be classified as non-formulary.

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

B. Implementation period. Because of the small number of unique utilizers affected (approximately 135 patients per quarter at all three POS), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

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