DOD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS INFORMATION FOR THE DOD BENEFICIARY ADVISORY PANEL

I. Uniform Formulary Review Process

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

II. Angiotensin Converting Enzyme Inhibitor Drug Class Review

P&T Comments

A. Relative Clinical Effectiveness: The Committee evaluated the relative clinical effectiveness of the ten ACEIs marketed in the US benazepril (Lotensin and various generics), captopril (Capoten and various generics), enalapril (Vasotec and various generics), fosinopril (Monopril and various generics), lisinopril (Prinivil, Zestril, and various generics), trandolapril (Mavik), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), and ramipril (Altace) and their respective combinations with hydrochlorothiazide (HCTZ). Perindopril, ramipril, and trandolapril are not available in combination with HCTZ. Information regarding their safety, effectiveness, and clinical outcome was considered. The clinical review included, but was not limited to the requirements stated in the Uniform Formulary Rule, 32 CFR 199.21.

1) *Safety and Tolerability:* The most common or serious adverse effects of the ACEIs are hypotension, dry cough, angioedema, hyperkalemia, rash, and acute renal impairment. Doses of captopril >100 mg have been associated with neutropenia and dysgeusia. Head to head trials of the ACEIs in hypertension, myocardial infarction, and heart failure reported withdrawal rates due to adverse events ranging from 0-39%, but there were no significant differences between the ACEIs in any trial.

2) *Efficacy for Hypertension*: All ten ACEIs are approved by the FDA for treating hypertension. All ACEIs reduce blood pressure when titrated to effect.

3) *Efficacy in High Cardiovascular Risk patients:* The Committee agreed that evidence of a favorable effect on clinical outcomes (i.e., irreversible outcomes such as death, myocardial infarction, stroke, need for dialysis or renal transplantation) is more important than evidence of favorable effects on physiologic outcomes (i.e., reversible outcomes that are surrogate markers of disease, such as changes in lab values).

Three ACEIs have been evaluated in large, well-conducted randomized trials enrolling more than 8,000 high cardiovascular risk patients. In the HOPE trial, ramipril 10 mg was found to reduce the incidence of cardiovascular death, all-cause death and cardiovascular events in diabetic and non-diabetic patients with severe coronary artery disease, compared with placebo. The use of appropriate background medications such as statins, aspirin, and beta blockers was low in this study. In the EUROPA trial, perindopril 8 mg reduced the incidence of cardiovascular events (non-fatal myocardial infarction, unstable angina), but did not show a benefit in reducing mortality in patients with stable coronary artery disease. The PEACE trial, where trandolapril 4 mg was evaluated in patients with stable coronary artery disease, did not show a benefit of the ACEI in reducing mortality or cardiovascular events. A large percentage of patients in the PEACE trial were receiving appropriate background therapy, and >50% had prior coronary artery bypass grafting or PTCA.

Ramipril when used at doses of 5-10 mg has shown a benefit in reducing cardiovascular events but not mortality in one trial enrolling 617 patients (PART-2 trial); however, no reduction in cardiovascular events was seen when ramipril doses of 1.25 mg were evaluated (DIABHYCAR trial). Quinapril was studied in one trial of 1700 patients, but no reduction in cardiovascular events was reported (QUIET trial). A small trial (229 patients) with enalapril administered with simvastatin reported a reduction in cardiovascular events.

In DoD, it is estimated that approximately 10% of the patients receiving ramipril meet the entry criteria established for the HOPE trial, e.g., patients with a history of cardiovascular disease (coronary artery disease, stroke, peripheral vascular disease, or diabetes), and one additional risk factor, including smoking, hypertension, hyperlipidemia, or renal insufficiency.

4) *Recent myocardial infarction (MI):* Placebo-controlled trials evaluating the use of ACEIs after an MI have shown a reduction in mortality with captopril, lisinopril, ramipril, and trandolapril. Enalapril and fosinopril have shown reductions in hospitalizations for heart failure.

5) *Chronic Heart Failure:* A meta-analysis of 32 placebo-controlled trials enrolling over 9,000 patients reported similar point estimates for a mortality reduction with benazepril, captopril, enalapril, lisinopril, perindopril, quinapril, and ramipril. When the meta-analysis was published (1995), there was limited evidence with benazepril and perindopril, and no evidence with moexipril or trandolapril. The American Heart Association and American College of Cardiology guidelines for treating heart failure state that the best evidence for a mortality reduction in patients with heart failure is with captopril, enalapril, ramipril, and trandolapril, as the dosage is known for these ACEIs.

6) *Diabetic and Non-Diabetic Renal Disease:*

   Type 1 Diabetic Nephropathy: Captopril is the only ACEI approved for diabetic nephropathy, based on one long-term trial (Collaborative trial) evaluating clinical endpoints (development of end-stage renal disease and death). Lisinopril,

ramipril, perindopril, and enalapril have shown benefits in reducing proteinuria, but have not been shown to prevent progression of renal failure in type 1 diabetic patients.

Type 2 Diabetic Nephropathy: A study of ramipril 1.25 mg in type 2 diabetics with nephropathy that evaluated both cardiovascular and renal outcomes did not show a benefit over placebo, but a reduction in albumin excretion rate was noted. A trial with benazepril 10 mg in type 2 diabetic patients did show a reduction in doubling of serum creatinine and need for dialysis; however, this benefit was seen in only 21 patients. A benefit on surrogate outcomes (reduction of microalbuminuria) has been seen with enalapril, lisinopril quinapril, and ramipril.

Non-Diabetic Renal Disease: Captopril, enalapril, benazepril, and ramipril have been shown in one meta-analysis to reduce the risk of end-stage renal disease in non-diabetic patients with renal insufficiency.

7.) *Prevention of Diabetes:* Subgroup analysis from large trials conducted with enalapril, captopril, and ramipril has shown a delay or prevention of the development of diabetes. An ongoing trial with ramipril and rosiglitazone (DREAM trial) is underway that will prospectively evaluate whether treatment with an ACEI or thiazolidinedione will delay the development of type 2 diabetes.

Clinical Effectiveness Conclusion: The Committee concluded that (1) all ten ACEIs have similar relative clinical effectiveness for treating hypertension; (2) ramipril has shown a reduction in mortality in patients at high cardiovascular risk; (3) captopril, enalapril, ramipril, lisinopril and trandolapril have the best evidence for reducing mortality in chronic heart failure and following MI; (4) captopril has the best evidence for improving clinical outcomes in type 1 diabetic renal disease; (5) no ACEI has shown a benefit in improving clinical outcomes in type-2 diabetic disease; (6) benazepril, ramipril, enalapril, and captopril show the best evidence for improving clinical outcomes in non-diabetic renal disease; and (7) no ACE is preferable relative to another in terms of adverse events.

Two alternative methods were used for comparing ACEIs on clinical effectiveness. When DoD utilization, therapeutic overlap and quality of evidence for various conditions were considered, ramipril, lisinopril, captopril, fosinopril, benazepril, and enalapril had higher clinical utility (overall clinical usefulness) relative to quinapril, perindopril, trandolapril, and moexipril. When using another model which only evaluated quality of evidence, the resulting ranking (from highest to lowest utility) was: ramipril, trandolapril, enalapril, perindopril, captopril, lisinopril, fosinopril, quinapril, benazepril, and moexipril. The committee considered both evaluations when formulating their recommendation.

The committee concluded that ramipril, captopril, lisinopril, benazepril, enalapril, trandolapril, and fosinopril have increased clinical effectiveness relative to moexipril, quinapril, and perindopril.

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

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

To determine the relative cost effectiveness of the ACEIs, two separate economic analyses were performed: a pharmacoeconomic analysis, and a budget impact analysis (BIA). From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that ACEIs have similar safety and tolerability, and similar relative clinical effectiveness in the treatment of hypertension. However the ACEIs differ in clinical outcome evidence supporting their effectiveness in patients with high cardiovascular risk, post myocardial infarction, heart failure, type 1 diabetes mellitus, type 2 diabetes mellitus, and non-diabetic nephropathy patients. In other words, the agents were shown to differ in relative clinical effectiveness.

First, a cost-minimization analysis (CMA) was performed to stratify the agents solely on cost. The results of the cost-minimization analysis revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included benazepril, captopril, enalapril, and lisinopril, whereas, the moderate cost cluster included fosinopril and trandolapril. Moexipril, perindopril, quinapril, and ramipril were included in the high cost cluster.

Given this conclusion, the relative cost effectiveness of the agents was determined through a cost-effectiveness analysis (CEA). In this type of analysis, agents within a therapeutic class are competed on two dimensions, cost and effect (outcomes). The cost used in the analysis was the total weighted average cost per day of treatment (for all three points of service). The effectiveness measure used for each agent was the composite score derived from the clinical effectiveness analysis that ranked the agents based on clinical outcome evidence. The results of the CEA were: captopril was the most cost-effective agent, followed by enalapril; lisinopril and benazepril, trandolapril, and ramipril were more effective but more costly; and the other agents were less cost effective.

The results of the CMA and CEA were subsequently incorporated into a budget impact analysis (BIA). A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more ACEIs 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 identify a group of ACEIs to be included on the UF which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA results revealed that a group of ACEIs that included benazepril, captopril, enalapril, fosinopril, lisinopril, and trandolapril best achieved this goal when compared to other combination groups of ACEIs, and thus were determined to be more cost-effective relative to other combination groups.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to recommend that moexipril, perindopril, quinapril, and ramipril (and their respective combinations with HCTZ, if any) be classified

as non-formulary, with benazepril, captopril, enalapril, fosinopril, lisinopril, and trandolapril (and their respective combinations with HCTZ, if any) remaining on the UF.

C. **Implementation Plan:** Because a substantial number of patients (158,000, or 21% of all patients receiving ACEIs) are currently receiving ramipril, moexipril, perindopril, or quinapril, the P&T Committee recommended an effective date no later than the first Wednesday following a 120 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA

COMMITTEE ACTION: The Committee voted to recommend an implementation period of 120 days.

III. Angiotensin Converting Enzyme Inhibitor Drug Class Review (cont.)

BAP Comments

A. **Relative Clinical Effectiveness***:* The P&T Committee's conclusion is stated in Section 2, paragraph A.

B. Relative Cost Effectiveness: The P&T Committee, based upon its collective professional judgment, voted to accept the ACEI cost-analysis presented by the PEC. The P&T Committee concluded that moexipril, perindopril, and quinapril were not cost-effective relative to the other ACEIs, since the agents were more costly and less effective. In pharmacoeconomic terms, these agents are considered to be "dominated." Although ramipril was shown to be more costly and more effective in the CEA, the P&T Committee did not value ramipril's clinical outcome evidence in high-risk cardiovascular patients enough to overcome its significantly higher cost (10-fold higher than the most cost-effective agent).

C. Uniform Formulary Recommendation: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ACEIs, and other relevant factors, the P&T Committee recommended that moexipril, perindopril, quinapril, and ramipril be classified as non-formulary under the UF and that benazepril, captopril, enalapril, fosinopril, lisinopril, and trandolapril be classified as formulary on the UF.

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

D. Implementation Plan: The Committee voted to recommend an implementation period of 120 days.

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

IV. Calcium Channel Blockers (CCB) Drug Class Review

P&T Comments

***A.* Relative Clinical Effectiveness:** The Committee evaluated the relative clinical effectiveness of the nine CCBs marketed in the U.S.: non-dihydropyridines diltiazem (Cardizem LA, Diltizaem CD/XR/XT, Tiazac, and various generics) and verapamil (Verelan, Verelan PM, Covera HS, Verapamil SR/IR, and various generics); and dihydropyridines nifedipine (Adalat CC, Procardia, Nifedipine CC/ER/XR, Nifedipine IR, and various generics), nicardipine (Cardene IR/SR), isradipine (DynaCirc IR/SR), felodipine (Plendil and various generics), amlodipine (Norvasc), nisoldipine (Sular), and nimodipine (Nimotop). Information regarding the safety, effectiveness, and clinical outcomes of the CCBs when used for cardiovascular conditions was considered. (Nimodipine is used for subarachnoid hemorrhage, but not for cardiovascular conditions; thus, it will not be discussed further in the clinical review.) The clinical review included, but was not limited to the requirements stated in the Uniform Formulary Rule, 32 CFR 199.21.

1.) Efficacy for Hypertension:

Place in Therapy: The Joint National Commission VII guidelines for treating hypertension state that CCBs are not first-line antihypertensive agents. CCBs are appropriate as add-on therapy with other antihypertensive agents, or in patients with compelling indications (coronary artery disease or diabetes).

Efficacy of CCBs vs CCBs: Head-to-head trials show that all are effective at lowering blood pressure, when titrated to effect. There are no head-to-head trials of the CCBs that assess clinical outcomes, such as mortality, stroke, myocardial infarction, or development of end-stage renal disease.

Efficacy of CCB vs Other Antihypertensive Agents: Sixteen large trials assessing clinical outcomes (mortality, stroke, myocardial infarction, development of end-stage renal disease) have been conducted with all the CCBs, except felodipine versus other anti-hypertensive agents, including diuretics, beta blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs). The overall quality of the evidence is poor. These 16 trials reported that the CCBs were similar, but not

better than the comparator drugs in reducing all-cause mortality. There were no differences between the CCBs. A meta-analysis has not been performed due to the heterogeneity of the trials, presence of patient co-morbidities, and differing clinical endpoints. Two new trials conducted with amlodipine (ASCOT and CAMELOT) do not change the efficacy assessment. Two trials evaluating felodipine with other anti-hypertensive agents did not have proper randomization (the STOP-2 trial), or did not evaluate felodipine as monotherapy (HOT trial).

2.) *Efficacy for Chronic Stable Angina*:

Place in Therapy: The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for treating chronic stable angina state that improved mortality has been shown with aspirin, lipid management, and beta blockers. CCBs help with improving symptoms, and are reserved for use in patients where a beta blocker is contraindicated, where beta blocker monotherapy is not successful, or in patients with unacceptable adverse effects to beta blockers.

Efficacy of CCB vs CCBs for Chronic Stable Angina: There are five head-to-head trials enrolling < 300 patients that have compared a CCB vs CCB, and evaluated symptom improvement (number of angina episodes/week, exercise duration, number of doses of sublingual nitroglycerin). For these five trials, there was no difference in symptom improvement with amlodipine, immediate release diltiazem, sustained release diltiazem, nisoldipine, nicardipine, or nifedipine. There have been no studies with felodipine or isradipine.

Efficacy of CCBs vs Beta Blockers for Chronic Stable Angina: Based on thirteen head-to-head trials comparing CCBs and beta blockers, diltiazem, amlodipine, nicardipine, sustained release nifedipine, nisoldipine, and verapamil all appeared to be similarly efficacious in treating angina symptoms.

3). *Efficacy in Systolic Dysfunction:*

Place in Therapy: The ACC/AHA guidelines for chronic heart failure do not recommend use of a CCB. However, CCBs are used in patients with systolic dysfunction to treat an underlying co-morbidity (hypertension, angina), without adversely compromising the patient's heart failure status.

Efficacy for Systolic Dysfunction: Amlodipine and felodipine have both been shown in one trial each to have no significant effect (neither positive nor negative) on all-cause mortality, or combined fatal and non-fatal events in patients with heart failure. In the V-HeFT III trial, there was no difference between placebo and felodipine in all-cause mortality in 450 patients with primarily New York Heart Association (NYHA) Class II heart failure symptoms. In the PRAISE trial, there was a 9% reduction in the relative risk of the composite outcome of all-cause mortality and cardiovascular morbidity with amlodipine, which was not significantly different from placebo, in 1,153 patients with primarily NYHA class III heart failure.

4). *Safety and Tolerability:* In general, the safety profile of an individual CCB reflects its pharmacologic class. The dihydropyridines (DHPs) are peripheral

vasodilators, and commonly cause edema, headache, flushing, reflux tachycardia, and dizziness (especially short-acting nifedipine). Verapamil has negative inotropic effects, while diltiazem does not exhibit negative inotropy.

There are no head–to-head trials of CCBs vs CCBs that assess clinical outcomes and adverse events. Individual trials in hypertension comparing the CCBs vs other anti-hypertensive agents that evaluated cardiovascular outcomes were insufficient to determine differences in the incidence of withdrawals due to adverse effects for amlodipine, diltiazem, nicardipine, nifedipine, and nisoldipine. For the trials evaluating CCBs in angina, there were no differences in withdrawal rates or adverse events with amlodipine, diltiazem, nicardipine, nifedipine, and nisoldipine. Two long-term observational studies reported that severe adverse events were highest with diltiazem, followed by verapamil, amlodipine, nifedipine, and nicardipine. Although there may be individual patient differences in the incidence of edema, the overall incidence of edema for all the CCBs ranges between 8-10%, and the rates of withdrawal due to edema are similar between CCBs.

5). *Other Factors:*

Special Populations: Amlodipine is the only DHP CCB indicated for pediatric use in patients aged 6-16 years with hypertension. Diltiazem and verapamil are used in the pediatric population.

Dosing Intervals: An evaluation of DHP dosing intervals in DOD showed that 10% of patients receiving sustained release nifedipine required more than 1 dose daily, vs 7% of amlodipine patients.

Formulations: The CCBs are available in a variety of immediate, sustained, and extended release preparations. Generic preparations are available for several of the products, but the products may not be bioequivalent due to differing release mechanisms. However, the products can be considered therapeutically equivalent, if they contain the same active ingredient. Immediate release nifedipine is no longer used for cardiovascular conditions due to a high incidence of reflux tachycardia and associated increased mortality. There are only 2,100 unique utilizers of immediate release nifedipine in DoD. This product will not be discussed further in the clinical review.

Chronotherapeutics: A higher incidence of cardiovascular events (stroke, myocardial infarction) has been noted in the early morning hours (between 6 AM and 10 AM). The concept of chronotherapeutics theorizes that administering an anti-hypertensive agent in the evening will result in a lowered incidence of next morning cardiovascular events. The verapamil products, Verelan PM and Covera HS, and the diltiazem product, Cardizem LA, are specifically labeled for administration at bedtime. While intriguing, the concept of chronotherapeutics has not been prospectively shown to improve outcomes.

Clinical Effectiveness Conclusion: The Committee concluded that (1) all eight CCBs have similar relative clinical effectiveness for treating hypertension; (2) there is insufficient evidence to conclude that verapamil, diltiazem, nifedipine, amlodipine,

nisoldipine, nicardipine, or isradipine is superior to another for reducing risk of cardiovascular outcomes in patients with hypertension, and that there is no evidence for felodipine; (3) there is no evidence of a difference in improving symptoms of angina with amlodipine, nifedipine, diltiazem, nisoldipine, nicardipine, or verapamil, and that there is no evidence for felodipine or isradipine; (4) amlodipine and felodipine do not adversely or positively affect mortality or morbidity in patients with systolic dysfunction; (5) there is insufficient evidence to clearly differentiate the CCBs on the basis of adverse events, and that the overall incidence of edema ranges between 8-10%, and (6) none of the CCBs should be designated as non-formulary on the UF based solely on the clinical evidence.

COMMITTEE ACTION: The Committee voted to accept the clinical effectiveness conclusions as stated above.

B. **Relative Cost Effectiveness*:***

1.) DHP CCBs

a.) DHP CCB Uniform Formulary Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of DHP CCBs in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but, was not limited to, sources of information listed in 32 C.F.R. 199.21(e)(2). From the preceding relative clinical effectiveness evaluation, the P&T Committee considered the clinical merits of the DHP CCBs with regard to:

- Clinical effectiveness in the treatment of hypertension and angina
- Clinical evidence for relative safety and tolerability
- Clinical outcome evidence supporting their effectiveness in heart failure
- Place in therapy (i.e., when do national guidelines recommend the use of these agents)

To determine the relative cost-effectiveness of the agents within the DHP calcium channel blocker therapeutic class, two separate economic analyses were performed: a cost-minimization analysis (CMA), and a budget impact analysis (BIA).

The cost used in the CMA was the total weighted average cost per day of treatment (for all three points of service). The results of the cost-minimization analysis revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included nifedipine immediate release (IR), nifedipine CC, felodipine, and nifedipine XL/ER, whereas the moderate cost cluster included amlodipine, nicardipine IR, and nisoldipine. Isradipine IR, isradipine controlled release

(CR), and nicardipine sustained release (SR) were included in the high cost cluster. Based on this use of cost-minimization to determine the relative cost-effectiveness of the agents within DHP calcium channel blocker therapeutic class, nifedipine immediate release, nifedipine CC/ER/XR, and felodipine were the most cost-effective agents.

The results of the CMA were subsequently incorporated into a budget impact analysis (BIA). A BIA accounts for other factors and costs associated with a potential decision to recommend that the status of one or more DHP CCBs be classified as non-formulary under the UF, 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 identify a group of DHP CCBs to be included on the UF which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA results revealed that a group of DHP CCBs that included nifedipine immediate release, nifedipine CC/ER/XR, felodipine, and nisoldipine best achieved this goal, when compared to other combination groups of DHP CCBs, and thus were determined to be more cost-effective relative to other combination groups.

2.) Verapamil

a.) Verapamil Uniform Formulary Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of verapamil agents in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 C.F.R. 199.21(e)(2). To determine the relative cost-effectiveness of the verapamil agents, two separate economic analyses were performed: a pharmacoeconomic analysis and a budget impact analysis (BIA). From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that verapamil agents have similar relative clinical effectiveness in the treatment of hypertension and angina, have similar safety and tolerability, but differ in their indications for night-time dosing. However, the Committee agreed that the night-time dosing indication was of minimal clinical importance as there was no literature evidence that night-time dosing has a positive benefit on clinical outcomes. Therefore, a cost-minimization analysis (CMA) was performed to stratify the agents solely on cost. The cost used in the analysis was the total weighted average cost per day of treatment (for all three points of service).

The results of the cost-minimization analysis revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included verapamil immediate release (IR) and verapamil sustained release (SR), whereas the moderate cost cluster included the Verelan brand of verapamil extended release capsules. Verelan PM and Covera HS, two long-acting, night-time dosed verapamil brands, represented the high cost cluster. Based on this use of cost-

minimization to determine the relative cost-effectiveness of the agents within the verapamil CCB therapeutic subclass, verapamil IR, and verapamil SR were the most cost-effective agents. The results of the CMA and CEA were subsequently incorporated into a budget impact analysis (BIA). A BIA accounts for other factors and costs associated with a potential decision to recommend that the status of one or more verapamil CCBs be changed from formulary to 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 identify a group of verapamil agents to be included on the UF, which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA results revealed that a group of verapamil agents that included verapamil IR and verapamil SR best achieved this goal when compared to other combination groups of verapamil agents, and thus were determined to be more cost-effective relative to other combination groups.

3.) Diltiazem

a.) Diltiazem Uniform Formulary Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of diltiazem agents in relation to safety, tolerability, effectiveness, and clinical outcomes to the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 C.F.R. 199.21(e)(2). To determine the relative cost-effectiveness of diltiazem agents, two separate economic analyses were performed: a pharmacoeconomic analysis and a budget impact analysis (BIA). From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that diltiazem agents have similar relative clinical effectiveness in the treatment of hypertension and angina, and similar safety and tolerability, but differ in their indications for night-time dosing. However, the Committee agreed that the night-time dosing indication was of minimal clinical importance as there was no literature evidence that night-time dosing has a positive benefit on clinical outcomes. Therefore, a cost-minimization analysis (CMA) was performed to stratify the agents solely on cost. The cost used in the analysis was the total weighted average cost per day of treatment (for all three points of service).

The results of the cost-minimization analysis (CMA) revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included diltiazem immediate release (IR), whereas the moderate cost cluster included diltiazem CD/XR/XT and diltiazem sustained release (SR). Diltiazem long acting (LA) represented the high cost cluster. The CMA showed that diltiazem IR, diltiazem CD/XR/XT, and diltiazem SR were the most cost-effective agents. The results of the CMA were subsequently incorporated into a budget impact analysis (BIA). A BIA accounts for other factors and costs associated with non-formulary decisions, 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 identify a group of diltiazem agents to be included on the UF which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA showed that the most cost-effective combination of diltiazem agents was diltiazem IR, diltiazem CD/XR/XT, and diltiazem SR.

COMMITTEE ACTION:

1.) DHP. The P&T Committee, based upon its collective professional judgment, voted to recommend that isradipine IR and CR, nicardipine IR and SR, and amlodipine be designated non-formulary, with nifedipine IR, nifedipine CC/XR/ER, felodpine, nimodipine and nisoldipine classified as formulary on the UF.

2.) Verapamil. The P&T Committee, based upon its collective professional judgment, voted to recommend formulary status for verapamil IR and verapamil SR, and non-formulary status for Verelan, Verelan PM and Covera HS.

3.) Diltiazem. The P&T Committee, based upon its collective professional judgment, voted to recommend formulary status for diltiazem IR and diltiazem CD/XR/XT, and non-formulary status for diltiazem LA..

C. **Implementation Plan***:* Because a substantial number of patients (268,000, or 73% of all patients receiving CCBs) are currently receiving CCBs recommended for non-formulary status, the P&T Committee recommended an effective date no later than the first Wednesday following a 150-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA

COMMITTEE ACTION: The Committee voted to recommend an implementation period of 150 days.

V. Calcium Channel Blockers Drug Class (cont.)

BAP Comments

A. **Relative Clinical Effectiveness***:* The P&T Committee's conclusion is stated in Section 4, paragraph A.

B. Relative Cost Effectiveness:

1.) DHP: The P&T Committee, based upon its collective professional judgment, voted to accept the DHP CCB cost-analysis presented by the PEC. The analysis concluded that isradipine IR and CR, and nicardipine IR and SR, and amlodipine were not cost-effective relative to the other DHP CCBs. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the DHP CCBs, and other relevant factors, the P&T Committee recommended that isradipine IR and CR, nicardipine IR and

SR, and amlodipine be classified as non-formulary, with nifedipine IR, nifedipine CC/XR/ER, felodpine, nimodipine, and nisoldipine classified as formulary on the UF.

2.) Verapamil: The P&T Committee, based upon its collective professional judgment, voted to accept the verapamil CCB cost-analysis presented by the PEC. The P&T Committee concluded that Verelan, Verelan PM, and Covera HS were not cost-effective relative to the other verapamil agents, as they were more costly and provided no additional clinically meaningful benefit over the most cost-effective agents. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the verapamil agents, and other relevant factors, the P&T Committee recommended that Verelan, Verelan PM and Covera HS be classified as non-formulary, and verapamil IR and verapamil SR be classified as formulary on the UF.

3.) Diltiazem: The P&T Committee, based upon its collective professional judgment, voted to accept the diltiazem cost-analysis presented by the PEC. The analysis concluded that diltiazem LA was not cost-effective relative to the other diltiazem agents, since it was more costly and provided no additional clinically-meaningful benefit over the most cost-effective agents. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the diltiazem agents, and other relevant factors, the P&T Committee recommended that diltiazem LA be classified as non-formulary, and diltiazem IR and diltiazem CD/XR/XT be classified as formulary on the UF.

C. **Uniform Formulary Recommendation:** Considering the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the calcium channel blockers, and other relevant factors, the P&T Committee recommended that:

1) DHP: Isradipine IR and CR, nicardipine IR and SR, and amlodipine be classified as non-formulary, with nifedipine IR, nifedipine CC/XR/ER, felodpine, nimodipine, and nisoldipine classified as formulary on the UF.

2) Verapamil: Verelan, Verelan PM and Covera HS be classified as non-formulary, and verapamil IR and verapamil SR be classified as formulary on the UF.

3) Diltiazem: diltiazem LA be classified as non-formulary, and diltiazem IR and diltiazem CD/XR/XT be classified as formulary on the UF.

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

D. Implementation Plan*:* The Committee voted to recommend an implementation period of 150 days.

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

VI. Alpha Blockers for Benign Prostatic Hypertrophy (BPH) Class Review

P&T Comments

A. **Relative Clinical Effectiveness***:* The P&T Committee evaluated the relative clinical effectiveness of alpha blockers FDA-approved for BPH: terazosin (Hytrin and various generics), doxazosin (Cardura and various generics), tamsulosin (Flomax) and alfuzosin (Uroxatral). First-generation (phenoxybenzamine) alpha-adrenergic antagonists have been replaced by second generation (terazosin, doxazosin) and third-generation (tamsulosin, alfuzosin) alpha blockers. The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including, but not limited to, sources of information listed in 32 C.F.R. 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

The P&T Committee agreed that in the Military Health System (MHS), alpha blockers are considered a gold standard for treating symptoms of benign prostatic hyperplasia (BPH). During a twelve-month period ending 30 April 2005, approximately 196,388 patients were prescribed an alpha blocker. This class is now ranked 25th in MHS drug class expenditures.

Efficacy: All alpha blockers are FDA-approved for the treatment of BPH. There are limited head-to-head trials comparing the four alpha blockers. The available placebo controlled trials, and meta-analyses were reviewed. Although all alpha blockers were found to be clinically effective when compared to placebo, variability in study design, demographics, and outcome measures precluded the ability to designate one alpha blocker as clinically superior. The Cochrane Database, Clinical Evidence, and the American Urological Association (evidence-based healthcare systematic reviews) concurred that all four alpha blockers are clinically interchangeable in regards to efficacy. In the tools used to measure effectiveness, all four drugs relieve BPH symptoms, improve standardized testing symptom scores, and improve urinary flow rates to the same extent. The alpha blockers appear to be similar in terms of clinical efficacy.

Safety/Tolerability: The P&T Committee found that the alpha blockers had similar safety data within their generation with respect to drug interactions, and adverse drug reactions. Adverse effects are primarily related to the agent's target receptor subtype (terazosin and doxazosin are nonselective; tamsulosin and alfuzosin are selective). As of August 2005, all agents have similar alpha-blocker postural hypotension warnings. Nonselective alpha blockers exhibit a higher rate of vasodilatory adverse effects (dizziness, asthenia, postural hypotension) relative to selective alpha blockers. Tamsulosin and alfuzosin appear to be better tolerated than terazosin and doxazosin as measured by withdrawals due to adverse events and discontinuation of therapy.

COMMITTEE ACTION: The P&T Committee voted that for the purposes of the UF clinical review, all alpha blockers have similar efficacy for treating BPH. All alpha blockers have similar safety and tolerability profiles within alpha blocker generations.

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

To determine the relative cost-effectiveness of the agents within the alpha blocker therapeutic class, two separate economic analyses were performed, a pharmacoeconomic analysis and a budget impact analysis (BIA). From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that alpha blockers have similar relative clinical effectiveness in the treatment of lower urinary tract symptoms often associated with benign prostatic hyperplasia, but differ in safety and tolerability, especially in comparison to non-selective alpha blockers with selective alpha blockers. The agents within the alpha blocker therapeutic class were thus shown to differ in relative clinical effectiveness.

First, a cost-minimization analysis (CMA) was performed to stratify the agents solely on cost. The results of the cost-minimization analysis revealed that non-selective alpha blockers were more cost-effective compared to non-selective alpha blockers, by nearly ten-fold based on the total weighted average cost per day of treatment (for all three points of service). Within the non-selective alpha blocker sub-class, doxazosin was found to be slightly more cost-effective compared to terazosin and within the selective alpha blocker sub-class alfuzosin was found to be considerably more cost-effective compared to tamsulosin (alfuzosin cost per day of treatment was 20% lower than tamsulosin's cost per day of treatment).

Given this conclusion, a cost-effectiveness analysis (CEA) was employed, which accounted for differences in safety and tolerability between the non-selective alpha blocker sub-class and the selective alpha blocker sub-class. In this type of analysis, agents within a therapeutic class are competed on two dimensions, cost and effect (outcomes). For this particular CEA, a Markov model was constructed based upon

the outcomes reported in the Medical Therapy of Prostatic Symptoms Study (MTOPS) for the doxazosin arm. The drug cost used in the analysis was the total weighted average cost per day of treatment (for all three points of service). Direct medical costs associated with disease clinical progression and treatment of adverse drug events were also incorporated into the model.

Two cost-effectiveness analyses were performed. In the first analysis, the effect (outcome) was defined as successfully treated patients. In the second analysis, the effect was defined as successfully treated patients without adverse drug events, more specifically, cardiovascular/ hypotensive adverse drug events associated with non-selective alpha blockers. The overall results from the first CEA paralleled the results obtained in the CMA: non-selective alpha blockers and selective alpha blockers were equally effective, non-selective alpha blockers were more cost-effective compared to selective alpha blockers, doxazosin was slightly more cost-effective compared to terazosin, and alfuzosin was considerably more cost-effective compared to tamsulosin. However, when the cost of adverse events associated with non-selective alpha blocker treatment was considered, the difference in cost per successfully treated patient between the non-selective and selective alpha blockers was two-fold, not ten-fold (as shown in the CMA). The results from the second CEA revealed selective alpha blockers were more effective (more patients successfully treated without adverse drug events), but more costly compared to non-selective alpha blockers. Although there was still approximately a two-fold difference in cost of treatment between the non-selective and selective alpha blockers, the incremental cost was less compared to the first CEA.

The results of the CMA and CEA were subsequently incorporated into a budget impact analysis (BIA). A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more alpha blockers 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 identify a group of alpha blockers to be included on the UF which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA results revealed that a group of alpha blockers that included alfuzosin, doxazosin, and terazosin best achieved this goal when compared to other combination groups of alpha blockers, and thus were determined to be more cost-effective relative to other combination groups.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to recommend formulary status for alfuzosin, doxazosin, and terazosin and non-formulary status for tamsulosin.

C. **Implementation Plan*:*** Because a number of patients are currently receiving tamsulosin from one of the three MHS pharmacy points of service (89,926 patients, 46% of all patients receiving alpha blockers), the P&T Committee proposed a 120-day transition period for implementation of the decision to classify tamsulosin as non-formulary.

COMMITTEE ACTION: The P&T Committee recommended an effective date no later than the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

VII. Alpha Blockers for Benign Prostatic Hypertrophy (BPH) Class Review (cont.)

BAP Comments

A. **Relative Clinical Effectiveness***:* The P&T Committee concluded that there is no compelling evidence to support clear superiority of one agent over another in terms of efficacy. All alpha blockers have been shown to have a positive effect on the symptoms of BPH. Selective alpha blockers appear to have a lower rate of adverse vasodilatory effects, a safety/tolerability advantage.

B. Relative Cost Effectiveness: The P&T Committee, based upon its collective professional judgment, voted to accept the BPH alpha-blocker cost-analysis presented by the PEC. The P&T Committee concluded that doxazosin and terazosin had similar relative cost-effectiveness in the non-selective alpha blocker subclass, but determined that tamsulosin was not cost-effective relative to alfuzosin in the selective alpha blocker sub-class.

C. Uniform Formulary Recommendation: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee recommended that tamsulosin be classified as non-formulary, and that alfuzosin, doxazosin, and terazosin be classified as formulary on the UF.

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

D. Implementation Plan*:* The P&T Committee recommended an effective date no later than the first Wednesday following a 120-day

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

VIII. PA REQUIREMENTS FOR PRAMLINTIDE (SYMLIN) INJECTION

Pramlintide, which is used with insulin to improve blood glucose control after meals, presents some unique concerns regarding appropriate patient selection, dosing, administration, potential for interaction with other medications, and required adjustment of insulin dosing due to the potential for severe hypoglycemia. Labeling for pramlintide includes specific recommendations for patient selection. Pramlintide should only be used by patients who have not reached their blood glucose goals despite managing their insulin therapy and diet well, monitoring blood glucose as directed, and following up with their providers on a regular basis. Patients using pramlintide must understand how to adjust pramlintide and insulin doses and be able to recognize hypoglycemia. Pramlintide is not indicated for use in pediatric patients.

COMMITTEE ACTION: Based on the need for careful patient selection to ensure safety and effectiveness, the P&T Committee recommended that a prior authorization be required for pramlintide. The Committee recommended that the PA should have an effective date no later than the first Wednesday following a 30-day implementation period. In order to avoid interruptions in therapy, which would require adjustments in insulin dosage, and potentially cause disruptions in blood glucose control for patients stabilized on therapy, the Committee further recommended that patients who received pramlintide from a DoD pharmacy point of service prior to the PA effective date should be allowed to continue to receive pramlintide. The implementation period will begin immediately following the approval by the Director, TMA.

IX. PA REQUIREMENTS FOR PRAMLINTIDE (SYMLIN) INJECTION (cont.)

BAP Comments

A. PA Criteria

Coverage is provided for the use of pramlintide as an adjunct treatment in type 1 and type 2 diabetic patients 18 or older who use mealtime insulin therapy and who meet all of the following criteria:

- are currently on insulin
- have an HbA1c ≤ 9%

- are monitoring blood glucose levels frequently (at least 3 or more times per day)
- have failed to achieve adequate control of blood glucose levels despite individualized management of their insulin therapy
- are receiving ongoing care under the guidance of a health care provider skilled in use of insulin and supported by the services of a diabetic educator

Coverage is not provided for patients who:

- have poor adherence to their current insulin regimen or blood glucose monitoring
- have a HbA1c >9%
- have experienced recurrent severe hypoglycemia requiring assistance within the past 6 months
- presence of hypoglycemia unawareness
- have a confirmed diagnosis of gastroparesis or require the use of drugs to stimulate gastrointestinal motility

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