# 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. Overactive Bladder Drug Class Review

### *P&T Comments*

**A. Relative Clinical Effectiveness:** The P&T Committee evaluated the relative clinical effectiveness of all the FDA-approved antimuscarinic drugs available in the U.S. for the treatment of overactive bladder. The Overactive Bladder therapeutic class was defined as the antimuscarinics: oxybutynin immediate release IR (Ditropan tablets/solution or generic) oxybutynin sustained SR (Detrol XL), oxybutynin transdermal (Oxytrol), tolterodine IR (Detrol), tolterodine SR (Detrol LA), trospium (Sanctura), solifenacin (Vesicare), and darifenacin (Enablex). The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 C.F.R. 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

During a twelve month period ending 30 Sept 2005, 147,508 MHS patients were prescribed an antimuscarinic drug for overactive bladder. This class is now ranked 28$^{th}$ in MHS drug class expenditures at a cost of $55 million annually.

*Efficacy measures.* The antimuscarinic drugs reviewed are FDA-approved for the treatment of Overactive Bladder. Efficacy measures used in clinical trials include the following:

a. Weekly number of urge incontinence episodes and total (urge plus non-urge) urinary incontinence episodes

b. Daily micturition frequency for up to 7 consecutive days during the baseline period and for one or more periods prior to clinic visits
c. Daily frequency of urgency episodes
d. Daily severity of urgency episodes
e. Volume voided per micturition
f. Number of incontinence episodes resulting in a change of pad or clothing per week
g. Nocturnal awakenings per week due to OAB symptoms
h. Volume to first urge sensation
i. Volume to first detrusor contraction
j. Bladder capacity (volume)
k. Post-void residual volume

*Efficacy results:* No differences in efficacy were reported when the following trials were assessed: four studies comparing oxybutynin immediate release (IR) and tolterodine IR; one study of trospium versus oxybutynin IR; four studies of oxybutynin sustained release (SR) versus oxybutynin IR; and one study comparing of tolterodine SR versus tolterodine IR.

Oxybutynin SR was found to be superior to tolterodine IR in one trial; conversely tolterodine SR was reported as superior in one comparative trial against oxybutynin IR. Conflicting results were reported in the trials comparing oxybutynin SR and tolterodine SR, however, the two products showed similar efficacy in the comparative clinical trial that had the most rigorous study design. Solifenacin (flexible dose) showed greater efficacy over tolterodine SR (fixed dose) in one trial, however the results may be explained by lack of dosage titration allowed in the tolterodine SR group. Another short term trial showed greater efficacy with solifenacin vs tolterodine IR in some, but not all, efficacy measures. There were no trials comparing darifenacin vs. other OAB drugs.

A comparison of the OAB drugs' effects on the primary efficacy was made by adjusting for placebo effect and standardizing for 24 hour results. This comparison was not designed to demonstrate superiority, but designed to provide a range of improvement. All of the OAB agents decreased incontinence episodes by 0.32 - 1.04 events per 24 hours and urinary frequency by 0.6 - 1.3 voids per 24 hours.

*Efficacy conclusion:* In controlled clinical trials in overactive bladder, there was a high placebo efficacy rate. All of the OAB drugs have shown statistical superiority over placebo in controlled trials, however the results are of questionable clinical significance. Despite the availability of several head-to-head comparative trials for the OAB drugs, it is difficult to determine superiority of one product over another, due to differences in study design. When the results of the comparative clinical trials are compared in terms of incontinent episodes, urinary frequency and volume/void, there is insufficient evidence to conclude that any one OAB drug is more efficacious than another.

*Safety/Tolerability:*

*Contraindications:* All the OAB drugs carry a similar contraindication of use in patients with gastric retention, urinary retention and uncontrolled narrow angle glaucoma.

*Serious side effects*: Irreversible urinary retention is a possible serious side effect with all the drugs in the OAB class. Cases are rare especially with the use of long acting agents.

*Common Side effects:* The majority of the side effects are due to the anti-cholinergic properties inherent to the class. The most prevalent side effects are dry mouth, constipation, dry eyes, somnolence and nausea. The newer agents (solifenacin [Vesicare], darifenacin [Enablex] and trospium [Sanctura]) cause similar rates of dry mouth as the older agents (tolterodine and oxybutynin). These newer OAB drugs cause more constipation than tolterodine and oxybutynin. In the clinical trials with the oxybutynin patch (Oxytrol), patients treated with the patch had a lower anti-cholinergic side effect profile verses patients receiving tolterodine and oxybutynin oral formulations. However, the patch was associated with significant dermatological side effects resulting in patient withdrawal. Oxybutynin IR (Ditropan) is listed on the Beer's Criteria indicating the drug's use should be limited in the elderly.

Evidence from short-term head-to-head comparison trials indicate a higher incidence of adverse events overall, and dry mouth specifically, with oxybutynin. The SR forms of each drug resulted in fewer adverse events and dry mouth when compared to IR formulations. Trospium causes less severe dry mouth although the overall incidence of dry mouth and short term adverse events are similar to oxybutynin IR. The difference between drugs based on withdrawals is less clear. Two trials of solifenacin versus tolterodine showed similar rates of adverse events overall; one trial showed lower rates of dry mouth for tolterodine SR versus solifenacin.

*Discontinuation Rates*: One comparative long-term study assessed the discontinuation rate of tolterodine and oxybutynin IR over a 6-month period. Oxybutynin IR treatment resulted in a higher discontinuation rate and earlier withdrawal from therapy than patients receiving tolterodine. The discontinuation rates and withdrawal rates were high for both drugs. Uncontrolled studies reported that dry mouth is the most common adverse event, and found similar rates of adverse events and withdrawals between oxybutynin and tolterodine. One head-to-head trial of trospium versus oxybutynin reported more adverse effects attributed with oxybutynin, especially dry mouth.

*Drug interactions:* There is the potential for induction or inhibition of hepatic cytochrome P450 isoenzymes with all the OAB drugs except Sanctura (trospium). There are few studies evaluating the clinical effects of these drug interactions. All the OAB drugs have the potential to increase the anti-cholinergic effects when used concomitantly with other anti-cholinergic drugs, which increases the risk for adverse effects and toxicity. All the OAB drugs can potentially increase the risk for sedation when taken with other drugs with sedating effects.

*Persistence:* Persistence rates of less than 10% with the OAB drugs have been reported in the literature. In the MHS, after a 12 month evaluation period, the

persistence rates for tolterodine SR (Detrol LA), oxybutynin SR (Ditropan XL), and oxybutynin IR (Ditropan) were 5% to16%. There were insufficient numbers of prescriptions refilled for the three newest OAB drugs to determine persistent rates. MHS beneficiaries using the Mail Order system were more persistent with OAB therapy than those beneficiaries using other point of service. Noted in the study were a number of patients refilling OAB drug prescriptions well after the due date. It is possible that patients are using the OAB drugs on an as needed basis as dictated by social situations

*Safety/tolerability conclusion:* Anti-cholinergic effects are the most bothersome adverse events with all the OAB drugs. The most frequently encountered adverse event is dry mouth, which occurs with a higher rate for IR formulations than with SR formulations. The highest frequency of dry mouth occurs with oxybutynin IR (Ditropan). The three newest OAB drugs (trospium [Sanctura], solifenacin [Vesicare], and darifenacin [Enablex]) do not substantially lower the rate of dry mouth compared with tolterodine or oxybutynin SR, but do cause a higher rate of constipation. An evaluation of prescription refill patterns in DoD shows low persistence rates with tolterodine and oxybutynin. There was not enough data available to adequately evaluate MHS persistence rates for trospium (Sanctura), solifenacin (Vesicare), and darifenacin (Enablex).

*Other Factors:*

*Dosing*: All of the agents in the class are dosed once daily except for trospium (Sanctura), oxybutynin IR (Ditropan), and tolterodine IR (Detrol). Once daily dosing theoretically increases compliance. Oxybutynin SR (Ditropan XL) is frequently dosed in a range of 5 mg to 15 mg daily in clinical trials. In contrast, DOD usage shows 20 mg to 30 mg daily more commonly used, which can potentially increase the risk of adverse events.

*Special populations: Pediatrics:* Oxybutynin IR and SR (Ditropan and Ditropan XL) are FDA-approved for use in children 6 years and older. The manufactures of tolterodine are pursuing an indication for use in pediatric patients. *Pregnancy*: All the OAB drugs are rated as pregnancy category C with the exception of oxybutynin which is rated category B.

*DoD Provider Comments*: DoD providers were most comfortable prescribing oxybutynin IR (Detrol) and tolterodine SR (Detrol LA); these two drugs have been included on the BCF since 2002. Most providers favored tolterodine SR (Detrol LA). A majority of respondents had heard of the newer agents, trospium (Sanctura), solifenacin (Vesicare) and darifenacin (Enablex), but over 80% had not yet prescribed the agents. Most providers reported that the side effect profiles seen with clinical usage were similar to what is reported in the literature. DoD providers overestimated MHS persistence rates at 43% compared to the actual rates of between 5% and 16%.

*Other Factors Conclusion:* There is no evidence to suggest clinical superiority of any one OAB drug over another based on differences in dosing and titration schedules or DoD provider opinion. For pediatric patients, oxybutynin is preferred at this time.

***COMMITTEE ACTION:*** The P&T Committee that for the purposes of the UF clinical review, all the drugs reviewed for overactive bladder were similar in terms of effectiveness and clinical outcome.

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

To determine the relative cost effectiveness of the OAB agents, two separate economic analyses were performed, a pharmacoeconomic analysis and budget impact analysis (BIA). From the preceding evidence-based relative clinical effectiveness evaluation, the P&T Committee concluded that, when comparing immediate release agents to immediate release agents and sustained release agents to sustained release agents, there was insufficient evidence to suggest that the OAB agents differed in regards to efficacy, safety, and tolerability in the treatment of OAB. Normally, such a conclusion would suggest cost-minimization to be the appropriate pharmacoeconomic analysis, however, in this case, to account for the differences in relative clinical effectiveness between the immediate release and sustained release agents in this therapeutic class, a cost-effectiveness analyses (CEA) was used. This was done based on the results of a sample based retrospective cohort database analysis. In a CEA, the agents within a therapeutic class are competed on two dimensions, cost and effect (outcomes).

A one-year sample-based retrospective cohort database analysis was performed on DoD MHS prescription data. The study population was comprised of DoD patients filling prescriptions for oxybutynin IR, oxybutynin XL, oxybutynin patch, tolterodine IR, tolterodine SR, and trospium between 01 July 2004 and 30 September 2005. Patients taking any OAB agent, in the 6 month period prior of their observed period of enrollment, were excluded to capture new users only. Note, darifenacin and solifenacin were not included in the study since these agents are new and lacked a year's worth of utilization data. The drug cost used in the analysis was the point of service adjusted total weighted average cost per day of treatment (for all three points of service) and the outcome of interest was adherence to treatment, where adherence to treatment was measured by total days of treatment. Theoretically, adherence to treatment is a surrogate indicator of efficacy, safety, and tolerability. In other words, a patient is more inclined to adhere to treatment if the agent works (efficacy) and is tolerated to the extent that the benefits of treatment outweighs the risk of side effects (tolerability and/or safety).

The results from the sample-based retrospective cohort database analysis were incorporated into a cost-effectiveness analysis. The cost used in the analysis for each agent was the mean cost of treatment for one year and the effect/outcome was

the mean days of treatment for one year. Overall, the results of the CEA were as follows:

- Overall, oxybutynin IR was determined to be the most cost-effective agent and tolterodine SR was determined to be significantly more costly and effective along the efficiency frontier
- Among the multi-dosed immediate release agents, oxybutynin IR was determined to be the most cost-effective agent; tolterodine IR was determined to be slightly more effective but significantly more costly (> 15-fold) compared to oxybutynin IR; and trospium IR was determined to be slightly less effective and significantly more costly (> 15-fold) compared to oxybutynin IR
- Among the once daily extended release agents, tolterodine SR was determined to be the most cost-effective agent; oxybutynin patch and SR tablet were dominated (more costly and less effective) compared to tolterodine SR

Although the evidence-based relative clinical effectiveness evaluation determined that there was insufficient evidence to suggest that the OAB agents differed in regards to efficacy, safety, and tolerability in the treatment of OAB, this CEA based on a sample-based retrospective cohort database analysis suggests that differences do exist among the agents in regards to adherence to treatment.

Since darifenacin and solifenacin lacked sufficient utilization data to be included in the CEA analysis, the agents were evaluated on their point of service adjusted total weighted average cost per day of treatment only. The manufacturers of darifenacin and solifenacin submitted highly competitive prices for their respective agents, which made them significantly less costly compared to the most cost-effective single-dosed extended release agent, tolterodine SR. For purposes of this evaluation, the DoD P&T Committee assumed that darifenacin and solifenacin would have similar relative clinical effectiveness compared to tolterodine SR, based upon the conclusion of the overall relative clinical effectiveness presentation.

The results of the CEAs were subsequently incorporated into a budget impact analysis (BIA). A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of OAB agent's best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. Based on the BIA results and other clinical and cost considerations (oxybutynin SR is projected to go generic in 2006), the Committee agreed that a group of OAB agents that included: darifenacin, oxybutynin IR, oxybutynin SR, solifenacin, and tolterodine SR best achieved this goal when compared to other combination groups of OAB agents, and thus were determined to be more cost-effective relative to other combination groups.

***COMMITTEE ACTION:*** The P&T Committee, based upon its collective professional judgment to recommend that tolterodine IR (Detrol), oxybutynin patch (Oxytrol), and trospium (Sanctura) be classified as non-formulary, with darifenacin (Enablex), oxybutynin IR (Ditropan), oxybutynin SR (Ditropan XL), solifenacin (Vesicare), and tolterodine SR (Detrol LA) remaining on the UF. In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in the Code of Federal Regulations (32 C.F.R. 199.21(e)(2).

**C. Implementation Plan:** Because of the low number of beneficiaries who would be affected by this formulary action (19,118 patients known to be taking tolterodine IR (Detrol), trospium (Sanctura), or oxybutynin patch (Oxytrol) across the MHS), the P&T Committee recommended an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

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

***COMMITTEE ACTION:*** The P&T Committee recommended an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

## III. Overactive Bladder Drug Class Review (cont.)

### *BAP Comments*

**A. Relative Clinical Effectiveness***:* The DoD P&T Committee concluded that: 1) when the results of the comparative clinical trials are compared in terms of incontinent episodes, urinary frequency and volume/void, there is insufficient evidence to conclude that any one OAB drug is more efficacious than another; 2) When similar dosage forms are compared (IR to IR; SR to SR) the side effect profiles are similar; 3) IR forms of the overactive bladder drugs induce more anti-cholinergic side effects than the SR forms; 4) the new agents, solifenacin (Vesicare) and darifenacin (Enablex), and trospium (Sanctura) have an increased rate of constipation compared to oxybutynin SR (Ditropan XL) and tolterodine SR (Detrol LA); 5) oxybutynin is the only product which is approved for use in children at this time; 6) MHS persistence rates with all drugs in this class are very low, ranging

between 16% and 55% at the end of a one year evaluation period; 7) DoD providers were most comfortable prescribing oxybutynin and tolterodine and had little experience with the newer agents.

**B. Relative Cost Effectiveness:** The P&T Committee, based upon its collective professional judgment, voted to accept the OAB pharmacoeconomic analyses presented by the PEC. The P&T Committee concluded that: tolterodine IR (Detrol), oxybutynin patch (Oxytrol), and trospium (Sanctura) were not cost-effective relative to the other OAB agents.

**C. Uniform Formulary Recommendation** Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the OAB agents, and other relevant factors, the P&T Committee recommended that tolterodine IR (Detrol), oxybutynin patch (Oxytrol), and trospium (Sanctura) be classified as non-formulary and that darifenacin (Enablex), oxybutynin IR (Ditropan), oxybutynin SR (Ditropan XL), solifenacin (Vesicare), and tolterodine ER (Detrol LA) remaining on the UF.

| *BAP Comment:* | ☐ Concur ☐ Non-concur<br>Additional Comments and Dissentions: |
|---|---|

**D. Implementation Plan:** The Committee voted to recommend an implementation period of 60 days.

| *BAP Comment:* | ☐ Concur ☐ Non-concur<br>Additional Comments and Dissentions: |
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## IV. Miscellaneous Antihypertensive Drug Class Review

### *P&T Comments*

***A.* Relative Clinical Effectiveness:** The P&T Committee evaluated the relative clinical effectiveness of the miscellaneous antihypertensive agents marketed in the United States. The drugs in the class included the ACE inhibitor/calcium channel blocker combinations [amlodipine/benazepril (Lotrel), felodipine/enalapril (Lexxel)], and verapamil sustained release (SR)/trandolapril (Tarka); the direct acting vasodilators (hydralazine, minoxidil); the centrally acting alpha-2 agonists (clonidine, methyldopa, guanabenz, guanfacine); the peripheral alpha-1 antagonists (prazosin);

the adrenergic antagonists (reserpine, guanadrel, guanethidine); and the ganglionic blockers (mecamylamine). Information regarding the safety, effectiveness, clinical outcomes, and patient persistence rates of the ACE inhibitor/calcium channel blocker combinations (ACE/CCB combos) was considered in depth. For the other miscellaneous antihypertensive agents, the Committee considered the place in therapy of the drugs in national hypertension guidelines, significant usage for conditions other than hypertension, existing MHS utilization, and adverse effect profiles. The clinical review included, but was not limited to the requirements stated in the Uniform Formulary Rule.

1.) *ACE inhibitor/CCB combinations:* The relative clinical effectiveness of the individual ACE inhibitors and calcium channel blockers was reviewed previously by the Committee. Refer to the minutes from the August 2005 P&T Committee meeting for the relative clinical effectiveness conclusion for these two drug classes.

*a) Pharmacology*: Both amlodipine/benazepril (Lotrel) and felodipine/enalapril (Lexxel) contain a dihydropyridine CCB. The verapamil component of verapamil SR/trandolapril (Tarka) is a non-dihyropyridine CCB. Verapamil reduces myocardial contractility and slows conduction through the AV node. The physiologic effect of slowed heart rate with the non-dihydropyridine CCBs is frequently used as a beneficial effect in patients with increased heart rate (e.g. atrial fibrillation). The dihydropyridines do not slow cardiac conduction, but have peripheral vasodilatory effects. The individual ACE inhibitor components of the combo products (benazepril, enalapril, trandolapril) exhibit similar pharmacologic properties.

The benefits of combining an ACE inhibitor with a CCB include additive BP lowering effect due to differing mechanisms of action, attenuation of CCB-induced edema through addition of the ACE inhibitor, patient convenience due to simplified drug regimens, decreased pill burden, and potentially improved adherence with antihypertensive therapy.

*b) Efficacy for Hypertension:*

*Place in Therapy:* The three ACE/CCB combinations are all approved for the treatment of mild to moderate hypertension. The Joint National Commission VII (JNC VII) guidelines acknowledge that combination antihypertensive therapy may be necessary, and is likely to be used as first-line treatment of hypertension. The guidelines recommend use of a combination regimen, which should usually include a diuretic, as first-line therapy for stage 2 hypertension (BP $\geq$160/100 mm Hg), or for patients with compelling indications. Compelling indications for use of an ACE inhibitor include heart failure, post-myocardial infarction, high risk of coronary artery disease, diabetes, chronic kidney disease, or previous stroke; compelling indications for use of a CCB include diabetes and patients with high risk of coronary artery disease.

*Efficacy for lowering BP:* All three products have clinical trial data showing enhanced efficacy when the combination product is compared to the single components administered individually. Data from the individual package inserts was used to compare BP lowering effects. Amlodipine/benazepril (Lotrel) reduces systolic blood pressure (SBP) by 10-25 mmHg and diastolic blood pressure (DBP) by 6-13 mmHg, felodipine/enalapril (Lexxel) reduces SBP by 14.2 mmHg and DBP by 12.6 mmHg, and verapamil/trandolapril (Tarka) reduces SBP by 13-22 mmHg, and DBP by 8-17 mmHg.

*Effects in sub- populations of patients with hypertension:* There are no published trials of felodipine/enalapril (Lexxel) in sub-populations of patients with hypertension. Both amlodipine/benazepril (Lotrel) and verapamil SR/trandolapril (Tarka) have several published trials supporting efficacy in patients with type 2 diabetes, patients with moderate to severe hypertension, and African Americans. Direct comparisons of BP lowering effects in the sub-populations are difficult, due to differences in study design.

*Effect on proteinuria*: The verapamil CCB component of verapamil SR/trandolapril (Tarka) physiologically decreases resistance of the afferent renal arteriole, which reduces glomerular pressure and proteinuria. DHP CCBs do not have this effect on the afferent arteriole. Evidence from one large clinical trial showed that a combination of verapamil with trandolapril over a 3 year period prolonged the time to onset of microalbuminuria in patients with type-2 diabetes and hypertension.

*Cardiovascular Outcomes*: There are no published trials with felodipine/enalapril (Lexxel) showing a benefit of the drug in reducing cardiovascular outcomes. There are no completed trials with amlodipine/benazepril (Lotrel) assessing cardiovascular outcomes; two ongoing trials are assessing cardiovascular mortality/morbidity (ACCOMPLISH trial) and progression to overt nephropathy (GUARD). There are no published trials assessing the efficacy of the specific Tarka formulation at reducing cardiovascular outcomes. Although a regimen comprised of verapamil SR and trandolapril used as add-on therapy showed a reduction in all-cause death, non-fatal myocardial infarction, and non-fatal stroke (INVEST trial), this open label trial did not show a difference in outcomes between a regimen of CCB and ACE inhibitor vs. beta blocker and diuretic. The INVEST trial did not randomize patients prospectively to the combination, thus cannot be used to support efficacy of the specific Tarka formulation in reducing cardiovascular outcomes.

*Clinical Efficacy Conclusion:* The Committee concluded that there is insufficient evidence to suggest that the BP lowering effects of the ACE/CCB combos differ significantly. The formulations of Lotrel and Tarka have shown efficacy in treating sub-populations of patients with hypertension; there is no data with Lexxel. Clinical trials assessing cardiovascular outcomes with the combination products Lexxel, Lotrel and Tarka have not been conducted, but there is some evidence of benefit with the individual components.

*c) Safety and Tolerability:*

*i) Serious Adverse Effects:* Verapamil SR/trandolapril (Tarka) is contraindicated for use in patients with impaired cardiac contractility (e.g. severe left ventricular dysfunction, SBP < 90 mm Hg), due to the verapamil component. All three ACE/CCB combos are contraindicated for use in patients with a history of angioedema to any ACE inhibitor.

*ii) Common Adverse Effects:* The safety profiles of the ACE/CCB combos are reflected by their individual CCB components. The products containing a dihydropyridine CCB [amlodipine/benazepril (Lotrel) and felodipine/enalapril (Lexxel)] commonly causes edema and headache, while the non-dihydropyridine CCB [verapamil SR/trandolapril (Tarka)] more commonly causes dyspnea, fatigue, and constipation. Comparison of the product labeling between amlodipine/benazepril (Lotrel) and felodipine/enalapril (Lexxel) due not suggest major differences in the incidence of edema, headache, or dizziness.

*iii) Discontinuations due to Adverse Effects:* Pooled data from clinical trials was used to compare the products in terms of the percentage of patients discontinuing therapy due to adverse events. For felodipine/enalapril (Lexxel), 2.8% of patients discontinued treatment vs. 1.3% with placebo, most commonly due to headache. The percentage of patients discontinuing therapy with amlodipine/benazepril was 4%, vs. 3% with placebo, most commonly due to edema. The discontinuation rate with verapamil SR/trandolapril (Tarka) was 2.6% vs. 1.9% with placebo, most commonly due to dyspnea and fatigue.

*iv). Safety and Tolerability Conclusion*: The DoD P&T Committee concluded that the discontinuation rate due to adverse events appears similar between the three ACE/CCB combos, based on pooled analysis from placebo controlled trials. The non-dihydropyridine component of verapamil SR/trandolapril (Tarka) imparts unique risks of impaired cardiac contractility. There is no evidence that amlodipine/benazepril (Lotrel) and felodipine/enalapril (Lexxel) differ markedly in adverse event profiles.

*d) Other Factors - Adherence/Persistence with antihypertensive therapy:* For the purposes of this review, the measure used to define persistence is the medication possession ratio, which is calculated based on the daily possession of drugs. There are no published trials with felodipine/enalapril (Lexxel) or verapamil SR/trandolapril (Tarka) showing improved rates of patient persistence. Data from two studies (one published, the other in abstract form) using pharmacy claims databases reported medication possession ratios ranging from 81%-88% with patients continuously refilling prescriptions for Lotrel, compared to 69%-73.8% for regimens containing an ACE inhibitor and CCB administered as separate components.

*Conclusion for Other Factors (Adherence/Persistence):* Two database claims studies suggest that patient persistence with Lotrel is improved by 7%-22%,

compared to regimens containing an ACE inhibitor and CCB administered as separate components.

2.) *Other Miscellaneous Antihypertensive Agents:* The Committee evaluated the other miscellaneous antihypertensive agents by considering the place in therapy of the drugs in national hypertension guidelines, significant usage for conditions other than hypertension, existing MHS utilization, and adverse effect profiles. The Committee also specifically evaluated the relative clinical effectiveness of clonidine tablets vs. clonidine patch.

*a) Clonidine oral tablets vs. Clonidine transdermal patches:* The JNC VII guidelines recommend clonidine as a 2nd or 3rd line choice for treating hypertension, due to adverse effects. Clonidine is frequently used for off-label indications, including treatment of menopausal symptoms, smoking cessation, pediatric behavioral problems, and alcohol or opiate withdrawal symptoms. Clonidine tablets require twice daily to three times a day dosing, and there is a high risk of rebound hypertension, if the tablets are abruptly discontinued. The clonidine patches are changed weekly and are associated with a lower risk of rebound hypertension, since plasma levels of drug slowly decline over a one-week period when the patch is removed. Other benefits of transdermal clonidine include that it is frequently used in patients with swallowing difficulties (e.g. stroke patients), its use can potentially improve compliance in patients requiring several drugs for BP control, and that its use can simplify the medication regimen in patients requiring several antihypertensive drugs. In the entire MHS, approximately 20,000 prescriptions for clonidine tablets are dispensed monthly, compared to 5,000 prescriptions for clonidine patches.

*b) Remaining miscellaneous antihypertensive agents in the class:* The remaining miscellaneous antihypertensive drugs in the class include hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, prazosin, reserpine, guanadrel, guanethidine, and mecylamine. All of these drugs are available in generic formulations and some no longer have marketed proprietary formulations (e.g. reserpine, guanethidine). Utilization of these drugs in the MHS is low (<5,000 prescriptions dispensed in FY 05), with the exception of hydralazine (40,000 Rxs), prazosin (22,000 Rxs), methyldopa (13,000 Rxs), and minoxidil (12,000 Rxs). Some of these products have been available for several decades; including reserpine, mecamylamine, hydralazine, methyldopa, and guanethidine, thus rigorously conducted clinical trials are not available.

*i) Place in therapy:* JNC VII guidelines support use of methyldopa, hydralazine, minoxidil, reserpine, and guanfacine as antihypertensive drugs, although clinical use is often limited due to tolerability issues. Methyldopa is commonly used for treating hypertension in pregnant patients, due to long-term studies supporting its safety. Hydralazine also has a role in treating symptoms of heart failure in patients who are intolerant of or who have contraindications to use of ACE inhibitors.

Guanfacine is also utilized in the setting of pediatric patients with behavioral problems. Guanabenz is rarely used clinically (<500 Rxs dispensed in the MHS in FY 05), as it requires twice daily dosing and has bothersome side effects. Minoxidil is an option for patients with stage 2 hypertension (SBP 160-179 / DBP 100-109 mm Hg) who have not responded to conventional antihypertensive drug regimens. Reserpine has evidence from randomized controlled trials that it reduces cardiovascular mortality and morbidity (VA trials, SHEP trials). Use of prazosin as an antihypertensive agent has fallen into disfavor, based on the results of the ALLHAT trial that showed an increased risk of development of heart failure in patients receiving the alpha blocker doxasozin. Guanadrel, guanethdine, and mecamylamine are rarely used today.

*ii) Adverse Effects:* The use of the other miscellaneous antihypertensive agents has largely been replaced by other drugs (e.g. ACE inhibitors, diuretics, CCBs, angiotensin receptor blockers, beta blockers) due to their side effect profiles. Hydralazine may cause drug-induced systemic lupus erythematosus. Minoxidil can cause hypertrichosis; and fluid retention and reflux tachycardia are frequent problematic effects. Common adverse effects of methyldopa, guanabenz and guanfacine include fluid retention, sedation, lethargy, postural hypotension, dizziness, dry mouth and headache. First-dose syncope is a risk with prazosin and other alpha blockers. Clinical use of reserpine is limited due to nasal stuffiness and the perception of increased risk of depression. Orthostatic hypotension is an issue with guanadrel and guanethidine, as is diarrhea, and sexual dysfunction. Postural hypotension is a limiting side effect of mecamlyamine. Other effects of mecamylamine due to its ganglionic blockading properties include tachycardia, mydriasis, paralytic ileus, syncope, and urinary retention.

*3) Overall clinical effectiveness conclusion for the miscellaneous antihypertensive agents:* The Committee concluded that: (1) for lowering blood pressure, there is no evidence that any one ACE/CCB combo is more effective relative to another; (2) there is more evidence to support the use of Lotrel and Tarka in sub-populations of patients with hypertension than Lexxel; (3) there is insufficient evidence to conclude that any one ACE/CCB combo is superior to another for reducing risk of cardiovascular outcomes in patients with hypertension; (4); the safety/tolerability profiles of the ACE/CCB combos are primarily dictated by the CCB component; (5) there is no evidence to suggest that Lotrel or Lexxel would be superior to the other in terms of safety/tolerability. Tarka has unique safety issues, due to the verapamil component; (6) persistence rates with Lotrel may be improved by 7%-22% compared to the individual agents administered together; (7) transdermal clonidine is not a candidate for non-formulary designation on the Uniform Formulary due to its unique niche in several patient sub-groups and lower risk of rebound hypertension upon drug discontinuation; (8) Use of the remaining miscellaneous antihypertensive drugs is limited by bothersome tolerability profiles, however, several drugs maintain unique roles for treating hypertension and non-cardiovascular conditions.

***COMMITTEE ACTION:*** The Committee voted to accept the clinical effectiveness conclusion as stated above

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

As with the relative clinical effectiveness evaluation, the primary focus of the relative cost-effectiveness presentation was limited to the combination antihypertensives [amlodipine/benazepril (Lotrel), felodipine/enalapril (Lexxel), verapamil/trandolapril (Tarka)] and clonidine patches. The DoD P&T Committee concluded that the other agents listed in the class, as previously described, should be maintained on the UF given their generic availability, low utilization, and low cost.

To determine the relative cost effectiveness of the miscellaneous antihypertensive agents, two separate economic analyses were performed, a pharmacoeconomic analysis and budget impact analysis (BIA).

A cost analysis was performed to compare clonidine patches and clonidine tablets. The comparison of cost was based on the point-of-service adjusted total weighted average cost per day of treatment. As expected, the results of the cost-analysis revealed that clonidine patches were significantly more costly compared to clonidine tablets.

Two different types of pharmacoeconomic analysis could have been performed to determine the cost-effectiveness of the combination antihypertensive agents within this therapeutic class. One alternative was to use cost-minimization to compare the combination antihypertensives to their respective agents given separately solely based on cost. However, this alternative would have neglected to account for the primary potential benefit of combination products, improved patient compliance with medication therapy. Therefore, to account for the potential differences in relative clinical effectiveness, a cost-effectiveness analysis (CEA) was performed based on the results of three observational studies examining compliance with combination antihypertensives.

The observational studies included two studies that examined compliance with the combination product Lotrel (amlodipine/benazepril) and another study that examined compliance with combination ACE/HCTZ products (enalapril/HCTZ and lisinopril/HCTZ). These studies revealed increased compliance ranging from 7% to 20% with the combination antihypertensives compared to the respective agents given separately. For purposes of the CEA, the increased compliance associated with combination antihypertensive products was assumed to be 10%. To determine the relative cost-effectiveness of the combination products, two simple cost-effectiveness decision models were constructed, one comparing the dihydropyridine/ACE combination products [Lotrel (amlodipine/benazepril) and Lexxel (felodipine/enalapril)] to their respective agents given separately and another

comparing the verapamil/ACE combination product (Tarka (verapamil/trandolapril)) to its respective agents given separately. The cost used in the model was the total cost of drug treatment for one-year. The outcome/effect was 'days of treatment'. Theoretically, 'days of treatment' is a surrogate indicator of compliance. Likewise, compliance with drug therapy theoretically results in overall improved blood pressure control.

The results from the CEAs are as follows:

- Dihydropyridine/ACE combination
    - The two agents given separately were more cost-effective compared to Lexxel (felodipine/enalapril) and Lotrel (amlodipine/benazepril). However, the incremental cost-effectiveness ratio was relatively low, indicating that the combination products may be a cost-effective alternative therapy.
- Verapamil/ACE combination
    - The two agents given separately were more cost-effective compared to Tarka (verapamil/trandolapril). For this comparison, the incremental cost-effectiveness ratio was relatively high, indicating that the combination product is not a cost-effective alternative therapy.

The results of the CEAs were subsequently incorporated into a budget impact analysis (BIA). A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of miscellaneous antihypertensive best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. Based on the BIA results and other clinical and cost considerations, the Committee agreed that a group of miscellaneous antihypertensive agents that included: clonidine patches and Lotrel (amlodipine /benazepril) best achieved this goal when compared to other combination groups of miscellaneous antihypertensive agents, and thus were determined to be more cost-effective relative to other combination groups.

***COMMITTEE ACTION:*** The P&T Committee, based upon its collective professional judgment, voted to recommend that Lexxel (felodipine/enalapril) and Tarka (verapamil/trandolapril) be classified as non-formulary, with clonidine tablets, clonidine patches, Lotrel (amlodipine/benazepril), hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine remaining on the UF.

***C.* Implementation Plan*:*** Due to the relatively low number of patients that will be affected by this formulary action, the P&T Committee recommended an effective date no later than the first Wednesday following a 60-day implementation period.

***COMMITTEE ACTION:*** The Committee voted to recommend an implementation period of 60 days.

## V. Miscellaneous Antihypertensive Drug Class (cont.)

### *BAP Comments*

***A.* Relative Clinical Effectiveness***:*** The Committee concluded that: (1) for lowering blood pressure, there is no evidence that any one ACE/CCB combo is more effective relative to another; (2) there is more evidence to support the use of Lotrel and Tarka in sub-populations of patients with hypertension than Lexxel; (3) there is insufficient evidence to conclude that any one ACE/CCB combo is superior to another for reducing risk of cardiovascular outcomes in patients with hypertension; (4); the safety/tolerability profiles of the ACE/CCB combos are primarily dictated by the CCB component; (5) there is no evidence to suggest that Lotrel or Lexxel would be superior to the other in terms of safety/tolerability. Tarka has unique safety issues, due to the verapamil component; (6) persistence rates with Lotrel may be improved by 7%-22% compared to the individual agents administered together; (7) transdermal clonidine is not a candidate for non-formulary designation on the Uniform Formulary due to its unique niche in several patient sub-groups and lower risk of rebound hypertension upon drug discontinuation; (8) Use of the remaining miscellaneous antihypertensive drugs is limited by bothersome tolerability profiles, however, several drugs maintain unique roles for treating hypertension and non-cardiovascular conditions.

**B. Relative Cost Effectiveness:** The P&T Committee, based upon its collective professional judgment, voted to accept the miscellaneous antihypertensive cost-analysis presented by the PEC. The P&T Committee concluded that Lexxel (felodipine/enalapril) and Tarka (verapamil/trandolapril) were not cost-effective relative to the other miscellaneous antihypertensive agents

**C. Uniform Formulary Recommendation:** Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the miscellaneous antihypertensive agents, and other relevant factors, the P&T Committee recommended that Lexxel (felodipine/enalapril) and Tarka (verapamil/trandolapril) be classified as non-formulary. The P&T Committee also recommended that clonidine tablets, clonidine patches, Lotrel (amlodipine/benazepril), hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine remaining on the UF.

| *BAP Comment:* | ☐ Concur ☐ Non-concur<br>Additional Comments and Dissentions: |
|---|---|

**D. Implementation Plan:** The Committee voted to recommend an implementation period of 60 days.

| *BAP Comment:* | ☐ Concur ☐ Non-concur<br>Additional Comments and Dissentions: |
|---|---|

## VI. GABA analog Drug Class Review

***P&T Comments***

***A.* Relative Clinical Effectiveness:** The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee evaluated the relative clinical effectiveness of the GABA analogs marketed in the US: [gabapentin (Neurontin and various generics), pregabalin (Lyrica), and tiagabine (Gabatril)]. Information regarding the safety, effectiveness, and clinical outcome of these drugs was considered. Although gabapentin, pregabalin, and tiagabine are all FDA indicated as adjunctive therapy (added to other antiepileptic drugs) in the treatment of partial seizures, the Committee's review focused primarily on the use of these agents for the treatment of various types of neuropathic pain. The clinical review included, but was not limited to the requirements stated in the UF Rule, 32 CFR 199.21.

*1) Efficacy*

*a) Endpoints:* The primary efficacy measure used in the clinical trials was pain experienced by the patients during the previous 24 hours, rated on an 11-point numerical scale (0= no pain; 10= worst possible pain). The primary efficacy parameter was the change in the mean daily pain score from baseline to the study end; the proportion of patients responding to therapy was a secondary outcome. A >50% reduction in mean pain scores between baseline and study end are considered relevant. Numbers needed to treat (NNT), defined as the number of patients needed to be treated with the drug to result in one patient obtaining a >50% reduction in mean pain score, were then calculated to give a measure of the effect size.

*b) Efficacy of GABA analogs for treatment of pain associated with diabetic peripheral neuropathy (DPN):*

*Place in Therapy:* Guidelines from the American Diabetes Association (ADA) recommend gabapentin and pregabalin and other therapies as initial therapy for the treatment of pain associated with DPN. There is no preference stated for gabapentin or pregabalin in the guidelines. The guidelines do not mention tiagabine.

*Clinical Trials for DPN-related pain*: There are no head-to-head clinical trials comparing pregabalin with gabapentin for DPN-related pain, and there are no clinical trials evaluating efficacy of tiagabine for this condition. The Committee reviewed the following trials evaluating the use of the GABA analogs in DPN: one comparative trial of gabapentin vs. amitriptyline; one active controlled trial of pregabalin and amitriptyline vs. placebo; a Cochrane review of four placebo controlled trials with gabapentin; and three placebo controlled trials with pregabalin.

In the comparative trial of gabapentin (900-1800 mg/day) vs. amitriptyline (25-75 mg/day), both treatments resulted in significant reductions in mean pain score from baseline; there was no difference between the two drugs at study endpoint. This trial was limited by small patient enrollment (N=28). In the active controlled trial of pregabalin (600 mg/day) and amitriptyline (75mg/day) vs. placebo, pregabalin did not differ from placebo in the change in mean pain score from baseline or in the proportion of patients achieving at least a 50% decrease in mean pain score at endpoint. These endpoints reached statistical significance when amitriptyline was compared to placebo. Direct comparisons of the efficacy of pregabalin vs. amitriptyline were not conducted in the trial. Overall, treatment with pregabalin 600 mg/d (200 mg three times a day) was no more effective than placebo in the treatment of DPN-related pain in this study.

A Cochrane review of four placebo controlled trials enrolling 281 patients that evaluated the efficacy of gabapentin for DPN pain favored gabapentin [relative risk 2.21 (95% confidence interval 1.65, 2.96)]. The gabapentin doses ranged from 900-3600 mg/day. Overall, 64% of patients improved with gabapentin compared to 28% with placebo. The combined NNT for effectiveness of gabapentin in DPN compared to placebo was 2.9.

The results of the three double-blinded, placebo controlled trials evaluating pregabalin in DPN were reported to the Committee. In two of the three trials, patients were excluded if they had not previously responded to gabapentin doses >1200 mg/day. Pregabalin in doses of 100 mg three times a day (300 mg/day) and 200 mg three times a day (600 mg/day) resulted in statistically significant improvements in the mean pain score at endpoint and in the proportion of patients obtaining at least a 50% reduction in pain score from baseline compared to placebo. The mean pain score at endpoint was 1.26 to 1.45 points lower with pregabalin (300 mg/day and 600 mg/day doses, respectively) than placebo. The percentage of patients responding to pregabalin 300 mg/day ranged from 40% to 46%; the percentage of responders to pregabalin 600 mg/day ranged from 39% to 48%, while the placebo responder rate was 15%. Although 600 mg/day was evaluated in these trials, the product labeling for pregabalin does not recommend doses above 300 mg/day for DPN, as doses of 600 mg/day do not provide greater benefit. The NNT

with pregabalin to achieve a 50% reduction in mean pain score at endpoint ranged from 3.4 to 4.0 for the three studies.

*DPN Conclusion:* Based on the primary efficacy measures of change in mean pain score at baseline, the percentage of patients responding to therapy, and the NNTs, the Committee concluded that there is no evidence to suggest that gabapentin or pregabalin is superior to the other in treating pain associated with DPN, when the individual results from the placebo controlled trials are compared. There are no trials evaluating efficacy of tiagabine in pain due to DPN.

*c) Efficacy of GABA analogs for treatment of pain associated with post herpetic neuralgia (PHN):*

*Place in therapy:* Practice guidelines endorsed by the American Academy of Neurology for the treatment of pain in patients with PHN give a Level A, class I recommendation (strongest evidence for efficacy) to gabapentin and pregabalin. First-line options for the treatment of PHN included gabapentin, pregabalin, lidocaine patch, tricyclic antidepressants and controlled release morphine or oxycodone. The guideline does not give a preference to either pregabalin or gabapentin for the treatment of PHN-related pain, and does not mention tiagabine.

*Clinical Trials for PHN pain:* There are no head to head clinical trials comparing pregabalin with gabapentin for treatment of pain in patients with PHN. There are no trials evaluating efficacy of tiagabine for PHN-related pain. The Committee evaluated two placebo controlled trials with gabapentin, and three placebo controlled trials with pregabalin for this pain syndrome.

Two double-blind placebo controlled trials compared gabapentin vs. placebo for the treatment of pain associated with PHN. Gabapentin doses ranging from 600 mg three times a day to 900 mg three times a day were evaluated in the two trials. In both trials, patients receiving gabapentin had a statistically significant reduction in mean daily pain score at study end, compared to placebo. The mean pain score at endpoint was 2.1 points lower with gabapentin (all doses) than placebo. In the 1st trial, 43% of patients receiving gabapentin 900 mg three times a day rated their pain as much improved vs. 12.1% with placebo. In the second trial, the responder rate was 14% with placebo, 32% with gabapentin 600 mg three times a day and 34% with gabapentin 800 mg three times a day.

A Cochrane review of the two placebo controlled trials discussed earlier (enrolling 563 patients) that evaluated the efficacy of gabapentin for PHN pain favored gabapentin [relative risk 2.50 (95% confidence interval 1.80, 3.48)]. Overall, 43% of patients improved with gabapentin compared to 17% with placebo. The combined NNT from these two studies for effectiveness compared to placebo was 2.9.

Three double-blind placebo controlled trials evaluated pregabalin for the treatment of pain associated with PHN. In two of the three trials, patients were excluded if they had not previously responded to gabapentin doses >1200 mg/day. Twice a day dosing of gabapentin was used in one trial, while a three times a day regimen was used in the remaining two trials; doses ranged from 150 mg/day to 600mg/day. All pregabalin doses resulted in significant reductions in mean pain scores compared to

placebo. The mean pain score at endpoint was 0.88 to 1.79 points lower with pregablin (all doses) than placebo. The percentage of patients responding to pregabalin 150 mg/day ranged from 26% to 27%, the percentage of responders to pregabalin 300 mg/day ranged from 27% to 28%, the percentage of responders to pregabalin 600 mg/day ranged from 38% to50%, while the placebo responder rate ranged from 8% to 10%. The NNT with pregabalin to achieve a 50% reduction in mean pain score at endpoint ranged from 3.3 to 6.3 in the three studies, depending on the dose of pregabalin.

*PHN Conclusion:* Based on the primary efficacy measures of change in mean pain score at baseline, the percentage of patients responding to therapy, and the NNTs, the Committee concluded that there is no evidence to suggest that gabapentin or pregabalin is superior to the other in treating pain associated with PHN, when the individual results from the placebo controlled trials are compared. There are no trials evaluating efficacy of tiagabine in pain due to PHN.

*d) Efficacy of GABA analogs for other neuropathic pain syndromes:*

*Clinical Trials:* The P&T Committee evaluated two trials assessing the efficacy of gabapentin, and one trial assessing the efficacy of tiagabine in other types of neuropathic pain syndromes. Gabapentin was evaluated in doses up to 2.4 g/day in 305 patients with a variety of different types of neuropathic pain syndromes, including complex regional pain syndrome, PHN, radiculopathy, and post laminectomy. The authors reported there was an overall significant difference in mean pain score favoring gabapentin over placebo, however there was no significant difference between gabapentin and placebo at weeks 7 and 8 (the differences at weeks 1,3,5,6 were significant). When gabapentin was compared to placebo in 19 patients with post-amputation limb pain, there was no statistical difference between gabapentin and placebo at study endpoint. The effect of tiagabine in painful neuropathy was studied in a 4-week, open-label, non-placebo-controlled pilot trial in 17 adults. Overall pain indices tended to decline, but results did not reach statistical significance for tiagabine vs. placebo, given the high and dropout rate (only 8 patients completed the study).

*Other Neuropathic pain syndromes conclusions:* The Committee concluded that gabapentin demonstrated modest clinical efficacy for other neuropathic pain syndromes, based on two placebo controlled trials. No conclusion can be made concerning the efficacy of tiagabine for neuropathic pain due to limited evidence (one poorly designed study and overall lack of trials evaluating the efficacy of tiagabine for neuropathic pain). Pregabalin has not been evaluated in other types of neuropathic pain syndromes.

*e) Efficacy of GABA analogs for treatment of partial seizures:*

*Place in Therapy:* A report endorsed by the American Academy of Neurology and the American Epilepsy Society assigned both gabapentin and tiagabine as Level A recommendations (highest recommendation) as adjunctive therapy for partial seizures. There was no mention of pregabalin due to publication of the guideline prior to FDA approval.

*Clinical Trials:* Gabapentin, pregabalin, and tiagabine have all been evaluated in the adjunctive treatment of epilepsy in placebo controlled trials. There are no head to head trials comparing efficacy of one GABA analog to another in seizure disorders. The results of one meta-analysis conducted with gabapentin and tiagabine, and three double-blinded placebo controlled trials with pregabalin support efficacy of all three agents in patients with epilepsy, based on the endpoint of 50% reduction in seizure frequency.

*Partial Seizures Conclusions:* The committee concluded that gabapentin, pregabalin, and tiagabine demonstrate clinical efficacy for adjunctive treatment of partial seizures. Since the GABA analogs are added onto regimens comprised of other antiepileptic drugs, there is no evidence to suggest clinical superiority of any GABA agent over another.

*Overall efficacy conclusion:* The Committee concluded that there is no evidence of superiority of gabapentin over pregabalin for treatment of pain associated with DPN or PHN. Efficacy of gabapentin for other types of neuropathic pain syndromes appears modest. There is insufficient evidence to make conclusions regarding the efficacy of tiagabine in DPN, PHN, or other types of neuropathic pain syndromes.

*2) Safety and Tolerability:* The Committee assessed the comparative safety and tolerability of gabapentin, pregabalin, and tiagabine including rare but serious adverse effects, common adverse effects, potential for drug interactions, and safety of use in special populations.

*Serious Adverse Effects:*
All three GABA analogs (gabapentin, pregabalin, and tiagabine) should be gradually tapered when therapy is discontinued, to minimize the potential for increased seizure frequency. Post-marketing reports have linked tiagabine with new onset seizures and status epilepticus in patients who did not have epilepsy. There are reports of sudden unexplained death in patients with epilepsy taking gabapentin or tiagabine, however, it is unknown whether the unexplained deaths were a direct result of gabapentin or tiagabine therapy. Tiagabine has been associated with cognitive/neuropsychiatric events such as impaired concentration, speech and language problems, confusion and fatigue. Pregabalin has been associated with creatine kinase elevations and three reports of rhabdomyolysis in premarketing clinical trials.

*Common Adverse effects:*
The most commonly reported side effects associated with gabapentin, pregabalin and tiagabine include dizziness, somnolence, and asthenia. These adverse effects appear to be dose related, and tend to decrease over time. Based on clinical trial experience, tiagabine appears more commonly associated with nervousness and tremor, while gabapentin and pregabalin are associated the weight gain, dizziness, somnolence and peripheral edema.

Due to differences in study design for the placebo controlled trials and the lack head to head trials, comparisons of adverse event rates between the GABA analogs are

difficult. In general, clinical trials using flexible dosing regimens and slow titration schedules result in fewer patients dropping out of the trial and lower adverse event rates than trials incorporating fixed dosing regimens and quick titration schedules.

A comparison of the product labeling for all three GABA analogs lists the following adverse events, which have been placebo-adjusted. Peripheral edema: 8.3% with gabapentin, and 9% with pregabalin; an incidence is not provided in the tiagabine package insert. Dizziness: 28% with gabapentin, 21% with pregabalin, and 27% with tiagabine. Somnolence: 21.4% with gabapentin, 12% with pregabalin, and 12% with tiagabine.

Numbers needed to harm (NNH) is another way of measuring adverse events and for the purpose of this review was defined as any adverse effect leading to patient withdrawal from a study. NNH could be calculated for two of the trials assessing pain in PHN. For gabapentin, the NNH was 11.2; for pregabalin, the NNH was 3.7. Although the NNH to harm is smaller with pregabalin, possibly indicating a less tolerable drug, the titration period with pregabalin was more rapid (over 1 week) compared to the gabapentin trial (over 4 weeks). A longer titration period may have led to fewer drop-outs in the gabapentin trial. When the NNHs were calculated from a clinical trial evaluating pregabalin for treatment of DPN and PHN in both fixed and flexible doses, the NNH was10.7 with the flexible dosing regimen, and 5.8 with the fixed dosing regimen. The flexible dosing regimen incorporated a longer titration schedule than with the fixed dose, which could possibly account for the more favorable NNH with the flexible dosing.

*Drug Interactions:*
Gabapentin and pregabalin are not metabolized by hepatic CYP450 enzymes, thus are not associated with significant drug interactions. Tiagabine is primarily metabolized by CYP450 and is highly protein bound, thus drug interactions have been reported with concomitant usage with other anticonvulsant drugs (carbamazepine, phenytoin, phenobarbital, primidone).

*Special populations:*
*Renal Impairment:* Gabapentin and pregabalin are both renally eliminated, and both drugs require dosage reductions with decreasing renal function. Reductions in gabapentin and pregabalin dosages may be required in patients who have age related compromised renal function.

*Hepatic Impairment:* Patients with impaired liver function may require reduced initial and maintenance doses of tiagabine or a longer dosing interval compared to patients with normal hepatic function.

*Pregnancy:* All three GABA analogs are rated as pregnancy category C, and should be used during pregnancy only if the potential benefit justifies the potential risk.

*Overall Safety and Tolerability Conclusion:* The Committee concluded withdrawal seizures occurring with sudden discontinuation of therapy have been reported with all three GABA analogs. Tiagabine is associated with serious adverse events, including neuropsychiatric and cognitive effects and development of seizures in

patients who did not previously have epilepsy. Dizziness and somnolence are the most commonly reported adverse effects with pregabalin and gabapentin, while tremors and nervousness are more commonly reported with tiagabine. Indirect comparisons, based on NNH and the percentage of patients discontinuing therapy due to adverse effects, show only minor differences in tolerability between gabapentin and pregabalin. Tiagabine has a greater drug interaction potential compared to gabapentin and pregabalin, due to hepatic metabolism. Both gabapentin and pregabalin require dose adjustment in patients with renal dysfunction.

*3) Other Factors:*
*FDA Approved indications:* Gabapentin and pregabalin are both FDA-approved for treating pain associated with DPN. Pregabalin is the sole agent in the class approved for treating pain associated with PHN, however, controlled clinical trial data support the use of gabapentin. Gabapentin, pregabalin, and tiagabine are approved as adjunctive therapy in seizure disorders.

*Controlled Substance Class:* Pregabalin is the only GABA analog that is a schedule V controlled substance. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms of insomnia, nausea, headache, or diarrhea, suggestive of dependence. Due to the schedule V status, no more than 5 refills can be obtained in a 6-month period.

*Use in Pediatrics:* Gabapentin is approved in for use as an anticonvulsant in patients as young as three years old. Tiagabine is approved for use in patients as young as 12 years old for treatment of epilepsy. Pregabalin has not been studied in pediatric patients.

*Pharmacokinetics:* Gabapentin exhibits non-linear pharmacokinetics; as the dose of gabapentin is increased, bioavailability decreases. In contrast, pregabalin exhibits linear pharmacokinetics, and the oral bioavailability of pregabalin is > 90% independent of dose. However, a linear dose response has not resulted in improved pain relief with pregabalin administered at higher doses (600mg/d) vs. lower doses (300 mg/d). In fact, the manufacturer of pregabalin does not recommend greater than 300 mg/d for DPN because 600 mg/d pregabalin has not been proven to significantly improve pain scores compared to 300 mg/d.

*Frequency of Dosing and Titration Schedules:* Pregabalin can be dosed twice daily for treatment of pain associated with PHN, while gabapentin requires three times a day dosing. For pain associated with DPN, both pregabalin and gabapentin require three times a day dosing. Twice a day dosing of pregabalin in DPN-related pain is not stated in the product labeling, as twice daily dosing did not show significant differences in efficacy as compared to placebo in unpublished trials available from the FDA. The dosage initiation schedule for pregabalin is less complex and requires a shorter time period than the dosage titration recommended with gabapentin. Statistical improvements in mean pain score in clinical trials have occurred within 1-2 weeks of initiation of pregabalin therapy, compared to 2 weeks with gabapentin.

*Provider Opinion:* A survey of DoD providers ranked gabapentin first in terms of clinical efficacy for neuropathic pain, due to more personal clinical experience, compared to tiagabine and pregabalin. Pregabalin was ranked second in terms of clinical efficacy, primarily due to ease of titration and twice daily dosing in PHN. The majority of providers' therapeutic strategy would include a trial of gabapentin first, followed by pregabalin if therapy with gabapentin was not successful. Tiagabine is most commonly used as adjunctive therapy to other treatments for neuropathic pain, not as an alternative to gabapentin or pregabalin. All three drugs (gabapentin, pregabalin, and tiagabine) were considered therapeutically interchangeable for use in patients with partial seizures.

*Other Factors Conclusions:* The Committee concluded that pregabalin is the only GABA analog that has restrictions in prescribing due to its controlled status. The linear pharmacokinetic profile of pregabalin has not resulted in significant improvement in efficacy with higher doses. Pregabalin may potentially have improved patient compliance compared to gabapentin, due to an easier titration schedule and twice a day dosing in patients with PHN. However, three times a day dosing is recommended for pregabalin in patients with DPN. There is no published data evaluating the efficacy of pregabalin in pediatrics.

*4) Overall Clinical Effectiveness Conclusion:* The Committee concluded that (1) the efficacy of gabapentin and pregabalin for treating pain associated with either DPN or PHN appears similar; (2) gabapentin is the only GABA analog that has shown modest efficacy in treating other types of neuropathic pain based on published clinical trials; (3) there is insufficient data regarding the efficacy of tiagabine in patients with neuropathic pain syndromes to make definitive conclusions; (4) there appear to be no major differences in the efficacy of gabapentin, pregabalin, or tiagabine for the use an adjunctive treatment of partial seizures; (5) the safety and tolerability profiles of gabapentin and pregabalin are more favorable compared to tiagabine; (6) there appear to be only minor differences in the tolerability profiles of gabapentin and pregabalin, when evaluating the incidence of somnolence, dizziness, and peripheral edema; (7) there are minor differences in other factors between the drugs, including use in pediatrics, pharmacokinetic profiles, titration schedules, onset of effect, and controlled substance status. Overall the Committee agreed that based on clinical usefulness alone, there is no basis for classifying any of the GABA analog as non-formulary.

***COMMITTEE ACTION:*** The DoD P&T Committee voted to accept the clinical effectiveness conclusion as stated above

***B.* Relative Cost Effectiveness*:*** In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). A cost-effectiveness analysis was used to determine the relative cost-effectiveness of agents within the GABA analog therapeutic class. A Monte Carlo simulation was

performed using data from three well designed randomized controlled trials of pregabalin and gabapentin in diabetic peripheral neuropathy and post herpetic neuralgia. Flexible dose (average 378 mg) and fixed dose (600 mg) pregabalin were compared to daily gabapentin doses of 600, 900, 1200, 1800 and 2400 mg. Costs used in the model were the total weighted average cost per day of treatment across all points of service in the MHS. The principal outcome of interest was the mean reduction in weekly pain scores at the 12th week.

Results of the cost-effectiveness analysis (CEA) showed gabapentin at doses of up to 2400 mg to be the most cost effective GABA analog drug in the treatment of neuropathic pain with the lowest average cost per patient over twelve weeks of treatment, and no clinically significant differences in outcomes.

The results of the above analyses were then incorporated into a Budget Impact Analysis (BIA), which accounted for other factors and costs associated with a potential decision regarding formulary status of GABA analog drugs within the UF. These factors included: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and switch costs. The results of the budget impact analysis further confirmed the results of the CEA. Gabapentin was found to be the most cost-effective GABA analog drug overall in the treatment of neuropathic pain.

***COMMITTEE ACTION:*** The P&T Committee agreed with the relative cost-effectiveness analysis of the GABA analog drugs presented.

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

***COMMITTEE ACTION:*** The P&T Committee recommended an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

## VII. GABA analog Drug Class Review (cont.)

### *BAP Comments*

***A.* Relative Clinical Effectiveness:** The Committee concluded that (1) the efficacy of gabapentin and pregabalin for treating pain associated with either DPN or PHN appears similar; (2) gabapentin is the only GABA analog that has shown modest efficacy in treating other types of neuropathic pain based on published clinical trials; (3) there is insufficient data regarding the efficacy of tiagabine in patients with neuropathic pain syndromes to make definitive conclusions; (4) there appear to be no major differences in the efficacy of gabapentin, pregabalin, or tiagabine for the

use an adjunctive treatment of partial seizures; (5) the safety and tolerability profiles of gabapentin and pregabalin are more favorable compared to tiagabine; (6) there appear to be only minor differences in the tolerability profiles of gabapentin and pregabalin, when evaluating the incidence of somnolence, dizziness, and peripheral edema; (7) there are minor differences in other factors between the drugs, including use in pediatrics, pharmacokinetic profiles, titration schedules, onset of effect, and controlled substance status. Overall the Committee agreed that based on clinical usefulness alone, there is no basis for classifying any of the GABA analog as non-formulary.

**B. Relative Cost Effectiveness:** Based on the results of the two analyses, the P&T Committee concluded that pregabalin was much more costly, and had similar relative clinical effectiveness compared to gabapentin in both neuropathic pain and partial seizures. Tiagabine also had similar relative clinical effectiveness in partial seizures as compared to gabapentin and pregabalin. However, due to its low utilization, and small, static market share, it was felt that tiagabine contributed minimally to the amount spent in this drug class.

**C. Uniform Formulary Recommendation:** The P&T Committee, based upon its collective professional judgment, recommended that pregabalin be classified as non-formulary, with gabapentin and tiagabine remaining on the UF.

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| *BAP Comment:* | ☐ Concur ☐ Non-concur<br>Additional Comments and Dissentions: |

**D. Implementation Plan:** The P&T Committee recommended an effective date no later than the first Wednesday following a 60-day

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| *BAP Comment:* | ☐ Concur ☐ Non-concur<br>Additional Comments and Dissentions: |