19 August 2005

DECISION PAPER:

AUGUST 2005 DoD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

1. **CONVENING**
2. **ATTENDANCE**
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4. **INTERIM DECISIONS/ADMINISTRATIVE ISSUES**
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6. **REVIEW OF RECENTLY APPROVED AGENTS**

The Committee reviewed one new product in a class previously reviewed for Uniform Formulary (UF) status. Revatio is a new sildenafil product approved for the treatment of pulmonary arterial hypertension (also known as primary pulmonary hypertension). Unlike the other phosphodiesterase-5 inhibitor products (sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra)), Revatio is not approved for erectile dysfunction. Cialis and Viagra have been classified as non-formulary under the UF.

COMMITTEE ACTION: The DoD Pharmacy and Therapeutics (P&T) Committee voted (17 for, 0 against, 0 abstained, 0 absent) to recommend that Revatio be added to the UF (see paragraph 6 on page 10 of P&T Committee minutes for rationale).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

BW

Approved, but modified as follows:

7. **PRIOR AUTHORIZATION (PA) REQUIREMENT FOR PRAMLINTIDE (SYMLIN) INJECTION**

The Committee agreed that a PA was needed for pramlintide (Symlin) subcutaneous injection due to safety issues.

COMMITTEE ACTION: Based on the need for careful patient selection to ensure safety and effectiveness, the P&T Committee recommended (17 for, 0 against, 0 abstained, 0 absent) that PA be required for pramlintide (see paragraph 7 on pages 10 – 11 of P&T Committee minutes for rationale and summary of PA criteria).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

BW

Approved, but modified as follows:

COMMITTEE ACTION: The Committee recommended that the PA for pramlintide should have an effective date no later than the first Wednesday following a 30-day implementation period. In order to avoid interruptions in therapy, the Committee 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, TRICARE Management Activity (TMA).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

BW

Approved, but modified as follows:

8. ANGIOTENSIN CONVERTING ENZYME INHIBITOR (ACEI) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the ACEIs: 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), as well as their respective combinations with hydrochlorothiazide (HCTZ), if any. The ACEI class is in the top 10 of Military Health System (MHS) drug class expenditures at $75M annually.

A. COMMITTEE ACTION: The P&T Committee concluded (16 for, 0 against, 0 abstained, 1 absent) that all ACEIs are similar in terms of safety and tolerability profiles and in efficacy for hypertension. The P&T Committee recognized that there are differences in efficacy for myocardial infarction, heart failure, diabetic nephropathy and patients at high cardiovascular risk. These differences were incorporated into the cost-effectiveness analysis (CEA). The P&T Committee concluded that moexipril, perindopril, and quinapril were not cost-effective relative to the other ACEIs, since these agents were more costly and less effective. 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).

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the ACEIs, and other relevant factors, the P&T committee recommended (16 for, 0 against, 0 abstained, 1 absent) that moexipril, perindopril, quinapril, and ramipril (and their respective combinations with HCTZ, if any) be classified as non-formulary under the UF, with benazepril, captopril, enalapril, fosinopril, lisinopril, and trandolapril (and their respective combinations with HCTZ, if any) remaining on the UF (see paragraphs 8A and 8B on pages 11 –15 of P&T Committee minutes for rationale).

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows: The committee conducted a thorough review of the ACE Inhibitor class of medications. One agent, Altace, was very carefully assessed. It provides clinical value to a small subset of beneficiaries, based on clinical trial criteria – HOPE trial. Applying medical necessity criteria, any MHS beneficiaries who meet HOPE trial criteria, will receive Altace, even following this formulary decision.

B. COMMITTEE ACTION: Based on the clinical evaluations of moexipril, perindopril, quinapril, and ramipril, 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 against, 0 abstained, 2 absent) medical necessity criteria for moexipril, perindopril, quinapril, and ramipril (and their respective combinations with HCTZ, if any). See paragraph 8C on pages 15 – 16 of P&T Committee minutes for criteria.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

BW

Approved, but modified as follows:

C. COMMITTEE ACTION: Because a substantial number of patients are currently receiving ramipril, moexipril, perindopril, or quinapril, the P&T Committee recommended (16 for, 0 against, 0 abstained, 1 absent) 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 (see paragraph 8D on page 16 of P&T Committee minutes for rationale).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

BW

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (15 for, 0 against, 1 abstained, 1 absent) to recommend lisinopril, lisinopril/HCTZ, and captopril as the Basic Core Formulary (BCF) agents (see paragraph 8E on pages 16 – 17 of P&T Committee minutes for rationale).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

BW

Approved, but modified as follows:

9. CALCIUM CHANNEL BLOCKER (CCB) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the nine CCBs marketed in the U.S.: the dihydropyridines nifedipine (Procardia, Adalat CC, and various generics), nicardipine (Cardene and Cardene SR), isradipine (DynaCirc and DynaCirc SR), felodipine (Plendil and various generics), amlodipine (Norvasc), nisoldipine (Sular), and nimodipine (Nimotop); and the non-dihydropyridines diltiazem (Cardizem, Cardizem CD, Cardizem LA, Tiazac, and various generics) and verapamil (Verelan, Verelan PM, Covera HS, Calan, Calan SR, and various generics). (See Table 3, Appendix C for a full listing of the CCBs that were

evaluated.) CCBs have extensive use in all DoD pharmacy points of service and a rank of 9th ($121M) in terms of total MHS drug expenditures.

A. COMMITTEE ACTION: The P&T Committee concluded (16 for, 0 against, 0 abstained, 1 absent) that (1) all eight CCBs have similar relative clinical effectiveness for treating hypertension; (2) that there is insufficient evidence to conclude that any one of the following CCBs (verapamil, diltiazem, nifedipine, amlodipine, nisoldipine, nicardipine, or isradipine) is superior for reducing risk of cardiovascular outcomes in patients with hypertension, and that there is no evidence for felodipine; (3) that 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) that amlodipine and felodipine do not adversely or positively affect mortality or morbidity in patients with systolic dysfunction; (5) that 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 can be designated as non-formulary under the UF based solely on the clinical evidence.

The P&T concluded (17 for, 0 against, 0 abstained, 0 absent) that isradipine immediate release and isradipine controlled release, nicardipine immediate release and nicardipine sustained release, amlodipine, Verelan, Verelan PM, Covera HS, and Cardizem LA were not cost-effective compared to nifedipine immediate release, nifedipine extended release, felodipine, nisoldipine, verapamil immediate release, verapamil sustained release, diltiazem immediate release, diltiazem sustained release, and diltiazem extended release. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the CCBs, the P&T Committee voted (17 for, 0 against, 0 abstained, 0 absent) to recommend formulary status for nifedipine immediate release, nifedipine extended release, felodipine, nimodipine, nisoldipine, verapamil immediate release, verapamil sustained release, diltiazem immediate release, diltiazem sustained release, and diltiazem extended release, and non-formulary status for isradipine immediate release and isradipine controlled release, nicardipine immediate release and nicardipine sustained release, amlodipine, Verelan, Verelan PM, Covera HS, and Cardizem LA. Nifedipine immediate release and nimodipine are not therapeutic alternatives to the other CCBs, as they are not used for cardiovascular conditions (see paragraph 9A & B on pages 17 – 24 of P&T Committee minutes for rationale).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

BW

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of isradipine immediate release and isradipine controlled release, nicardipine immediate release and nicardipine sustained release, amlodipine, Verelan, Verelan PM, Covera HS, and Cardizem LA, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (17 for, 0 against, 0 abstained, 0 absent) medical necessity criteria for the isradipine immediate release and isradipine controlled release, nicardipine

immediate release and nicardipine sustained release, amlodipine, Verelan, Verelan PM, Covera HS, and Cardizem LA (see paragraph 9C on page 25 of P&T Committee minutes for criteria).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: BW

C. COMMITTEE ACTION: Because a substantial number of patients are currently using a CCB recommended for non-formulary status on the UF (268,00 patients, 73% of MHS patients receiving CCBs), the P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) 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 (see paragraph 9D on page 25 of P&T Committee minutes for rationale.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: BW

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing nifedipine extended release (vote: 17 for, 0 opposed, 0 abstained, 0 absent); verapamil sustained release (vote: 17 for, 0 opposed, 0 abstained, 0 absent), and diltiazem extended release (vote: 17 for, 0 opposed, 0 abstained, 0 absent) on the BCF. (See paragraph 9A and 9B on pages 17 – 24 of P&T Committee minutes for rationale.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: BW

10. ALPHA BLOCKERS FOR BENIGN PROSTATIC HYPERTROPHY (BPH) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the alpha blockers used to treat BPH. Four agents were considered in the review, and were classified as either selective or non-selective based upon the agent's target receptor subtype. The two non-selective agents considered in the review were doxazosin (Cardura and various generics) and terazosin (Hytrin and various generics). The two selective agents were alfuzosin (Uroxatral) and tamsulosin (Flomax). There has been an increase in the use of selective BPH alpha blockers over the past several years resulting in the entire class (selective and non-selective) being ranked 32nd in terms of annual MHS drug class expenditures at $38M.

A. COMMITTEE ACTION: The P&T Committee concluded (16 for, 0 against, 0 abstained, 1 absent) that none of the alpha blockers have a significant clinically meaningful therapeutic

advantage in terms of efficacy over other alpha blockers; however, the selective agents may have a marginal benefit over the non-selective agents with respect to safety and tolerability. Within subgroups, the two non-selective agents (doxazosin and terazosin) were found to be similar in terms of cost-effectiveness; however, tamsulosin was found not to be cost-effective relative to alfuzosin in the selective alpha blocker sub-class. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the BPH alpha blockers, and other relevant factors, the P&T Committee recommended (16 for, 0 against, 0 abstained, 1 absent) that tamsulosin be classified as non-formulary under the UF, and that doxazosin, terazosin, and alfuzosin be classified as formulary under the UF (see paragraphs 10A and 10B on pages 25 – 28 of P&T Committee minutes for rationale).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

BW

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of tamsulosin, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (16 for, 0 against, 0 abstained, 1 absent) medical necessity criteria for tamsulosin (see paragraph 10C on page 28 of P&T Committee minutes for criteria).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

BW

Approved, but modified as follows:

C. COMMITTEE ACTION: Because a substantial 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 recommended (16 for, 0 against, 0 abstained, 1 absent) 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 (see paragraph 10D on pages 28 – 29 of P&T Committee minutes for rationale).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

BW

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 against, 0 abstained, 1 absent) to recommend terazosin and alfuzosin as the BCF agents (see paragraph 10E on page 29 of P&T Committee minutes for rationale).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

BW

Approved, but modified as follows:

11. ANTIDEPRESSANTS (EXCLUDING MONOAMINE OXIDASE INHIBITORS AND TRICYCLIC ANTIDEPRESSANTS)

Portions of the clinical review were presented to the Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing an appropriate cost-effectiveness model. Both the clinical and economic analyses will be completed during the November 2005 meeting; no action necessary.

12. CHOLINESTERASE AND N-METHYL D-ASPARTATE (NMDA) INHIBITORS FOR ALZHEIMER'S DISEASE

Portions of the clinical review were presented to the Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing an appropriate cost-effectiveness model. Both the clinical and economic analyses will be completed during the November 2005 meeting; no action necessary.

APPENDIX A – TABLE 1: Implementation Status of UF Decisions

APPENDIX B – TABLE 2: Newly Approved Drugs

APPENDIX C – TABLE 3: Calcium Channel Blockers

APPENDIX D – TABLE 4: Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

William Winkenwerder, Jr.

William Winkenwerder, Jr., M.D.

Date: 13 October 2005

Department of Defense
Pharmacy and Therapeutics Committee Minutes

19 August 2005

1. CONVENING

The DoD Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 17, 18, and 19 August 2005 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
MAJ Travis Watson, MS, USA	Alternate, DoD Pharmacy Programs, TMA
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
Maj Nicholas Conger, MC	Air Force, Internal Medicine Physician
Lt Col Everett McAllister, BSC	Air Force, Pharmacy Officer
Lt Col Brian Crownover, MC	Air Force, Physician at Large
LCDR Roger Akins, MC	Navy, Pediatrics Physician
CDR Brian Alexander, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Joel Schmidt, MC	Army, Physician at Large
COL Isaiah Harper, MS	Army, Pharmacy Officer
CDR Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
LTC Donald DeGroff, MS, USA	Contracting Officer Representative, TMOP
CDR Jill Pettit, MSC, USN	Contracting Officer Representative, TRRx

B. Voting Members Absent

CDR William Blanche, MSC	Director, DoD Pharmacy Programs, TMA
LCDR Chris Hyun, MC	Navy, Internal Medicine Physician
Joe Canzolino	Department of Veterans Affairs

C. Non-Voting Members Present

Lynn T. Burleson	Assistant General Counsel, TMA
Martha Taft	Resource Management Directorate, TMA
Capt Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

COL Kent Maneval, MS, USA	Defense Medical Standardization Board

E. Others Present

Col Gregory Wickern, MC	Air Force, Alternate for Internal Medicine (present only 19 August)
Mr. Dan Remund	DoD Pharmacoeconomic Center (present only 17 August)
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
CAPT Donald Nichols, MC, USN	DoD Pharmacoeconomic Center
Lt Col David Bennett, BSC, USAF	DoD Pharmacoeconomic Center
Lt Col Barbara Roach, MC, USAF	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center (present 18 & 19 August)
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC , USA	DoD Pharmacoeconomic Center
CPT Ryan Young, USA	Reservist, Assigned to 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
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Francine Goodman	Department of Veterans Affairs

3. REVIEW MINUTES OF LAST MEETING

Dr. William Winkenwerder, Jr., M.D. approved the minutes of the May 2005 DoD P&T Committee on 14 July 2005.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

A. DoD P&T Committee Charter – CAPT Buss reported that the charter has been changed to provide for the following: Each voting member and non-voting member may have a designated alternate who can represent the member, including voting (if representing a voting member), at P&T Committee meetings in the event the member cannot attend.

5. ITEMS FOR INFORMATION

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

A. Beneficiary Advisory Panel (BAP) Briefing: TMA briefed the members of the DoD P&T committee regarding the 27 June 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: PEC staff and TMA briefed the members of the Committee on the implementation status of UF decisions arising from the February and May 2005 meetings (see Table 1, Appendix A). The Committee noted that the five drug classes reviewed at the February and May 2005 meetings represent 12% of total Military Health System (MHS) drug spend dollars. These five drug classes plus the four drug classes covered by existing pharmaceutical contracts represent 30% of all MHS drug spend dollars.

6. REVIEW OF RECENTLY-APPROVED AGENTS

The PEC presented clinical information on five new medications approved by the U.S. Food and Drug Administration (FDA), and introduced to the U.S. market since February 2005 (see Table 2, Appendix B). Four of the five medications fall into drug classes not yet reviewed by the DoD P&T Committee; therefore, UF consideration of these medications was deferred until drug class reviews are completed.

The fifth medication is a new sildenafil product that is FDA-approved for the treatment of pulmonary arterial hypertension (also known as primary pulmonary hypertension (PPH)) and marketed under the name of Revatio. Revatio is supplied as a 20-mg tablet, and must be given three times daily for the treatment of PPH; it is not approved for erectile dysfunction. Viagra, which is approved only for erectile dysfunction, is available in 25-, 50-, and 100-mg tablets. Viagra (sildenafil) and a similar medication, Cialis (tadalafil), are non-formulary under the UF.

Since the phosphodiesterase-5 (PDE-5) inhibitors were reviewed in May 2005, the Committee considered Revatio to be a newly-approved medication in a previously reviewed drug class. The Committee considered the following issues with regard to Revatio:

- Existing medical necessity criteria for Viagra allow reduction of the non-formulary cost share to the formulary cost share in patients with PPH.
- The clinical and cost effectiveness of Revatio relative to other medications used for the treatment of this rare, serious condition (e.g., eproprostenol, treprostinil, bosentan).

***COMMITTEE ACTION*:** The Committee voted (17 for, 0 against, 0 abstained, 0 absent) to recommend that Revatio be added to the UF. The Committee decided not to recommend a change in existing prior authorization (PA) criteria for Viagra to preclude its use for PPH, since some patients may be stabilized on Viagra.

The Committee noted that PA requirements previously established for the PDE-5 inhibitor drug class apply to Revatio. A PA is required for all patients receiving sildenafil (Revatio or Viagra) for PPH.

Since all patients receiving Revatio must meet PA requirements, the Committee did not recommend a specific quantity limit for Revatio. Quantity limits for Cialis, Levitra, and Viagra for the treatment of erectile dysfunction (combined limit of 6 units per 30 days, or 18 per 90 days) continue to apply at all DoD points of service.

7. PA REQUIREMENTS FOR PRAMLINTIDE (SYMLIN) INJECTION

At the May 2005 meeting, the Committee discussed the potential need for a PA requirement for pramlintide (Symlin) subcutaneous injection, and requested that the PEC develop PA criteria to be reviewed at the next meeting. Pramlintide, which is used with insulin by diabetic patients 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 PA be required for pramlintide (17 for, 0 against, 0 abstained, 0 absent). 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.

The Committee agreed that the following PA criteria should apply (17 for, 0 against, 0 abstained, 0 absent). PA approvals would be valid indefinitely.

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 a glycosylated hemoglobin (HbA1c) $\leq 9\%$
- 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
- have experienced the presence of hypoglycemia unawareness
- have a confirmed diagnosis of gastroparesis or require the use of drugs to stimulate gastrointestinal motility

8. ANGIOTENSIN CONVERTING ENZYME INHIBITOR (ACEI) DRUG CLASS REVIEW

A. ACEI UF Relative Clinical Effectiveness: The Committee evaluated the relative clinical effectiveness of the ten ACEIs marketed in the U.S.: 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 the safety, effectiveness, and clinical outcome of these drugs was considered. The clinical review included, but was not limited to the requirements stated in the UF Rule, 32 CFR 199.21.

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 (MI), 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.

   Conclusion: The DoD P&T Committee concluded that there is no evidence that any ACEI is associated with a lower risk of serious complications than any other ACEI.

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

   Conclusion: The Committee agreed that there is no evidence that any one ACEI is more efficacious than the others for lowering blood pressure.

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, MI, 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 MI, 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 percutaneous transluminal coronary angioplasty.

   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.

Conclusion: The Committee agreed that in patients with high cardiovascular risk, ramipril 10 mg is the only ACEI reported to have shown a reduction in both mortality and cardiovascular events, based on the HOPE trial. Perindopril 8 mg (EUROPA), and simvastatin have shown a reduction in major cardiovascular events, but not mortality in patients with coronary artery disease. A large trial with trandolapril did not show a reduction in major cardiovascular events, but the use of appropriate background medications was high. Quinapril has also not shown a benefit in reducing cardiovascular events.

4) *Recent 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.

   Conclusion: In patients following an MI, a mortality benefit has been documented with captopril, lisinopril, ramipril, and trandolapril.

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 College of Cardiology (ACC) and American Heart Association (AHA) 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.

   Conclusion: In patients with chronic heart failure, the best evidence for a mortality benefit has been documented with captopril, enalapril, lisinopril, ramipril, and trandolapril.

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.

   Conclusion: For type 1 diabetic nephropathy, captopril reduced the risk of end stage renal disease and death in poorly controlled patients. Enalapril, lisinopril, ramipril, and perindopril reduce microalbuminuria, but have not been shown to reduce the risk of end stage renal disease in type 1 diabetes mellitus (DM). For type 2 diabetic nephropathy, no ACEI has shown a benefit on clinical outcomes. Lisinopril, enalapril, quinapril, ramipril

and trandolapril appear beneficial based on various surrogate markers of renal disease, but have not been shown to impact clinical outcomes in type 2 DM. In patients with non-diabetic nephropathy, benazepril, ramipril, enalapril, captopril, and enalapril have shown a reduction in clinical outcomes.

7) *Prevention of DM:* 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 DM.

   Conclusion: Post-hoc studies with enalapril, captopril, and ramipril have shown a delay or prevention of DM, but this has not been proven in a prospectively designed trial.

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

B. ACEI UF 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 CFR 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 MI, heart failure, type 1 DM mellitus, type 2 DM 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 CMA 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 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.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) 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). 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.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend that moexipril, perindopril, quinapril, and ramipril (and their respective combinations with HCTZ, if any) be classified as non-formulary under the UF, with benazepril, captopril, enalapril, fosinopril, lisinopril, and trandolapril (and their respective combinations with HCTZ, if any) remaining on the UF.

C. ACEI UF Medical Necessity Criteria: Based on the clinical evaluation of the ACE inhibitors and the conditions for establishing medical necessity for a non-formulary medication provided

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

1.) Use of the formulary ACEIs (lisinopril, enalapril, captopril, benazepril, fosinopril, and trandolapril) is contraindicated, and the use of a nonformulary ACEI (ramipril, moexipril, quinapril, or perindopril) is not contraindicated.

2). The patient has experienced or is likely to experience significant adverse effects from the formulary ACEIs, and the patient is reasonably expected to tolerate a non-formulary ACEI.

3) Use of the formulary ACEI resulted in therapeutic failure, and the patient is reasonably expected to respond to a non-formulary ACEI, i.e., therapeutic failure as outlined on medical necessity form.

4) The patient has previously responded to a non-formulary ACEI, and changing to a formulary ACEI would incur unacceptable risk.

5) There is no alternative pharmaceutical agent on the formulary.

The Committee noted that criteria 4 and 5 would reasonably apply only to a small subset of patients receiving ACEIs, such as patients at high cardiovascular risk similar to those included in the HOPE trial.

COMMITTEE ACTION: The Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the ACEI medical necessity criteria.

D. ACEI UF 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 (16 for, 0 opposed, 0 abstained, 1 absent) to recommend an implementation period of 120 days.

E. ACE Inhibitor Basic Core Formulary (BCF) Review and Recommendations: The P&T Committee reviewed the ACEIs recommended for inclusion on the UF to select the BCF ACEIs. It had previously been decided that at least two, but no more than three ACEIs, would be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

There are currently two ACEIs on the BCF: captopril and lisinopril. From a clinical and economic standpoint, captopril and lisinopril are rational selections for the BCF. Lisinopril is the highest utilized ACEI in the entire MHS (military treatment facility (MTF), TRICARE Retail Pharmacy (TRRx) program, and TRICARE Mail Order Pharmacy (TMOP)), has a wide range of FDA indications, is generically available, and has mortality data for heart failure and following MI. Captopril has a wide range of FDA indications, has mortality data for heart failure and following MI, has outcomes evidence in type 1 diabetic renal disease, is generically available, and has a short half-life which is good for titrating patients in the immediate post-MI setting and in frail patients.

Since no BCF prices were submitted for any of the ACEIs, the DoD P&T Committee evaluated the relative cost-effectiveness for BCF selection based on the cost-effectiveness information provided for the UF formulary recommendation. Both the CMA and CEA revealed that

captopril was the most cost-effective ACEI and for this reason should be maintained on the BCF. The CEA showed that lisinopril is a very cost-effective agent, and it currently has a 68% market share at the MTFs.

Additionally, there was discussion regarding addition of an ACEI in combination with HCTZ to the BCF. There currently is no designated BCF ACEI/HCTZ combination, and it was noted that some facilities have seen a shift toward an angiotensin receptor blocker (ARB)/HCTZ combination. Addition of lisinopril in combination with HCTZ is lower in cost than other ACEIs combined with HCTZ, and may offer a convenience benefit to patients.

Conclusion: The P&T Committee concurred with the recommendation to place lisinopril, lisinopril in combination with HCTZ, and captopril on the BCF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to recommend lisinopril, lisinopril in combination with HCTZ, and captopril as the BCF agents.

9. CALCIUM CHANNEL BLOCKER (CCB) DRUG CLASS REVIEW

A. CCB UF Relative Clinical Effectiveness: The Committee evaluated the relative clinical effectiveness of the nine CCBs marketed in the U.S.: the dihydropyridines (DHPs) nifedipine (Procardia, Adalat CC, and various generics), nicardipine (Cardene and Cardene SR), isradipine (DynaCirc and DynaCirc SR), felodipine (Plendil and various generics), amlodipine (Norvasc), nisoldipine (Sular), and nimodipine (Nimotop); and the non-dihydropyridines diltiazem (Cardizem, Cardizem SR, Cardizem CD, Cardizem LA, Tiazac, and various generics) and verapamil (Verelan, Verelan PM, Covera HS, Calan, Calan SR, and various generics). (See Table 3, Appendix C for a full listing of the CCBs that were evaluated.) 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 UF 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 DM).

Efficacy of CCB vs CCB: 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, MI, or development of end-stage renal disease.

Efficacy of CCB vs Other Antihypertensive Agents: Sixteen large trials assessing clinical outcomes (mortality, stroke, MI, development of end-stage renal disease) have been conducted with all the CCBs, except felodipine versus other anti-hypertensive agents, including diuretics, beta blockers, ACEIs, and 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).

Conclusion: The DoD P&T Committee concluded that, for lowering blood pressure, there is no evidence that any one CCB is more effective relative to another. There is insufficient evidence to conclude that any one CCB (amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, or verapamil) is superior to another for reducing risk of cardiovascular outcomes in patients with hypertension. There is no evidence for felodipine when used as a monotherapy for reducing cardiovascular outcomes in patients with hypertension.

2) *Efficacy for Chronic Stable Angina*:

Place in Therapy: The 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 CCB for Chronic Stable Angina: There are five head-to-head trials enrolling fewer than 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.

Conclusion: The Committee agreed that there is no evidence to conclude that there is any difference in efficacy of amlodipine, nifedipine, diltiazem, nisoldipine, nicardipine, or verapamil in improving angina symptoms. There is no evidence for felodipine or isradipine in head-to-head trials with other CCBs.

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.

Conclusion: Based on the clinical evidence, the Committee agreed that when used in patients with heart failure, amlodipine or felodipine do not adversely affect outcomes.

4) *Safety and Tolerability:* In general, the safety profile of an individual CCB reflects its pharmacologic class. The 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 CCB vs CCB 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.

   Conclusion: The DoD P&T Committee agreed that there is insufficient evidence to clearly differentiate the CCBs on the basis of adverse events. The most common adverse events are dizziness, peripheral edema, headache, and flushing.

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 (for conditions other than cardiovascular disease) in DoD. This product will not be discussed further in the clinical review.

   Chronotherapeutics: A higher incidence of cardiovascular events (stroke, MI) 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.

Conclusion: The Committee agreed that there are differences amongst the CCBs in terms of other factors as discussed above.

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

B. CCB UF Relative Cost Effectiveness:

1) DHP CCBs

a) DHP CCB UF 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 CFR 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 CMA, and a 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 CMA revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included nifedipine immediate release, nifedipine extended release, and felodipine, whereas the moderate cost cluster included amlodipine, nicardipine immediate release, and nisoldipine. Isradipine immediate release, isradipine controlled release, and nicardipine sustained release 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 extended release, and felodipine were the most cost-effective agents.

The results of the CMA were subsequently incorporated into a 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 extended release, 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.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to accept the DHP CCB cost-analysis presented by the PEC. The analysis concluded that isradipine immediate release, isradipine controlled release, nicardipine immediate release, nicardipine sustained release, 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 immediate release, isradipine controlled release, nicardipine immediate release, nicardipine sustained release, and amlodipine be classified as non-formulary under the UF, with nifedipine immediate release, nifedipine extended release, felodpine, nimodipine, and nisoldipine classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend that that isradipine immediate release, isradipine controlled release, nicardipine immediate release, nicardipine sustained release, and amlodipine be classified as non-formulary under the UF, with nifedipine immediate release, nifedipine extended release, felodpine, nimodipine and nisoldipine classified as formulary on the UF. Nifedipine immediate release and nimodipine are not therapeutic alternatives to the other CCBs, as they are not used for cardiovascular conditions.

b) DHP CCBs BCF Review and Recommendations: The P&T Committee reviewed the DHP CCBs recommended for inclusion on the UF to select the BCF DHP CCBs. It had previously been decided that one DHP calcium channel blocker could be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

Currently the only DHP calcium channel blocker on the BCF is nifedipine extended release (Adalat CC or equivalent). From a clinical and cost-effective standpoint, this remains a rational selection for the BCF. MTFs continue to enjoy a good price for this agent, and the VA is expected to complete a sole-source generic contract for a nifedipine extended release product in the next few months. BCF prices were submitted for amlodipine and nisoldipine. However, the BIA revealed that neither was competitive, and that nifedipine CC was the most cost-effective DHP calcium channel blocker, and for this reason should be maintained on the BCF. MTFs can add additional DHP CCBs from the UF to their local formularies if needed to meet the needs of their specific patient populations.

Conclusion: The P&T Committee concurred with the recommendation to place nifedipine extended release on the BCF. As the CC formulation is currently the most cost-effective choice, the BCF listing will state that MTFs are required to carry the CC formulation of nifedipine extended release, until a new DoD/VA sole source contract for nifedipine extended release is completed.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend nifedipine extended release as the BCF agent.

2) Verapamil

a) Verapamil UF 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 CFR 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 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 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 CMA revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included verapamil immediate release and verapamil sustained release, 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. Within the verapamil CCB therapeutic subclass, verapamil immediate release and verapamil sustained release were the most cost-effective agents. The results of the CMA and CEA were subsequently incorporated into a 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 immediate release and verapamil sustained release 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.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) 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 under the UF, and verapamil immediate release and verapamil sustained release be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend formulary status for verapamil immediate release and verapamil sustained release, and non-formulary status for Verelan, Verelan PM and Covera HS on the UF.

b) Verapamil BCF Review and Recommendations: The P&T Committee reviewed the verapamil agents recommended for inclusion on the UF to select the BCF verapamil agent. It had previously been decided that one verapamil agent would be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

Verapamil sustained release is currently on the BCF. From a clinical and economic standpoint, this remains a rational selection for the BCF. MTFs continue to enjoy a good price for this agent, which represents the majority of verapamil use in the MHS. Verapamil sustained release is currently the most cost-effective long acting verapamil agent. For this reason, it should be maintained on the BCF. MTFs may add verapamil immediate release to their local formularies if needed to meet the needs of their specific patient populations.

Conclusion: The P&T Committee concluded that verapamil sustained release should remain on the BCF.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend retaining verapamil sustained release as the BCF agent.

3) Diltiazem

a) Diltiazem UF 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 CFR 199.21(e)(2). To determine the relative cost-effectiveness of diltiazem agents, two separate economic analyses were performed: a pharmacoeconomic analysis and a 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 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 CMA revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included diltiazem immediate release, whereas the moderate cost cluster included diltiazem extended release and diltiazem sustained release. Cardizem LA represented the high cost cluster. The CMA

showed that diltiazem immediate release, diltiazem extended release, and diltiazem sustained release were the most cost-effective agents. The results of the CMA were subsequently incorporated into a 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 immediate release, diltiazem extended release, and diltiazem sustained releae.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to accept the diltiazem cost-analysis presented by the PEC. The analysis concluded that Cardizem 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 Cardizem LA be classified as non-formulary under the UF Formulary, and diltiazem immediate release, diltiazem sustained release, and diltiazem extended release be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend formulary status for diltiazem immediate release, diltiazem sustained release, and diltiazem extended release, and non-formulary status for Cardizem LA under the UF.

b) Diltiazem BCF Review and Recommendations: The P&T Committee reviewed the diltiazem agents recommended for inclusion on the UF to select the BCF diltiazem agent. It had previously been decided that one diltiazem agent would be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

Diltiazem extended release is currently on the BCF. From a clinical and economic standpoint, this remains a rational selection for the BCF. The MTFs continue to enjoy a good price for this agent, and 97% of usage in the DoD MHS is for the diltiazem extended release product. The Tiazac brand of diltiazem extended release is currently the most cost-effective diltiazem extended release agent and should be selected for the BCF. MTFs may add additional diltiazem agents from the UF to their local formularies, if needed to meet the needs of their specific patient populations.

Conclusion: The P&T Committee concurred with the recommendation to place diltiazem extended release on the BCF. As the Tiazac formulation is currently the most cost-effective choice, the BCF listing will state that MTFs are required to carry the Tiazac formulation of extended release diltiazem.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend diltiazem extended release as the BCF agent.

C. CCB UF Medical Necessity Criteria: Based on the clinical evaluation of the CCBs and the conditions for establishing medical necessity for a non-formulary medication provided for in

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

1) Use of the formulary CCBs (nifedipine immediate release, nifedipine extended release, felodipine, nimodipine, nisoldipine, verapamil immediate release, verapamil sustained release, diltiazem immediate release, diltiazem sustained release and diltiazem extended release is contraindicated, and the use of non-formulary CCBs (isradipine immediate release, isradipine controlled release, nicardipine immediate release, nicardipine sustained release, amlodipine, Verelan, Verelan PM, Covera HS, and Cardizem LA) is not contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from the formulary CCBs, and the patient is reasonably expected to tolerate a non-formulary CCB.

3) Use of the formulary CCBs resulted in therapeutic failure, and the patient is reasonably expected to respond to a non-formulary CCB [therapeutic failure as outlined on medical necessity form].

4) The patient has previously responded to a non-formulary CCB, and changing to a formulary CCB would incur unacceptable risk.

5) There is no alternative pharmaceutical agent on the formulary.

The Committee noted that criteria 4 and 5 would reasonably apply only to a small subset of patients receiving CCBs, such as patients with NYHA Class III or IV heart failure similar to those in the V-HeFT and PRAISE trials or clinically fragile patients with angina and multiple comorbidities who are stable on amlodipine. The Committee also noted that amlodipine is the only long-acting DHP CCB approved by the FDA for pediatric patients. The Committee recommended that medical necessity be automatically approved for patients younger than 18 years of age, if this is technically feasible (i.e., if the Pharmacy Data Transaction Service can be programmed to permit scripts for beneficiaries age <18 years to be filled without medical necessity being established).

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to approve the medical necessity criteria.

D. CCB UF 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 (16 for, 0 opposed, 0 abstained, 1 absent) to recommend an implementation period of 150 days.

10. ALPHA BLOCKERS FOR BENIGN PROSTATIC HYPERTROPHY (BPH) DRUG CLASS REVIEW

A. Alpha Blocker UF 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), alfuzosin (Uroxatral) and tamsulosin (Flomax). 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 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

The P&T Committee agreed that in the MHS, alpha blockers are considered a gold standard for treating symptoms of 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; alfuzosin and tamsulosin 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. Alfuzosin and tamsulosin appear to be better tolerated than terazosin and doxazosin as measured by withdrawals due to adverse events and discontinuation of therapy.

Conclusion: 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.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) 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. Alpha Blocker 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 CFR 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 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 BPH, 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 CMA was performed to stratify the agents on cost. The results of the CMA 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 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 CEAs 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 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.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 1 absent) 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. 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 under the UF, and that doxazosin, terazosin, and alfuzosin be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 1 absent) to recommend formulary status for doxazosin, terazosin, and alfuzosin, and non-formulary status for tamsulosin under the UF.

C. Alpha Blocker UF Medical Necessity Criteria: Based on the clinical evaluation of the alpha blockers and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee concluded that the following general medical necessity criteria would apply for these agents:

1) Use of a formulary alpha blocker (terazosin, doxazosin, alfuzosin) is contraindicated, and the use of a nonformulary alpha blocker (tamsulosin) is not contraindicated.

2) The patient has experienced or is likely to experience significant adverse effects from a formulary alpha blocker, and the patient is reasonably expected to tolerate a non-formulary alpha blocker.

3) Use of the formulary alpha blocker resulted in therapeutic failure, and the patient is reasonably expected to respond to a non-formulary alpha blocker [therapeutic failure as outlined on medical necessity form].

Because the UF would include both selective and nonselective agents, the Committee agreed that the situations covered by general criterion 4 (changing to a formulary agent would incur unacceptable risk) and general criterion 5 (no alternative pharmaceutical agent on the formulary) would not apply in this category. The Committee also noted it would be reasonable for a patient who experienced adverse effects (e.g., dizziness, postural hypotension) on terazosin or doxazosin, and who could not be treated with alfuzosin, to meet medical necessity requirements for tamsulosin without requiring that the patient fail or be unable to take both formulary non-selective agents.

D. Alpha Blocker UF 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 under the UF.

COMMITTEE ACTION: The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) 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.

E. Alpha-Blocker Basic Core Formulary (BCF) Review and Recommendations: The P&T Committee reviewed the alpha blockers recommended for inclusion on the UF to select the BCF alpha blockers. It had previously been decided that at least one, but no more than two alpha blockers, would be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

Terazosin is currently the only alpha blocker on the BCF, has a current MTF market share of 63%, and, when properly titrated, is safe and effective in the majority of patients requiring treatment for BPH. Although marginally less costly, doxazosin has a much lower MTF market share and offers no clinical advantage compared to terazosin.

There are three arguments supporting placement of alfuzosin on the BCF:

1) Provides increased access to a selective alpha blocker for MTF patients who cannot tolerate a non-selective alpha blocker, or in whom a non-selective alpha blocker is contraindicated due to co-morbid conditions
2) The CEA suggests the difference in the cost of treatment between selective alpha blocker and non-selective alpha blocker is not ten-fold (total weighed average cost per day of treatment at all three points of service), but closer to two-fold when the costs of non-selective alpha blocker adverse drug events are considered.
3) Based on the total weighted average cost per day of treatment for MTFs, alfuzosin is 43% less costly than tamsulosin.

The primary disadvantage of adding a selective alpha blocker to the BCF is that it would require those MTFs who currently do not have a selective alpha blocker on their formulary to add alfuzosin, and thus increase MTF pharmacy expenditures. However, utilization of selective alpha blockers is increasing at MTFs, and adding alfuzosin now would reduce the unit cost for a selective alpha blocker.

Conclusion: The P&T Committee recommended placing alfuzosin and terazosin on the BCF.

COMMITTEE ACTION: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to recommend alfuzosin and terazosin as the BCF agents.

11. ANTIDEPRESSANTS (EXCLUDING MONOAMINE OXIDASE INHIBITORS AND TRICYCLIC ANTIDEPRESSANTS)

PEC staff presented a clinical review of the antidepressant medications listed below to the Committee. Although the receptor-binding characteristics and pharmacological classification of these medications vary, the Committee agreed that there is sufficient overlap in their clinical use to review them as a single class of medications.

- *Selective Serotonin Reuptake Inhibitors (SSRIs)* - citalopram, escitalopram (Lexapro), fluoxetine, fluvoxamine, paroxetine, and sertraline (Zoloft)
- *Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)* - venlafaxine (Effexor, Effexor XR), duloxetine (Cymbalta)
- *Norepinephrine Dopamine Reuptake Inhibitors (NDRIs)* - bupropion
- *Alpha-2 antagonists* - mirtazapine
- *Serotonin modulators* – nefazodone, trazodone

Seven of these medications are currently on the BCF: the SSRIs citalopram, fluoxetine (excludes Sarafem, Prozac Weekly), paroxetine (excludes Paxil CR), and sertraline; the SNRI venlafaxine sustained release (Effexor XR); the NDRI bupropion sustained release (excludes Wellbutrin XL); and the serotonin modulator trazodone.

The Committee provided expert opinion regarding the key questions in this drug class and clinical outcomes of importance for the purpose of developing an appropriate cost effectiveness model. Both the clinical and cost effectiveness analyses will be completed during the November 2005 meeting; no action necessary.

12. CHOLINESTERASE AND N-METHYL D-ASPARTATE (NMDA) INHIBITORS FOR ALZHEIMER'S DISEASE

PEC staff presented a clinical review of the cholinesterase and NMDA inhibitors used for the treatment of Alzheimer's disease. The agents in this class include: tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne, formerly Reminyl), and memantine (Namenda). The current BCF agent for this class is donepezil.

The Committee provided expert opinion regarding the key questions in this drug class and clinical outcomes of importance for the purpose of developing an appropriate cost-effectiveness model. Both the clinical and cost-effectiveness analyses will be completed during the November 2005 meeting; no action necessary.

13. ADJOURNMENT

The third day of the meeting adjourned at 1230 hours on August 18, 2005. The dates of the next meeting are November 16–18, 2005.

Patricia Buss

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

List of Appendices

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Appendix A – Table 1: Implementation Status of UF Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Non-Formulary Decision	BCF/ECF
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: MTFs may add vardenafil to formulary based on local needs
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: MTFs must have nystatin and clotrimazole topical products on formulary.
May 05	MS-DMDs	-	ECF	Interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-	ECF selection effective 14 Jul 05: MTFs must have Avonex on formulary if local needs necessitate having medications in this class on formulary.
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: MTFs must have telmisartan and telmisartan/HCTZ on formulary.
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: MTFs must have omeprazole and rabeprazole on formulary.

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; MN = Medical Necessity; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; ARBs = Angiotensin Receptor Blockers; PPIs = Proton Pump Inhibitors; HCTZ = hydrochlorothiazide

*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

Medication & Mechanism of Action	FDA Approval Date; FDA-Approved Indications	Committee Recommendation
Sildenafil (Revatio; Pfizer)	6 Jun 2005; treatment of pulmonary arterial hypertension (WHO group I) to improve exercise capacity. Efficacy has not been evaluated in patients currently on bosentan therapy. Pulmonary arterial hypertension is also known as primary pulmonary hypertension.	UF Drug Class: PDE-5 Inhibitors Committee Recommendation: Add to the UF Note: Prior authorization (PA) requirements previously established for the PDE-5 inhibitor class apply to Revatio. Since all patients receiving Revatio must meet PA requirements, the Committee did not recommend a specific quantity limit.
Exenatide injection (Byetta; Amylin)	28 Apr 2005; adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but have not achieved adequate glycemic control.	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Isosorbide dinitrate / hydralazine tabs (BiDil; Nitromed)	23 Jun 2005; treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status.	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Bromfenac ophthalmic solution 0.09% (Xibrom; ISTA)	24 Mar 2005; indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Paracalcitol caps (Zemplar; Abbott) Synthetically manufactured analog of calcitriol, the metabolically active form of Vitamin D	26 May 2005; prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 3 and 4. [The injectable formulation is approved for patients requiring dialysis (stage 5).]	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.

Appendix C – Table 3: Calcium Channel Blocker Brand and Generic Names

Generic Name	Brand (Manufacturer)	Generic products available
Dihydropyridines (DHPs)		
Amlodipine	***Norvasc*** (Pfizer)	**No**
Felodipine	Plendil (AstraZeneca)	Yes
Isradipine	***DynaCirc*** [immediate release formulation] (Reliant) ***DynaCirc CR*** (Reliant) [Gastrointestinal Therapeutic System (GITS)]	**No** **No**
Nicardipine	Cardene [immediate release formulation] (Roche) ***Cardene SR*** (Roche) [granules/powder mix]	Yes **No**
Nifedipine	**Immediate Release*** Procardia (Pfizer) **Extended Release** Adalat CC (Bayer); Afeditab CR (Watson); Nifediac CC (Teva); [core coat] Procardia XL (Pfizer); Nifedical XL (Teva) [GITS]	 Yes Yes Yes
Nimodipine	Nimotop*	No
Nisoldipine	***Sular*** (First Horizon) [core coat]	**No**
Non-dihydropyridines (non-DHPs): Verapamil products		
Verapamil	**Immediate Release** Isoptin (FSC); Calan (Searle) **Sustained Release** Calan SR; Isoptin SR (Par) **Extended Release** ***Verelan*** (Elan) **Extended Release for bedtime dosing** ***Verelan PM*** (Elan) ***Covera HS*** (Searle)	 Yes, to Isoptin Yes to Isoptin SR **No** **No** **No**
Non-dihydropyridines (non-DHPs): Diltiazem products		
Diltiazem	**Immediate Release** Cardizem (Kos) **Sustained Release** Diltiazem HCL (Cardizem SR) **Extended Release** Cardizem CD (Biovail) Dilacor XR (Watson); Diltia XT (Andrx) Cardizem CD; Cartia XT (Andrx) Tiazac (Biovail), Taztia XT (Andrx) Tiazac (Forest, Inwood) **Extended Release for bedtime dosing** ***Cardizem LA*** (Kos)	 Yes Yes Yes, except 360 mg does not have generics Yes Yes Yes Yes, except 420 mg does not have generics **No**

***Nifedipine immediate release and nimodipine are not therapeutic alternatives to the other calcium channel blockers, as they are not used for cardiovascular conditions.**

Appendix D – Table 4: Table of Abbreviations

ACC	American College of Cardiology
ACEI	angiotensin converting enzyme inhibitor
AHA	American Heart Association
ARB	angiotensin receptor blocker
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BPH	benign prostatic hypertrophy
CCB	calcium channel blocker
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CMA	cost-minimization analysis
DHP	Defense Health Program
DM	diabetes mellitus
DoD	Department of Defense
FDA	Food and Drug Administration
HbA1c	hemoglobin A1c (glycosylated hemoglobin)
HCTZ	hydrochlorothiazide
MHS	Military Health System
MI	myocardial infarction
MTF	military treatment facility
NDRI	norepinephrine dopamine reuptake inhibitor
NYHA	New York Heart Association
P&T	Pharmacy and Therapeutics
PA	prior authorization
PDE-5	phosphodiesterase-5
PEC	Pharmacoeconomic Center
PPH	primary pulmonary hypertension
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Pharmacy
UF	Uniform Formulary
VA	Veterans Administration