DECISION PAPER:

FEBRUARY 2006
DEPARTMENT OF DEFENSE PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

1. CONVENING

2. ATTENDANCE

3. REVIEW MINUTES OF LAST MEETING

4. ITEMS FOR INFORMATION

5. REVIEW OF RECENTLY APPROVED AGENTS

The P&T Committee was briefed on two new agents that had been approved by the Food and Drug Administration (FDA) (Appendix B – Table 2). Neither of the medications fall into drug classes already reviewed by the P&T Committee, therefore Uniform Formulary (UF) consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits. Sorafenib (Nexavar) is an oral multi-kinase inhibitor approved for treatment of patients with advanced renal cell carcinoma. It is available in 200 mg tablets and is administered in a dose of 2 tabs given twice daily. Quantity limits were recommended for sorafenib since there is a risk of discontinuation of therapy due to poor patient prognosis or drug-related adverse effects. Other oral chemotherapy drugs (imatinib, erlortinib) have quantity limits. The manufacturer of sorafenib has instituted a restricted distribution system which limits the quantity dispensed to a 30-day supply. Sorafenib is not currently available from the TMOP, due to the restricted distribution system.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend that sorafenib have quantity limits of 180 tablets per 45 days (TMOP), should the product become available from the TMOP, or 120 tablets per 30 days from the TRRx. (See paragraph 5 on pages 10-11 of P&T Committee minutes.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

6. OVERACTIVE BLADDER (OAB) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the antimuscarinic drugs used to treat over active bladder. The overactive bladder therapeutic class was defined as: oxybutynin immediate release (Ditropan tablets/solution or generic) oxybutynin sustained release (Detrol XL), oxybutynin transdermal (Oxytrol), tolterodine

immediate release (Detrol), tolterodine sustained release (Detrol LA), trospium (Sanctura), solifenacin (Vesicare), and darifenacin (Enablex). This class is now ranked 28th in Military Health System (MHS) drug class expenditures at a cost of $55 million annually.

The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) that for the purposes of the UF clinical review none of the OABs have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other OABs.

Based on the results of the cost-effectiveness analysis (CEA) and other clinical and cost considerations, the Committee agreed (15 for, 0 opposed, 0 abstention, 3 absent) that a group of OAB agents including tolterodine sustained release, oxybutynin sustained release, oxybutynin immediate release, solifenacin, and darifenacin represented the best overall value to the DoD for the treatment of OAB across all three points of service.

A. COMMITTEE ACTION: 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 voted (15 for, 0 opposed, 0 abstention, 3 absent) to recommend that tolterodine immediate release, oxybutynin patch, and trospium be classified as non-formulary under the UF and that tolterodine sustained release, oxybutynin sustained release, oxybutynin immediate release, solifenacin and darifenacin classified as formulary on the UF. (See paragraphs 6A and 6B on pages 11-16 of P&T Committee minutes for criteria.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of tolterodine immediate release, oxybutynin patch, trospium and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) medical necessity criteria for the OAB agents. (See paragraph 6C on pages 16-17 of P&T Committee minutes for criteria.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P&T Committee recommended (13 for, 2 opposed, 1 abstained, 2 absent) 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. (See paragraph 6D on page 17 of P&T Committee minutes for rationale.)

Director, TMA, Decision: BW ☐ Approved ☑ Disapproved

Approved, but modified as follows: I note that the BAP NCommended a 120 day implementation period. I have increased the implementation period to 90 days.

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend oxybutynin immediate release and tolterodine sustained release as the Basic Core Formulary (BCF) agents. (See paragraph 6E on page 17 of P&T Committee minutes for rationale.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

7. MISCELLANEOUS ANTIHYPERTENSIVE AGENTS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the miscellaneous antihypertensive agents marketed in the United States. The class was defined to include the angiotensin converting enzyme (ACE) inhibitor/calcium channel blocker (CCB) combinations amlodipine/benazepril (Lotrel), felodipine/enalapril (Lexxel), and verapamil sustained release/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). Together these drugs account for approximately $27M annually and are ranked 53rd in MHS drug class expenditures.

The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) that for the purposes of the UF clinical review the following clinical conclusions applied: (1) there is no evidence that any one ACE/CCB combo is more effective relative to another for lowering blood pressure; (2) there is more evidence to support the use of amlodipine/benazepril and verapamil sustained release/trandolapril in sub-populations of patients with hypertension than felodipine/enalapril; (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) safety/tolerability profiles of the ACE/CCB combos are primarily dictated by the CCB component; (5) there is no evidence to suggest that amlodipine/benazepril or felodipine/ enalapril would be superior to the other in terms of safety/tolerability. Verapamil sustained release/trandolapril has unique safety issues, due to the verapamil component; (6) persistence rates with amlodipine/benazepril 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 UF 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.

Based on the results of the CEA and other clinical and cost considerations, the Committee agreed (16 for, 0 opposed, 1 abstention, 1 absent) that a group of miscellaneous antihypertensive agents including amlodipine/benazepril, the direct acting vasodilators (hydralazine, minoxidil); the centrally acting alpha-2 agonists [(clonidine tablets and patches), methyldopa, guanabenz, guanfacine]; the peripheral alpha-1 antagonists (prazosin); the adrenergic antagonists (reserpine, guanadrel, guanethidine); and the ganglionic blockers

(mecamylamine) represented the best overall value to the DoD in the class of miscellaneous antihypertensive agents.

A. COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (11 for, 4 opposed, 2 abstention, 1 absent) to recommend that felodipine/ enalapril (Lexxel) and verapamil/trandolapril (Tarka) be classified as non-formulary under the UF, with clonidine tablets, clonidine patches, amlodipine/benazepril (Lotrel), hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine remaining on the UF. (See paragraphs 7A and 7B on pages 18-24 of P&T Committee minutes for criteria.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows: I note the BAP's concern about having Lotrel as UF agent when amlodipine is non-formulary. 50K beneficiaries use Lotrel. I keep this drug on the UF maintains the option of an ACE/CCB combo for Peds and ehd beneficiaries.

B. COMMITTEE ACTION: Based on the clinical evaluation of felodipine/enalapril (Lexxel) and verapamil/trandolapril (Tarka) and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) medical necessity criteria for these agents. (See paragraph 7C on page 24 of P&T Committee minutes for criteria.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 absent) 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. (See paragraph 7D on page 24 of P&T Committee minutes for rationale.)

Director, TMA, Decision: BW ☐ Approved ☑ Disapproved

Approved, but modified as follows: I note the BAP recommended a 120 day implementation period. I have increased the implementation period to 90 days.

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) to recommend one combination agent [amlodipine/benazepril (Lotrel)] and two single agents (hydralazine and clonidine tablets) as the BCF agents. (See paragraph 7E on page 24 of P&T Committee minutes for rationale.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

8. GAMMA-AMINOBUTYRIC ACID (GABA)-ANALOG DRUG CLASS REVIEW

The DoD P&T Committee evaluated the relative clinical effectiveness of the GABA-analog agents marketed in the United States. The class was defined to include gabapentin (Neurontin and various generics), pregabalin (Lyrica) and tiagabine (Gabatril). Although gabapentin, pregabalin, and tiagabine all have FDA indicates as adjunctive therapy (added to other antiepileptic drugs) in the treatment of partial seizures, the Committee's review focused most heavily on the use of these agents for the treatment of various types of neuropathic pain. Together these drugs account for approximately $148M annually and are ranked 6th in MHS drug class expenditures.

The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) that for the purposes of the UF clinical review the following clinical conclusions applied: (1) the efficacy of gabapentin and pregabalin for treating pain associated with either diabetic peripheral neuropathy (DPN) or post-herpetic neuropathy (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 use as 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 based on clinical usefulness alone, there was no basis for classifying any of the GABA analogs as non-formulary.

Based on the results of the clinical and cost-effectiveness analyses, the Committee agreed (16 for, 0 opposed, 0 abstained, 2 absent) that gabapentin was the more cost effective GABA-analog drug for the treatment of neuropathic pain.

A. COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the GABA-analog drugs, and other relevant factors, the P&T Committee recommended (14 for, 2 opposed, 0 abstained, 2 absent) that pregabalin be classified as non-formulary under the UF, with gabapentin and tiagabine remaining on the UF. (See paragraphs 8A and 8B on pages 24-31 of P&T Committee minutes for criteria.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows: I agree with the concerns noted by some BAP members regarding off-label use of new drugs as first line therapy when there are "tried and true" alternatives with known safety profiles. Lyrica remains available to those who need it under medical necessity criteria.

B. COMMITTEE ACTION: Based on the clinical evaluations of pregabalin and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (15 for, 1 opposed, 0 abstained, 2 absent) medical necessity criteria for the GABA-analog agents. (See paragraph 8C on pages 31-32 of P&T Committee minutes for criteria.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Due to the relatively low number of patients that will be affected by this formulary action, the P&T Committee recommended (15 for, 0 opposed, 0 abstained, 3 absent) 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. (See paragraph 8D on page 32 of P&T Committee minutes for rationale.).

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to recommend gabapentin as the BCF agent. (See paragraph 8E on page 32 of P&T Committee minutes for rationale.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

9. ABBREVIATED CLASS REVIEWS: THIAZOLIDINEDIONES (TZDS), ORAL ANTIEMETIC AGENTS; CONTRACEPTIVE AGENTS

Portions of the clinical reviews of each class were presented to the Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing appropriate cost effectiveness models. Both the clinical and economic analyses of each class will be completed during the May 2006 meeting; no action necessary.

APPENDIX A – TABLE 1. Implementation Status of UF Decisions

APPENDIX B – TABLE 2. Newly Approved Drugs

APPENDIX C – TABLE 3. Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

William Winkenwerder, Jr., M.D.
Date: 26 April 2006

Department of Defense
Pharmacy and Therapeutics Committee Minutes

17 February 2006

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 14 February 2006 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P& T Committee Chair
CDR Mark Richerson, MSC, USN	DoD P& T Committee Recorder
CDR Bill Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Maj David Carnahan, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
LtCol Brian Crownover, MC	Air Force, Physician at Large
LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer
LCDR Scott Akins, MC	Navy, Pediatrics Physician
CDR Brian Alexander, MC	Navy, Physician at Large
LCDR Joe Lawrence MSC *for* CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
MAJ Paul Garrett MC *for* COL Joel Schmidt, MC	Army, Physician at Large
LTC Peter Bulatao, MS *for* COL Isiah Harper, MS	Army, Pharmacy Officer
CDR Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
CDR Jill Pettit, MSC, USN	TRRx/TMOP COR
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

LCDR Chris Hyun, MC	Navy, Internal Medicine Physician
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Joel Schmidt, MC	Army, Physician at Large
COL Isiah Harper, MS	Army, Pharmacy Officer

C. Non-Voting Members Present

COL Kent Maneval, MS, USA	Defense Medical Standardization Board
Mr. Lynn T. Burleson	Assistant General Counsel, TMA
Mr. John Felicio *for* Ms Martha Taft	Health Plan Operations, TMA

Capt Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

None	

E. Others Present

Col Nacy Misel, BSC, USAF Reserve	IMA DoD Pharmacoeconomic Center
Lt Col David Bennett, BSC, USAF	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC, USA	DoD Pharmacoeconomic Center
CPT Ryan Young, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Dan Remund	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Julie Liss	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Dave Flowers	DoD Pharmacoeconomic Center
David Meade	DoD Pharmacoeconomic Center
Harsha Mistry	DoD Pharmacoeconomic Center
Catherine Kelly	Department of Veterans Affairs
Charles R. Brown	TMA/CMB

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the minutes – November 2005 DoD P&T meeting minutes were approved as written, with no corrections noted.

B. November minutes approval – Dr. William Winkenwerder, Jr., M.D. approved the minutes of the November 2005 DoD P&T Committee on 19 January 2006.

4. ITEMS FOR INFORMATION

TMA and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing: CAPT Buss, LtCol Bennett and LtCol Crownover briefed the members of the DoD P&T committee regarding the 15 December 2005 BAP meeting. The Committee was briefed on BAP comments regarding DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions: Mr. Dave Bretzke briefed the members of the Committee on the progress of implementation for drug classes reviewed for UF status since

February of 2005 (see Appendix A – Table 1). The Committee made the following observations:

- Utilization in all UF classes remains stable suggesting continued access to drugs within the reviewed classes.
- Collectively, as a percent of prescriptions dispensed, utilization of UF agents across all reviewed drug classes and points of service (MTF, mail, retail) have increased, while utilization of non-formulary agents has decreased. Among the UF decisions that have been implemented since the first UF DoD P&T meeting in February 2005 DoD there has been a 34% reduction in the use of non-formulary agents. Among all drug classes reviewed by the Committee to date, including those classes where implementation has only just begun, there has been a 17% reduction in the use of agents designated as non-formulary.
- Success in terms of generating increased market share for UF agents (while decreasing market share for non-formulary agents) varies by class and by point of service.
    - Formulary decisions resulting in a higher degree of drug class restrictiveness (i.e., phosphodiesterase-5 inhibitors) are generating better market share results than formulary decisions allowing multiple UF options within a drug class (i.e., angiotensin receptor blockers).
    - Market shares by point of service reflect the degree of utilization management applied to each point of service. The more highly managed points of service (ie., MTF, mail) are generating higher market shares of UF agents than the unmanaged point of service (i.e., retail).
- Overall market share projections for UF agents of 80% have not yet been realized. Although these projections were based on an implementation plan utilizing a one year time horizon, it is unlikely this degree of conversion will be achieved across all three points of service.
    - Models used to describe the relative economic comparison of agents within a drug class have been adjusted to reflect this information.
    - For the February 2006 drug classes evaluated for UF status, switch rates were reduced from 80% at all three points of service to approximately 70% at the MTF point of service and 30% in the retail and mail order sectors.

5. REVIEW OF RECENTLY-APPROVED AGENTS

The P&T Committee was briefed on two new agents recently approved by the Food and Drug Administration (FDA) (Appendix B – Table 2). Neither of the medications fall into drug classes already reviewed by the P&T Committee, therefore UF consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits. Sorafenib (Nexavar) is an oral multi-kinase inhibitor approved for treatment of patients with advanced renal cell carcinoma. Sorafenib is available in 200 mg tablets and is administered in a dose of 2 tabs given twice daily. Quantity limits were recommended for sorafenib since there is a risk of discontinuation of therapy due to poor patient prognosis or drug-related adverse effects. Other oral chemotherapy drugs (imatinib, erlortinib) do have quantity limits. The manufacturer of sorafenib has instituted a restricted distribution system

which limits the quantity dispensed to a 30-day supply. Sorafenib is not currently available from the TMOP, due to the restricted distribution system.

COMMITTEE ACTION: The DoD Pharmacy and Therapeutics (P&T) Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend that sorafenib have quantity limits of 180 tablets per 45 days (TMOP), should the product become available from the TMOP, or 120 tablets per 30 days (TRRx).

6. OVERACTIVE BLADDER (OAB) DRUG CLASS REVIEW.

A. OAB Medications Relative Clinical Effectiveness Review: 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 OAB therapeutic class was defined as the antimuscarinics: oxybutynin immediate release (Ditropan tablets/solution or generic), oxybutynin sustained release (Detrol XL), oxybutynin transdermal (Oxytrol), tolterodine immediate release (Detrol), tolterodine sustained release (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 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.

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

1) Efficacy

Efficacy measures. The antimuscarinic drugs reviewed are FDA-approved for the treatment of OAB. 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 and tolterodine immediate

release; one study of trospium versus oxybutynin immediate release; four studies of oxybutynin sustained release versus oxybutynin immediate release; and one study comparing of tolterodine sustained release versus tolterodine immediate release.

Oxybutynin sustained release was found to be superior to tolterodine immediate release in one trial; conversely tolterodine sustained release was reported as superior in one comparative trial against oxybutynin immediate release. Conflicting results were reported in the trials comparing oxybutynin sustained release and tolterodine sustained release, 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 sustained release (fixed dose) in one trial, however the results may be explained by lack of dosage titration allowed in the tolterodine sustained release group. Another short term trial showed greater efficacy with solifenacin vs tolterodine immediate release 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.

2) Safety and 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, darifenacin and trospium) 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, 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 immediate release 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 sustained release forms of each drug resulted in fewer adverse events and dry mouth when compared to formulations. Trospium causes less severe dry mouth although the overall incidence of dry mouth and short

term adverse events are similar to oxybutynin immediate release. 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 sustained release versus solifenacin.

Discontinuation Rates: One comparative long-term study assessed the discontinuation rate of tolterodine and oxybutynin immediate release over a 6-month period. Oxybutynin immediate release 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 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 sustained release, oxybutynin sustained release, and oxybutynin immediate release were 5% to 16%. There were insufficient numbers of prescriptions refilled for the three newest OAB drugs to determine persistent rates. MHS beneficiaries using TMOP were more persistent with OAB therapy than those beneficiaries using other points 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 immediate release formulations than with SR formulations. The highest frequency of dry mouth occurs with oxybutynin immediate release. The three newest OAB drugs (trospium, solifenacin, and darifenacin) do not substantially lower the rate of dry mouth compared with tolterodine or oxybutynin sustained release, 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, solifenacin, and darifenacin.

3) Other Factors

Dosing: All of the agents in the class are dosed once daily except for trospium, oxybutynin immediate release, and tolterodine immediate release. Once daily dosing theoretically increases compliance. Oxybutynin sustained release 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 immediate release and sustained release 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 immediate release and tolterodine sustained release; these two drugs have been included on the BCF since 2002. Most providers favored tolterodine sustained release. A majority of respondents had heard of the newer agents, trospium, solifenacin and darifenacin, 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.

Overall Clinical Effectiveness Conclusion: 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 (immediate release to immediate release; sustained release to sustained release) the side effect profiles are similar; 3) immediate release forms of the overactive bladder drugs induce more anti-cholinergic side effects than the sustained release forms; 4) the new agents, solifenacin and darifenacin, and trospium have an increased rate of constipation compared to oxybutynin sustained release and tolterodine sustained release; 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.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) that for the purposes of the UF clinical review, all the drugs reviewed for OAB were similar in terms of effectiveness and clinical outcome.

B. OAB UF Relative Cost Effectiveness:

The P&T Committee evaluated the relative cost-effectiveness of the OAB 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 CFR 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 immediate release, oxybutynin sustained release, oxybutynin patch, tolterodine immediate release, tolterodine sustained release, 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 CEA. 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 immediate release was determined to be the most cost-effective agent and tolterodine sustained release was determined to be significantly more costly and effective along the efficiency frontier.
- Among the multi-dosed immediate release agents, oxybutynin immediate release was determined to be the most cost-effective agent; tolterodine immediate release was determined to be slightly more effective but significantly more costly (> 15-fold) compared to oxybutynin immediate release; and trospium immediate release was determined to be slightly less effective and significantly more costly (> 15-fold) compared to oxybutynin immediate release
- Among the once daily extended release agents, tolterodine sustained release was determined to be the most cost-effective agent; oxybutynin patch and sustained release tablet were dominated (more costly and less effective) compared to tolterodine sustained release.

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 sustained release. For purposes of this evaluation, the DoD P&T Committee assumed that darifenacin and solifenacin would have similar relative clinical effectiveness compared to tolterodine sustained release, based upon the conclusion of the overall relative clinical effectiveness presentation.

The results of the CEAs were subsequently incorporated into a 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 sustained release is projected to go generic in 2006), the Committee agreed that a group of OAB agents that included: darifenacin, oxybutynin immediate release, oxybutynin sustained release, solifenacin, and tolterodine sustained release 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.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 2 abstention, 1 absent) to accept the OAB pharmacoeconomic analyses presented by the PEC. The P&T Committee concluded that: tolterodine immediate release, oxybutynin patch, and trospium were not cost-effective relative to the other OAB agents. 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 immediate release, oxybutynin patch, and trospium be classified as non-formulary under the UF and that darifenacin, oxybutynin immediate release, oxybutynin sustained release, solifenacin, and tolterodine sustained release be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstention, 3 absent) to recommend that tolterodine immediate release, oxybutynin patch, and trospium be classified as non-formulary under the UF, with darifenacin, oxybutynin immediate release, oxybutynin sustained release, solifenacin, and tolterodine sustained release 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 32 CFR 199.21(e)(2).

C. OAB Drug UF Medical Necessity Criteria: Based on the clinical evaluation of overactive bladder drugs, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following medical necessity criteria for these agents.

1) Use of the formulary overactive bladder drugs (oxybutynin immediate release, oxybutynin sustained release, tolterodine sustained release, solifenacin and darifenacin) are contraindicated, and the use of tolterodine immediate release, trospium, or oxybutynin patch is not contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from the formulary overactive bladder drugs (oxybutynin immediate release, oxybutynin sustained release, tolterodine sustained release, solifenacin and darifenacin) and the patient is expected to tolerate tolterodine immediate release, trospium, or oxybutynin patch.

3) Use of the formulary overactive bladder drugs (oxybutynin immediate release, oxybutynin sustained release, tolterodine sustained release, solifenacin and darifenacin) resulted in

therapeutic failure, and the patient is expected to respond to tolterodine immediate release, trospium, or oxybutynin patch (therapeutic failure as outlined on medical necessity form).

4) The patient has previously responded to the oxybutynin patch, and changing to the formulary overactive bladder drugs (oxybutynin immediate release, oxybutynin sustained release, tolterodine sustained release, solifenacin and darifenacin) would incur unacceptable risk. The Committee agreed that this criterion could apply because of the potentially lower risk of CNS effects with the oxybutynin patch.

5) There is no alternative formulary agent: The Committee agreed that this criterion could apply to the oxybutynin patch if the patient could not take oral medications.

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

D. OAB Drug UF 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 immediate release, trospium, or oxybutynin patch 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 immediate release, trospium, or oxybutynin patch 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 immediate release, trospium, or oxybutynin patch 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 (13 for, 2 opposed, 1 abstained, 2 absent) 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.

E. OAB Drug Basic Core Formulary (BCF) Review and Recommendations. The P&T Committee had previously determined that at least one but no more that two overactive bladder drugs would be added to the BCF based on the clinical and cost effectiveness reviews. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that oxybutynin immediate release and tolterodine sustained release be added to the BCF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to include oxybutynin immediate release and tolterodine sustained release on the BCF.

7. MISCELLANEOUS ANTIHYPERTENSIVE AGENTS DRUG CLASS REVIEW

A. Miscellaneous Antihypertensive Agents UF 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 angiotensin converting enzyme (ACE) inhibitor/calcium channel blocker (CCB) combinations amlodipine/benazepril (Lotrel), felodipine/enalapril (Lexxel), and verapamil sustained release/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/CCB 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 UF 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 and felodipine/enalapril contain a dihydropyridine (DHP) CCB. The verapamil component of verapamil sustained release /trandolapril is a non-dihyropyridine CCB. Verapamil reduces myocardial contractility and slows conduction through the atrioventricular node. The physiologic effect of slowed heart rate with the non-DHP CCBs is frequently used as a beneficial effect in patients with increased heart rate (e.g. atrial fibrillation). The DHPs 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 blood pressure (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 reduces systolic blood pressure (SBP) by 10-25 mmHg and diastolic blood pressure (DBP) by 6-13 mmHg, felodipine/enalapril reduces SBP by 14.2 mmHg and DBP by 12.6 mmHg, and verapamil/trandolapril 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 and verapamil sustained release /trandolapril 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 sustained release/ trandolapril 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 showing a benefit of the drug in reducing cardiovascular outcomes. There are no completed trials with amlodipine/benazepril 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 sustained release 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 amlodipine/benazepril and verapamil sustained release/trandolapril 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, amlodipine/benazepril and verapamil sustained release/trandolapril have not been conducted, but there is some evidence of benefit with the individual components.

c) Safety and Tolerability:

Serious Adverse Effects: Verapamil sustained release/trandolapril 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.

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

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, 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 sustained release/trandolapril was 2.6% vs. 1.9% with placebo, most commonly due to dyspnea and fatigue.

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-DHP component of verapamil sustained release/trandolapril imparts unique risks of impaired cardiac contractility. There is no evidence that amlodipine/benazepril and felodipine/enalapril 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 or verapamil sustained release/trandolapril 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 amlodipine/benazepril, 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 amlodipine/benazepril 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 second or third 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

mecamylamine. 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 fiscal year 2005), 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.

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 fiscal year 2005), 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.

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.

COMMITTEE RECOMMENDATION: *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 amlodipine/benazepril and verapamil sustained release/trandolapril in sub-populations of patients with hypertension than felodipine/ enalapril; (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 amlodipine/benazepril or felodipine/ enalapril would be superior to the other in terms of safety/tolerability. Verapamil sustained release/trandolapril has unique safety issues, due to the verapamil component; (6) persistence rates with amlodipine/benazepril 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 UF 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 (16 for, 0 opposed, 1 absent; 1 abstain) to accept the clinical effectiveness conclusion as stated above.

B. Miscellaneous Antihypertensives UF Relative Cost Effectiveness: The 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 CFR 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, felodipine/enalapril, verapamil/trandolapril) 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 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 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 amlodipine/benazepril and another study that examined compliance with combination ACE/hydrochlorothiazide (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 DHP/ACE combination products (amlodipine/benazepril and felodipine/enalapril) to their respective agents given separately and another comparing the verapamil/ACE combination product (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:

- DHP/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 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 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.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 1 abstention, 1 absent) to accept the miscellaneous antihypertensive cost-analysis presented by the PEC. The P&T Committee concluded that felodipine/enalapril and verapamil/trandolapril were not cost-effective relative to the other miscellaneous antihypertensive agents. 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 felodipine/enalapril and verapamil/trandolapril be classified as non-formulary under the UF. The P&T Committee also recommended that clonidine tablets, clonidine patches, amlodipine/ benazepril, hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted 11 for, 4 opposed, 2 abstention, 1 absent) to recommend that felodipine/ enalapril and verapamil/trandolapril be classified as non-formulary under the UF, with clonidine tablets, clonidine patches, amlodipine/benazepril, hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine remaining on the UF.

C. Miscellaneous antihypertensive agents Medical Necessity Criteria. The P&T Committee concluded that because the only miscellaneous antihypertensive agents classified as non-formulary under the UF are the combination agents felodipine/enalapril and verapamil/

trandolapril, and because the individual components of both of these agents are available separately on the UF, only two of the five general medical necessity criteria could potentially apply. Therefore, based on the clinical evaluation of felodipine/enalapril and verapamil/ trandolapril and conditions for establishing medical necessity for a non-formulary medication provided in the UF rule, the following medical necessity criteria may apply:

1) Use of a formulary pharmaceutical agent is contraindicated, and the use of a non-formulary agent is not contraindicated.

2) The patient previously responded to the non-formulary pharmaceutical agent and changing to a formulary pharmaceutical agent would incur an unacceptable clinical risk.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to accept the miscellaneous medical necessity criteria.

D. Miscellaneous Antihypertensive Agents UF Implementation Period: The Committee recommended an effective date no later than the first Wednesday following a 60-day implementation.

COMMITTEE ACTION: The DoD P&T Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to recommend an implementation period of 60 days.

E. Miscellaneous Antihypertensive Agents Basic Core Formulary (BCF) Review and Recommendations. The P&T Committee had previously determined that at least one but no more that two miscellaneous antihypertensive agents would be added to the BCF based on the clinical and cost effectiveness reviews. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that amlodipine/benazepril, hydralazine and clonidine tablets be added to the BCF.

Conclusion: Lotrel (amlodipine /benazepril), hydralazine and clonidine tablets were recommended for inclusion on the BCF.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 1 abstained, 1 absent) to include Lotrel (amlodipine /benazepril), hydralazine and clonidine tablets on the BCF

8. GAMMA-AMINOBUTYRIC ACID (GABA)-ANALOG DRUG CLASS REVIEW

A. GABA-Analogs Relative Clinical Effectiveness: The DoD 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 (Gabitril). 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 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 NNT, 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 first 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 pregabalin 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 pregabalin (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, gabapentin was significantly better than 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 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 either gabapentin or pregabalin for treatment of pain associated with DPN or PHN. Efficacy of gabapentin for other types of neuropathic pain syndromes appears modest, but there is no efficacy evidence for pregabalin in other types of neuropathic pain. 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 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 a more favorable NNH 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 was 10.7 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 PHN. Pregabalin is the sole agent in the class approved for treating pain associated with DPN, however, controlled clinical trial data support the efficacy of gabapentin. Gabapentin, pregabalin, and tiagabine are all 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 significantly 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, and greater than 600 mg/d for PHN.

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 recommended by the manufacturer, 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 both gabapentin pregabalin therapy.

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 lack of clinical experience, but providers did prefer 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 was rarely used in neuropathic pain, and if chosen, it was preferred 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.

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 (16 for, 0 opposed, 1 abstain, 1 absent) to accept the clinical effectiveness conclusion as stated above.

B. Relative CEA: 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 CFR 199.21(e)(2). A CEA 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 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 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 BIA 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.

Conclusion: The P&T Committee concluded that gabapentin was the more cost effective GABA-analog drug for the treatment of neuropathic pain. The cost-effectiveness of tiagabine was also considered, and it was determined that nothing would be gained clinically or economically by making tiagabine non-formulary.

COMMITTEE ACTION: The P&T Committee agreed (16 for, 0 opposed, 0 abstained, 2 absent) with the relative CEA of the GABA-analog drugs presented.

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. Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the GABA-analog drugs, and other relevant factors, the P&T Committee recommended (14 for, 2 opposed, 0 abstained, 2 absent) that pregabalin be classified as non-formulary under the UF, with gabapentin and tiagabine remaining on the UF.

C. GABA analogs UF Medical Necessity Criteria: Based on the clinical evaluation of the GABA analogs and conditions for establishing medical necessity for a non-formulary

medication provided in the UF rule, the P&T Committee concluded that the following general medical necessity criteria would apply for these agents:

1) Use of formulary agents is contraindicated, and the use of pregabalin is not contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from the formulary agents, and the patient is expected to tolerate pregabalin.

3) Treatment with formulary agents has resulted in a therapeutic failure, and the patient is expected to respond to pregabalin.

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

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 1 opposed, 0 abstained, 2 absent) to accept the GABA-analog medical necessity criteria.

D. GABA-analog UF Implementation Period: The Committee recommended an effective date no later than the first Wednesday following a 60-day implementation.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to recommend an implementation period of 60 days.

E. GABA-analog BCF Review and Recommendations: The P&T Committee reviewed the GABA analogs recommended for inclusion on the UF to select the BCF GABA analog.

Gabapentin is currently included on the BCF. From a clinical and economic standpoint, all strengths and formulations of gabapentin are rational selections for the BCF. Gabapentin is the highest utilized GABA-analog in all three points of service (MTF, TRRx, and TMOP), is efficacious in treating a variety of neuropathic pain syndromes, and is now generically available.

Conclusion: The Committee concurred with the recommendations to place all formulations and strengths of gabapentin on the BCF.

COMMITTEE ACTION: The DoD P&T Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to maintain all formulations and strengths of gabapentin on the BCF.

9. ABBREVIATED CLASS REVIEWS: THIAZOLIDINEDIONES (TZDS), ORAL ANTIEMETIC AGENTS; CONTRACEPTIVE AGENTS

Portions of the clinical reviews were presented to the Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing appropriate cost effectiveness models. Both the clinical and economic analyses of each class will be completed during the May 2006 meeting; no action necessary.

10. ADJOURNMENT

The third day of the meeting adjourned at 1130 hours on February 16, 2006. The dates of the next meeting are May 9 – 11, 2006.

Patricia Buss

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

List of Appendices

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

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Decision	Comments
Feb 06	OABs	tolterodine IR (Detrol) oxybutynin patch (Oxytrol) trospium (Sanctura)	BCF	oxybutynin IR (Ditropan tabs/soln) tolterodine SR (Detrol LA)	Pending approval	Pending approval	
Feb 06	Misc Antihypertensive Agents	felodipine/enalapril (Lexxel) verapamil/trandolapril (Tarka)	BCF	amlodipine/benazepril (Lotrel) hydralazine clonidine tablets	Pending approval	Pending approval	
Feb 06	GABA-analogs	pregabalin (Lyrica)	BCF	gabapentin (Neurontin)	Pending approval	Pending approval	
Nov 05	Alzheimer's Drugs	tacrine (Cognex)	ECF	donepezil (Aricept)	19 Jan 06	19 April (90 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Nasal Corticosteroids	beclomethasone dipropionate (Beconase AQ, Vancenase AQ) budesonide (Rhinocort AQ) triamcinolone (Nasacort AQ)	BCF	fluticasone (Flonase)	19 Jan 06	19 April (90 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Macrolide/ Ketolide Antibiotics	azithromycin 2gm (Zmax) telithromycin (Ketek)	BCF	azithromycin (Z-Pak) erythromycin salts and bases	19 Jan 06	22 March 2006 (60 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Antidepressants (excluding MAOIs and TCAs)	paroxetine HCL CR (Paxil) fluoxetine 90mg (weekly regimen – Prozac Weekly) fluoxetine (special packaging for PMDD – Sarafem) escitalopram (Lexapro) duloxetine (Cymbalta) buproprion extended release (Wellbutrin XL)	BCF	citalopram fluoxetine (excluding weekly regimen and special packaging for PMDD) sertraline (Zoloft) trazadone buproprion sustained release	19 Jan 06	19 July 2006 (180 day implementation period)	BCF selections effective 19 Jan 06

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Decision	Comments
Aug 05	Alpha Blockers for BPH	tamsulosin (Flomax)	BCF	terazosin alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05
Aug 05	CCBs	amlodipine (Norvasc) isradipine IR (Dynacirc) isradipine ER (Dynacirc CR) nicardipine IR (Cardene, generics) nicardipine SR (Cardene SR) verapamil ER (Verelan) verapamil ER for bedtime dosing (Verelan PM, Covera HS) diltiazem ER for bedtime dosing (Cardizem LA)	BCF	nifedipine ER (Adalat CC) verapamil SR diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150-day implementation period)	BCF selections effective 13 Oct 05
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	moexipril (Univasc), moexipril / HCTZ (Uniretic) perindopril (Aceon) quinapril (Accupril) quinapril / HCTZ (Accuretic) ramipril (Altace)	BCF	captopril lisinopril lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05
May 05	PDE-5 Inhibitors	sildenafil (Viagra) tadalafil (Cialis)	ECF	vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90-day implementation period)	ECF selection effective 14 Jul 05
May 05	Topical Antifungals*	econazole ciclopirox oxiconazole (Oxistat) sertaconazole (Ertaczo) sulconazole (Exelderm)	BCF	nystatin clotrimazole	14 Jul 05	17 Aug 05 (30-day implementation period)	BCF selection effective 14 Jul 05
May 05	MS-DMDs	-	ECF	interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-	ECF selection effective 14 Jul 05
Feb 05	ARBs	eprosartan (Teveten) eprosartan/HCTZ (Teveten HCT)	BCF	telmisartan (Micardis) telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05

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

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Decision	Comments
Feb 05	PPIs	esomeprazole (Nexium)	BCF	omeprazole rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = UF
ER = extended release; IR = immediate release; SR = sustained release
ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors
*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs February 2006 DoD P&T Committee Meeting

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Deferasirox (Exjade; Novartis) tablets for oral suspension; iron chelator	Nov 05; treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years and older	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Sorafenib (Nexavar) tablets; multi-kinase inhibitor	Dec 05 (priority review); treatment of patients with advanced renal cell carcinoma	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed. Quantity limits recommended: TMOP: 180 tablets per 45 days (if the product becomes available in this point of service; Retail Network: 120 tablets per 30 days

Appendix C – Table 3. Table of Abbreviations

ACE	angiotensin converting enzyme
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BP	blood pressure
CCB	calcium channel blocker
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
DHP	dihydropyridine
DM	diabetes mellitus
DoD	Department of Defense
DPN	diabetic peripheral neuropathy
ECF	Extended Core Formulary
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
HCTZ	hydrochlorothiazide
JNC VII	Joint National Commission VII
MHS	Military Health System
MTF	military treatment facility
NNH	number needed to harm
NNT	number needed to treat
OAB	overactive bladder
P&T	Pharmacy and Therapeutics
PEC	Pharmacoeconomic Center
PHN	post-herpetic neuralgia
SBP	systolic blood pressure
SUI	stress urinary incontinence
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
TZDs	thiazolidinediones
UF	Uniform Formulary