

17 November 2005

DECISION PAPER:**NOVEMBER 2005 DoD PHARMACY AND THERAPEUTICS COMMITTEE
RECOMMENDATIONS****1. CONVENING****2. ATTENDANCE****3. REVIEW MINUTES OF LAST MEETING**

A. Corrections to the minutes: Four committee vote counts were incorrectly recorded in the minutes of August 2005 DoD Pharmacy and Therapeutics (P&T) meeting. Corrections are as follows:

- 1) Item 8a: *The P&T Committee concluded that all ACEIs are similar in terms of safety and tolerability profiles and in efficacy for hypertension.* The recorded vote of: (16 for, 0 against, 0 abstained, 1 absent) CORRECTED TO: (15 for, 0 against, 1 abstained, 1 absent)
- 2) Item 9a: *The P&T Committee voted to accept the clinical effectiveness conclusions presented for the calcium channel blocker class.* The recorded vote of: (16 for, 0 against, 0 abstained, 1 absent) CORRECTED TO: (14 for, 2 against, 0 abstained, 1 absent)
- 3) Item 9b: *The P&T Committee voted to accept the cost effectiveness conclusions presented for the calcium channel blocker class.* The recorded vote of: (17 for, 0 against, 0 abstained, 0 absent) CORRECTED TO: (14 for, 2 against, 0 abstained, 1 absent)
- 4) Item 9c: *The P&T Committee voted to accept the medical necessity criteria for the calcium channel blocker class.* The recorded vote of: (16 for, 0 against, 0 abstained, 1 absent) CORRECTED TO: (14 for, 2 against, 0 abstained, 1 absent)

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES**5. ITEMS FOR INFORMATION****6. REVIEW OF RECENTLY APPROVED AGENTS**

The P&T Committee was briefed on six new agents that had been approved by the FDA, of which five have been introduced to the U.S. market since the August 2005 meeting. None of the medications fall into drug classes already reviewed by the P&T Committee, therefore Uniform Formulary (UF) consideration was deferred until the corresponding drug class reviews are completed. The Committee did review one new drug for quantity limits.

Mometasone furoate oral inhaler is a new corticosteroid for asthma that has a unique deliver device (Asmanex Twisthaler 220 mcg). The device delivers 200 mcg per actuation, and is available in several sizes providing 14 inhalations (for institutional use), 30 inhalations, 60 inhalations (for patients requiring 1 dose/day) or 120 inhalations (for patients requiring more than 1 dose/day). There are quantity limits for the other inhaled corticosteroids; therefore, quantity limits for Asmanex Twisthaler are recommended.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to recommend that mometasone furoate oral inhaler 220 mcg (Asmanex Twisthaler) have

quantity limits of 120 inhalations per 30-days (retail pharmacy network), or 360 inhalations per 90-days (TRICARE Mail Order Pharmacy (TMOP)), consistent with the limits imposed with other inhaled corticosteroids (see paragraph 6 on page 14 of P&T Committee minutes for rationale and summary of PA criteria).

Director, TMA, Decision: Approved Disapproved

Approved, but modified as follows:

7. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR MECASERMIN (INCRELEX) INJECTION

The Committee agreed that a PA was needed for mecasermin (Increlex) subcutaneous injection due to potential confusion with other growth products and misuse potential.

COMMITTEE ACTION: Based on the need for careful patient selection to ensure safety and effectiveness, the P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) that PA be required for mecasermin (see paragraph 7 on pages 14 – 15 of P&T Committee minutes for rationale and summary of PA criteria).

Director, TMA, Decision: Approved Disapproved

Approved, but modified as follows:

COMMITTEE ACTION: The Committee recommended (17 for, 0 against, 1 abstained, 1 absent) that the PA for mecasermin should have an effective date no later than the first Wednesday following a 30-day implementation period. The implementation period will begin immediately following the approval by the Director, TRICARE Management Activity (TMA) (see paragraph 7 on page 15 of P&T Committee minutes).

Director, TMA, Decision: Approved Disapproved

Approved, but modified as follows:

8. QUANTITY LIMITS

A. Etanercept (Enbrel) – Etanercept was initially approved as a 25 mg twice-weekly injection for the treatment of RA and was available only as a 25-mg vial in sealed packages containing 4 vials (2 weeks supply for RA, psoriatic arthritis, or ankylosing spondylitis or 1-2 weeks supply for psoriasis). Dosing recommendations for etanercept have changed to allow weekly dosing for all indications, and etanercept recently became available as a 50 mg/mL pre-filled syringe, which is now the preferred method of dosing. The current days supply limit of a 4-week supply in retail, a 6-week supply in the TMOP program, and up to a 6-week supply at military treatment facilities (MTFs) (based on instructions for use on the prescription) is

problematic for the 50 mg/mL pre-filled syringes, which are supplied in sealed packages containing 4 syringes.

The Committee agreed that, given the cost of etanercept and the existence of similar quantity limits for other biologics for the treatment of RA and/or psoriasis, a day's supply limit should be retained, but adjusted to 8 weeks supply in mail order and MTFs to allow for dispensing of whole packages.

COMMITTEE ACTION. The Committee voted (16 for, 0 opposed, 2 abstained, 1 absent) to recommend changing the quantity limits for etanercept (Enbrel) subcutaneous injection to a four-week supply in retail, an eight-week supply in the TMOP program, and up to an eight-week supply at MTFs, based on instructions for use on the prescription (see paragraph 8A on pages 15 – 16 of P&T Committee minutes for rationale and summary of quantity limits).

Director, TMA, Decision:

Approved Disapproved

Approved, but modified as follows:

B. Zolmitriptan (Zomig) – The current quantity limit for zolmitriptan tablets and orally disintegrating tablets (Zomig, Zomig-ZMT) is 8 tablets per 30 days or 24 tablets per 90 days. Currently, zolmitriptan tablets are available in blister packs of 3 or 6 tablets. The current quantity limit for zolmitriptan nasal spray, which is packaged in boxes of 6 unit-dose nasal spray units, is 12 unit-doses per 30 days or 36 unit-doses per 90 days. The Committee agreed that the quantity unit for zolmitriptan tablets should be increased to be consistent with the quantity limit for the nasal spray and to allow for dispensing of whole packages of zolmitriptan tablets.

COMMITTEE ACTION. The Committee voted (16 for, 1 opposed, 1 abstained, 1 absent) to recommend changing the quantity limit for zolmitriptan tablets and orally disintegrating tablets (Zomig, Zomig-ZMT) to 12 tablets per 30 days or 36 tablets per 90 days (see paragraph 8B on page 16 of P&T Committee minutes for rationale and summary of quantity limits).

Director, TMA, Decision:

Approved Disapproved

Approved, but modified as follows:

9. ALZHEIMER'S DRUG CLASS REVIEW. ACETYLCHOLINESTERASE INHIBITOR AND N-METHYL D-ASPARTATE (NMDA) RECEPTOR ANTAGONIST

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the acetylcholinesterase inhibitors donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne), and tacrine (Cognex), and the NMDA receptor antagonist memantine (Namenda) used to treat the cognitive symptoms of Alzheimer's disease. Together these drugs account for approximately \$65M annually in Military Health System (MHS) drug class expenditures.

A. COMMITTEE ACTION: The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) that for the purposes of the UF clinical review, with the exception of tacrine, none of the acetylcholinesterase inhibitors have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other acetylcholinesterase inhibitors; and that memantine has a place in therapy due to its indication for treatment of dementia in moderate to severe Alzheimer's disease. The P&T Committee agreed that among the acetylcholinesterase inhibitors, tacrine differed significantly in terms of safety due to its potential to cause hepatic injury.

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the acetylcholinesterase inhibitors and memantine, and other relevant factors, the P&T committee recommended (10 for, 6 against, 2 abstained, 1 absent) that tacrine be classified as non-formulary under the UF, with memantine, donepezil, rivastigmine, and galantamine remaining on the UF (see paragraphs 9A – B on pages 16 – 20 of P&T Committee minutes for rationale).

Director, TMA, Decision:

Approved Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluation of tacrine 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, 1 abstained, 1 absent) medical necessity criteria for tacrine. (See paragraph 9C on page 20 of P&T Committee minutes for criteria).

Director, TMA, Decision:

Approved Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 9D on page 20 of P&T Committee minutes for rationale).

Director, TMA, Decision:

Approved Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to recommend donepezil as the Extended Core Formulary agent (see paragraph 9E on pages 20 – 21 of P&T Committee minutes for rationale).

Director, TMA, Decision:

Approved Disapproved

Approved, but modified as follows:

10. NASAL CORTICOSTEROIDS FOR ALLERGIC RHINITIS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the nasal corticosteroids used to treat allergic rhinitis. Six agents were considered in the review, beclomethasone dipropionate (Beconase AQ, Vancenase AQ, and Vancenase AQ DS), budesonide (Rhinocort AQ), flunisolide (Nasarel), fluticasone propionate (Flonase), mometasone furoate (Nasonex), and triamcinolone acetonide (Nasacort AQ). The nasal corticosteroids rank in the top 20 in terms of MHS drug class expenditures at \$60.2M annually.

A. COMMITTEE ACTION: The P&T Committee concluded (17 for, 0 against, 1 abstained, 1 absent) that no one nasal corticosteroid has a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other nasal corticosteroids.

The cost analysis showed that flunisolide, fluticasone propionate, and mometasone furoate are more cost effective than the other nasal corticosteroids. The budget impact analysis also concluded that flunisolide, fluticasone propionate, and mometasone furoate represent the best value to DoD.

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the nasal corticosteroids, and other relevant factors, the P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent), that beclomethasone dipropionate (Beconase AQ, Vancenase AQ, Vancenase AQ DS), budesonide (Rhinocort AQ), and triamcinolone acetonide (Nasacort AQ) be classified as non-formulary under the UF, and that flunisolide (Nasarel), fluticasone propionate (Flonase), and mometasone furoate (Nasonex) be classified as formulary under the UF (see paragraphs 10A – B on pages 21 – 25 of P&T Committee minutes for rationale).

Director, TMA, Decision:

Approved Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of beclomethasone dipropionate, budesonide, and triamcinolone acetonide 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, 1 abstained, 1 absent) medical necessity criteria

for the nasal corticosteroids. (See paragraph 10C on page 25 of P&T Committee minutes for criteria).

Director, TMA, Decision: Approved Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Due to the relatively low number of patients that will be affected by this formulary action, the P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 10D on page 25 of P&T Committee minutes for rationale).

Director, TMA, Decision: Approved Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to recommend fluticasone propionate as the Basic Core Formulary (BCF) agent (see paragraph 10E on page 25 of P&T Committee minutes for rationale).

Director, TMA, Decision: Approved Disapproved

Approved, but modified as follows:

11. ANTIDEPRESSANTS GROUP 1 (AD1) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the antidepressant medications, with the exception of the monoamine oxidase inhibitors and tricyclic antidepressants. The AD1s accounted for \$290 million in MHS expenditures in FY05. Individual agents in the AD1 drug class are listed below.

- *Selective Serotonin Reuptake Inhibitors (SSRIs)* – citalopram (generics, Celexa); escitalopram (Lexapro); fluoxetine (generics, Prozac); fluoxetine 90-mg delayed release capsules (Prozac Weekly); fluoxetine in special packaging for the treatment of premenstrual dysphoric disorder (PMDD) (Sarafem); fluvoxamine (generics); paroxetine immediate release (generics, Paxil, Pexeva); paroxetine controlled release (Paxil CR); and sertraline (Zoloft)
- *Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)* - venlafaxine (Effexor, Effexor XR); duloxetine (Cymbalta)

- *Norepinephrine Dopamine Reuptake Inhibitors (NDRIs)* - bupropion immediate and sustained release (generics, Wellbutrin, Wellbutrin SR); bupropion extended release (Wellbutrin XL)
- *Alpha-2 antagonists* – mirtazapine (generics, Remeron)
- *Serotonin modulators* – nefazodone (generics); trazodone (generics, Desyrel)

A. COMMITTEE ACTION: The P&T Committee concluded (17 for, 0 against, 1 abstained, 1 absent) that: 1) the AD1s offer similar efficacy in treating major depressive disorder (MDD) with the exception of limited data supporting slightly greater efficacy with venlafaxine compared to the SSRIs and with escitalopram compared to citalopram; 2) FDA approval of fluoxetine for MDD in children, and broad usefulness of paroxetine and sertraline in psychiatric conditions other than MDD were considered clinical advantages; 3) with the exception of venlafaxine, where nausea is a greater problem, there are little data to support a substantial difference among AD1s with respect to patient tolerability; however, adverse effect profiles do differ across AD1s; 4) bupropion, mirtazapine, nefazodone, and trazodone appear to have a lower risk of sexual dysfunction compared with SSRIs and SNRIs; 5) fluvoxamine, fluoxetine, paroxetine and duloxetine have a higher potential for drug interactions than citalopram, escitalopram, sertraline, and venlafaxine; 6) the likelihood of discontinuation syndrome with the SSRIs corresponds with half-life (shortest half-life = greatest risk). fluvoxamine > paroxetine > sertraline > escitalopram > citalopram > fluoxetine, and venlafaxine may be associated with more discontinuation symptoms than SSRIs; while discontinuation symptoms appear rare with bupropion; 7) rare but serious adverse effects are associated with duloxetine (recent case reports of hepatotoxicity), bupropion (seizure), nefazodone (hepatotoxicity), mirtazapine (agranulocytosis), and trazodone (priapism); and 8) drugs of concern in specific patient populations include duloxetine (hepatic insufficiency, substantial alcohol use, liver disease, narrow angle glaucoma), paroxetine (recent epidemiological evidence of increased risk in pregnancy), and bupropion (avoid in patients with increased seizure risk).

Relative Cost Effectiveness Analysis: Differences in efficacy, safety, and tolerability among the AD1s were incorporated into two separate cost effectiveness analyses (CEAs). The first CEA was based on the results obtained via a multi-attribute utility theory (MAUT) analysis, which included differences between agents in clinical outcome, evidence and/or FDA-approved indications supporting use for psychiatric and non-psychiatric conditions other than MDD, such as generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), diabetic peripheral neuropathic pain (DPNP), as well as usefulness in the pediatric population, and safety/tolerability factors such as risk of drug interactions, use in pregnancy, contraindications, potential for rare but serious adverse events, and risk of sexual dysfunction. The second CEA (CEA-Response) was based on findings reported in the DoD Pharmacoeconomic Center's clinical review and the Oregon Health & Science University's Drug Class Review on Second Generation Antidepressants as part of the Drug Effectiveness Review Project. This CEA assessed the costs and outcomes of treatment for MDD during the acute phase of treatment.

Based on the results of the two analyses, the P&T Committee concluded (17 for, 0 against, 1 abstained, 1 absent) that: 1) fluoxetine 90-mg delayed release capsules (Prozac Weekly) and fluoxetine in special packaging for treatment of PMDD (Sarafem) were greater than seven-fold more costly, and had similar relative clinical effectiveness compared to generic fluoxetine; 2)

sertraline had equal (CEA-Response) or slightly greater (CEA-MAUT) relative clinical effectiveness, but was significantly more costly compared to fluoxetine (however, sertraline is projected to go generic in June 2006); 3) escitalopram was shown to have lower overall relative clinical effectiveness (CEA-MAUT) compared to fluoxetine, but potentially greater relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to citalopram; however, at a significantly greater cost; 4) the CEA-MAUT and CEA-Response both showed that paroxetine and paroxetine CR had similar relative clinical effectiveness, but paroxetine CR was significantly more costly compared to paroxetine; 5) venlafaxine was shown to have greater overall relative clinical effectiveness (CEA-MAUT) and greater relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to duloxetine for a similar cost; and 6) bupropion XL was shown to have greater overall relative clinical effectiveness (CEA-MAUT) but similar relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to bupropion SR at a significantly greater cost.

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the antidepressants, and other relevant factors, the P&T Committee recommended (12 for, 5 against, 1 abstained, 1 absent) that escitalopram (Lexapro), fluoxetine 90-mg delayed release capsules (Prozac Weekly), fluoxetine in special packaging for PMDD (Sarafem), paroxetine controlled release (Paxil CR), duloxetine (Cymbalta), and bupropion extended release (Wellbutrin XL) be classified as non-formulary under the UF, with citalopram, fluoxetine, fluvoxamine, paroxetine immediate release, sertraline, venlafaxine, venlafaxine extended release, nefazodone, trazodone, bupropion immediate and sustained release, and mirtazapine remaining on the UF. In addition, the P&T Committee recommended that existing quantity limits for fluoxetine 90-mg delayed release capsules (Prozac Weekly) of 4 capsules per 30 days, 12 capsules per 90 days be continued. (See paragraphs 11 A – B on pages 26 – 40 of the P&T Committee minutes for criteria).

Director, TMA, Decision:

Approved Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluation of the AD1s 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, 1 abstained, 2 absent) medical necessity criteria for escitalopram (Lexapro), fluoxetine 90-mg delayed release capsules (Prozac Weekly), fluoxetine in special packaging for PMDD (Sarafem), paroxetine controlled release (Paxil CR), duloxetine (Cymbalta), and bupropion extended release (Wellbutrin XL). (See paragraph 11C on pages 40 – 41 of P&T Committee minutes for rationale).

Director, TMA, Decision:

Approved Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Because a substantial number of patients are currently receiving non-formulary AD1s, and the need to carefully assess and monitor patients taking this class of medication, the P&T Committee recommended (16 for, 0 against, 1 abstained, 2 absent) an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 11D on page 41 of P&T Committee minutes for rationale).

Director, TMA, Decision: Approved Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to recommend fluoxetine (excluding Prozac Weekly and Sarafem, which are non-formulary), citalopram, sertraline, trazodone, and bupropion sustained release as the BCF agents (see paragraph 11E on pages 41 – 42 of P&T Committee minutes for rationale).

Director, TMA, Decision: Approved Disapproved

Approved, but modified as follows:

12. ORAL MACROLIDE/KETOLIDE DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the macrolide/ketolide class of antibiotics. All forms of oral erythromycin (salts and base) were considered in addition to the oral forms of azithromycin, clarithromycin, and telithromycin. Zmax, a 2-gram extended release suspension form of azithromycin was also considered, but was evaluated separately from the other forms of azithromycin. The macrolide/ketolide class of antibiotics ranks 31st in terms of MHS drug class expenditures at \$40.7M annually.

A. COMMITTEE ACTION: The P&T Committee concluded (17 for, 0 against, 1 abstained, 1 absent) that although the macrolide/ketolide agents have significant overlapping antimicrobial activity within the class and with agents in other antibiotic classes, there are some minor differences in terms of safety, effectiveness, and clinical outcomes between the agents. Advantages of a good safety profile, ease of dosing, provider acceptability, and generic availability made azithromycin stand out as a preferred agent in this class. Erythromycin also stood out as a preferred agent in this class due to its many FDA indications, safety, generic availability and familiarity among providers.

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the macrolide/ketolide class of antibiotics, and other relevant factors, the P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) that Zmax and telithromycin be classified as non-formulary under the UF, with all oral forms of azithromycin (except Zmax), all forms of clarithromycin, and all oral forms of erythromycin

remaining on the UF (see paragraphs 12 A – B on pages 42 – 48 of P&T Committee minutes for rationale).

Director, TMA, Decision: Approved Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of telithromycin and the Zmax formulation of azithromycin 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, 1 abstained, 1 absent) medical necessity criteria for Zmax and telithromycin (see paragraph 12C on pages 48 – 49 of P&T Committee minutes for criteria).

Director, TMA, Decision: Approved Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Because of the acute nature of this class of medications and the relatively low number of beneficiaries that would be affected by this formulary action, the P&T Committee recommended (16 for, 1 against, 1 abstained, 1 absent) an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 12D on page 49 of P&T Committee minutes for rationale).

Director, TMA, Decision: Approved Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to recommend azithromycin 250mg tablets and at least one form of oral erythromycin base or salt (with selection left to each MTF) as the BCF agents (see paragraph 12E on page 49 of P&T Committee minutes for rationale).

Director, TMA, Decision: Approved Disapproved

Approved, but modified as follows:

13. ANTI-MUSCARINIC OVERACTIVE BLADDER MEDICATIONS

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 February 2006 meeting; no action necessary.

APPENDIX A – TABLE 1. Implementation Status of UF Decisions

APPENDIX B – TABLE 2. Newly Approved Drugs

APPENDIX C – TABLE 3. Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

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William Winkenwerder, Jr., M.D.

Date: January 19, 2005

Department of Defense Pharmacy and Therapeutics Committee Minutes

17 November 2005

1. CONVENING

The DoD Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 15 November 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
CDR Bill Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Maj Nicholas Conger, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Maj Charlene Reith, BSC	Air Force, Pharmacy Officer
LCDR Chris Hyun, MC	Navy, Internal Medicine Physician
LCDR Scott 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
LTC Peter Bulatao, MS	Army, Pharmacy Officer
CDR Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
CDR Jill Pettit, MSC, USN	Contracting Officer Representative, TRRx
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

LTC Don DeGroff, MS	Contracting Officer Representative, TMOP
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C. Non-Voting Members Present

Lynn T. Burselson	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
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E. Others Present

Col Nancy Misel, BSC, USAF Reserve	IMA DoD Pharmacoeconomic Center
Lt Col David Bennett, BSC, USAF	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC , USA	DoD Pharmacoeconomic Center
CPT Ryan Young, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Dan Remund	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
David Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Julie Liss	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Dave Flowers	DoD Pharmacoeconomic Center
David Meade	DoD Pharmacoeconomic Center
Harsha Mistry	DoD Pharmacoeconomic Center
Debbie Khachikian	Department of Veterans Affairs

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the minutes – Four committee vote counts were incorrectly recorded in the minutes of the August 2005 DoD P&T meeting. Corrections are as follows:

- 1) Item 8a. *The P&T Committee concluded that all ACEIs are similar in terms of safety and tolerability profiles and in efficacy for hypertension.* The recorded vote of: (16 for, 0 against, 0 abstained, 1 absent) CORRECTED TO: (15 for, 0 against, 1 abstained, 1 absent)
- 2) Item 9a: *The P&T Committee voted to accept the clinical effectiveness conclusions presented for the calcium channel blocker class.* The recorded vote of: (16 for, 0 against, 0 abstained, 1 absent) CORRECTED TO: (14 for, 2 against, 0 abstained, 1 absent)
- 3) Item 9b: *The P&T Committee voted to accept the cost effectiveness conclusions presented for the calcium channel blocker class.* The recorded vote of: (17 for, 0 against, 0 abstained, 0 absent) CORRECTED TO: (14 for, 2 against, 0 abstained, 1 absent)
- 4) Item 9c: *The P&T Committee voted to accept the medical necessity criteria for the calcium channel blocker class.* The recorded vote of: (16 for, 0 against, 0 abstained, 1 absent) CORRECTED TO: (14 for, 2 against, 0 abstained, 1 absent)

B. August minutes approval – Dr. William Winkenwerder, Jr., M.D. approved the minutes of the August 2005 DoD P&T Committee on 13 October 2005.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

A. CAPT Buss reported TRICARE Management Activity (TMA) funds in support of travel and lodging for DoD P&T members to attend quarterly meetings have been approved.

5. ITEMS FOR INFORMATION

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

- A. Beneficiary Advisory Panel (BAP) Briefing:** LtCol Bennett briefed the members of the DoD P&T committee regarding the 28 September 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, May and August 2005 meetings (see Table 1, Appendix A). The Committee noted that the five drug classes reviewed at the 2005 February and May meetings represent 17% of total Military Health System (MHS) drug spend dollars. These five drug classes plus the four drug classes covered by existing pharmaceutical contracts represent 35% of all MHS drug spend dollars.

6. REVIEW OF RECENTLY-APPROVED AGENTS

The PEC presented clinical information on six new medications approved by the U.S. Food and Drug Administration (FDA). All of the products have been introduced to the U.S. market, with the exception of mecasermin injection (Increlex). (See Table 2, Appendix B). All six medications fall into drug classes not yet reviewed by the DoD P&T Committee; therefore, UF consideration of these products was deferred until drug class reviews are completed.

One of the medications, mometasone furoate oral inhaler (Asmanex Twisthaler), is included as a part of the inhaled corticosteroids drug class, for which there are existing quantity limits. Asmanex Twisthaler provides 200 mcg of mometasone furoate per inhalation, and is available in several sizes, including 14 inhalations (for institutional use), 30 inhalations, 60 inhalations (for patients requiring 1 dose/day) or 120 inhalations (for patients requiring more than 1 dose/day).

COMMITTEE ACTION: The DoD Pharmacy and Therapeutics (P&T) Committee voted (17 for, 0 against, 1 abstained, 1 absent) to recommend that mometasone furoate oral inhaler 220 mcg (Asmanex Twisthaler) have quantity limits of 120 inhalations per 30-days (TRICARE Retail Pharmacy (TRRx) Network), or 360 inhalations per 90-days (TRICARE Mail Order Pharmacy (TMOP) program), consistent with the limits imposed with other inhaled corticosteroids.

7. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR MECASERMIN (INCRELEX) INJECTION

Mecasermin is used for the long-term treatment of growth failure in children with severe primary insulin-like growth factor (IGF)-1 deficiency (primary IGFD) or with growth hormone (GH) gene deletion that have developed neutralizing antibodies to GH. Severe primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; these patients are not GH deficient, and therefore cannot be expected to respond adequately to exogenous GH treatment. Mecasermin presents some unique concerns regarding appropriate patient selection, dosing, administration, potential for misuse, and monitoring for possible low blood glucose levels (hypoglycemia), because it has insulin-like hypoglycemic effects. Labeling for mecasermin includes specific recommendations for patient selection. Mecasermin should only be used by patients who have the clinical diagnosis of

severe Primary IGFD and are receiving care from appropriate providers (e.g., pediatric endocrinologist/ nephrologist) on a regular basis. Patients using mecasermin must understand how to adjust mecasermin, and be able to recognize hypoglycemia. Mecasermin is not indicated for use in patients with closed epiphyses (bone growth plates).

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 mecasermin (17 for, 0 against, 1 abstained, 1 absent). The Committee recommended that the PA should have an effective date no later than the first Wednesday following a 30-day implementation period. 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, 1 abstained, 1 absent). PA approvals would be valid for one year.

Coverage is provided for the use of mecasermin as treatment in severe Primary IGFD and in patients who meet all of the following criteria:

- Height standard deviation score ≤ -3 and
- Basal IGF-1 standard deviation score ≤ -3 and
- Normal or elevated GH
- Are receiving ongoing care under the guidance of a health care provider skilled in the diagnosis and management of patients with growth disorders.
- Thyroid and nutritional deficiencies corrected before initiating mecasermin treatment.
- Have been educated on monitoring and management of hypoglycemia.

Coverage is not provided for patients who:

- Have closed epiphyses (bone growth plates are closed).
- Have active or suspected neoplasia (therapy should be discontinued if evidence of neoplasia develops).
- Have other cases of growth failure (secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids).

8. QUANTITY LIMITS

A. Etanercept (Enbrel) – Currently, etanercept (Enbrel) subcutaneous injection is limited to a 4-week supply in retail, a 6-week supply in the TMOP, and up to a 6-week supply at military treatment facilities (MTFs), based on instructions for use on the prescription. No multiple fills for multiple co-pays are allowed in TRRx and TMOP. The purpose of the quantity limit is to decrease potential wastage and excess cost if etanercept is prematurely discontinued.

The current recommended dose of etanercept for adult patients with rheumatoid arthritis (RA), psoriatic arthritis, or ankylosing spondylitis is 50 mg per week; for adult patients with psoriasis 50 mg twice weekly for 3 months, followed by 50 mg weekly as a maintenance dose; and for pediatric patients with juvenile rheumatoid arthritis 0.8 mg/kg weekly, up to a maximum of 50 mg per week. Etanercept was initially approved as a 25 mg twice-weekly injection for the treatment of RA and was available only as a 25-mg vial in sealed packages containing 4 vials (2 weeks supply for RA or 1-2 weeks supply for psoriasis). It recently became available as a 50 mg/mL pre-filled syringe, which is now the preferred method of dosing. The pre-filled syringes are packaged in sealed packages containing 4 syringes, causing difficulty in dispensing a 6-week supply.

The Committee agreed that, given the cost of etanercept and the existence of similar quantity limits for other biologics for the treatment of RA and/or psoriasis, a quantity limit should be retained, but adjusted to an 8-week supply in mail order and MTFs to allow for dispensing of whole packages.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 2 abstained, 1 absent) to recommend changing the quantity limits for etanercept (Enbrel) subcutaneous injection to a 4-week supply in retail, an 8-week supply in the TMOP program, and up to an 8-week supply at MTFs, based on instructions for use on the prescription.

B. Zolmitriptan (Zomig) – The current quantity limit for zolmitriptan tablets and orally disintegrating tablets (Zomig, Zomig-ZMT) is 8 tablets per 30 days, or 24 tablets per 90 days. Based on safety recommendations in triptan labeling, the safety of treating more than 4 migraine attacks in a 30-day period has not been established. Doses of both the tablets and nasal spray can be repeated after two hours if the first dose is ineffective.

Currently, zolmitriptan tablets are available in blister packs of 3 or 6 tablets. Zolmitriptan is also available as a nasal spray, packaged in boxes of 6 unit-dose nasal spray units. The current quantity limit for zolmitriptan nasal spray is 12 unit-doses per 30 days or 36 unit-doses per 90 days.

The Committee agreed that the quantity unit for zolmitriptan tablets should be increased to be consistent with the quantity limit for the nasal spray and to allow for dispensing of whole packages of zolmitriptan tablets.

COMMITTEE ACTION: The Committee voted (16 for, 1 opposed, 1 abstained, 1 absent) to recommend changing the quantity limit for zolmitriptan tablets and orally disintegrating tablets (Zomig, Zomig-ZMT) to 12 tablets per 30 days, or 36 tablets per 90 days.

9. ALZHEIMER'S DRUG CLASS REVIEW. ACETYLCHOLINESTERASE INHIBITORS AND N-METHYL D-ASPARTATE (NMDA) RECEPTOR ANTAGONISTS

A. Alzheimer's Medications Relative Clinical Effectiveness Review: The P&T Committee evaluated the relative clinical effectiveness of all the FDA-approved acetylcholinesterase inhibitors and NMDA receptor antagonists available in the U.S. for the treatment of Alzheimer's disease. The Alzheimer's disease therapeutic class was defined as the acetyl-cholinesterase inhibitors: donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne) and tacrine (Cognex); and the NMDA receptor antagonist memantine (Namenda). The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 C.F.R. 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

During a twelve month period ending July 31, 2005, 69,940 MHS patients were prescribed an acetylcholinesterase inhibitor or NMDA receptor antagonist. This class is now ranked 29th in MHS drug class expenditures at a cost of \$65 million annually.

1.) *Efficacy.* All acetylcholinesterase inhibitors have FDA-approved indications for the treatment of mild to moderate Alzheimer's disease. The NMDA receptor antagonist

memantine is FDA approved for moderate to severe Alzheimer's disease. As there are no well-designed head-to-head trials comparing the four acetylcholinesterase inhibitors or memantine, the available placebo controlled trials and meta-analyses were reviewed.

Endpoints: Outcome measures used to assess the beneficial effects of the medications used in the treatment of Alzheimer's disease measure functioning in four categories which include cognitive function, global assessment, activities of daily living and behavioral disturbance. The two most consistent outcome measures used in randomized, controlled trials evaluate cognitive function (Alzheimer's Disease Assessment Scale, ADAS-Cog) and global assessment (Clinician's Interview Based Assessment of Change-Plus, CIBIC-Plus). The ADAS is an 11-item scale with scores ranging from 0 (no impairment) to 70 (very severe impairment). On average, untreated patients with moderate AD decline 7 to 11 points per year while treated patients with mild or severe disease decline 0 to 5 points per year. Generally, an improvement of 4 or more points is considered to be clinically meaningful, roughly equivalent to a six-month delay in cognitive decline. In clinical trials, improvement is characterized by a slowing of deterioration as opposed to improvement above baseline.

Mild to moderate Alzheimer's disease: The acetylcholinesterase inhibitors have been studied in mild to moderate Alzheimer's disease. Outcome measures included the ADAS-Cog and the CIBIC-plus. In well-designed, randomized, controlled trials involving donepezil vs. placebo, rivastigmine vs. placebo, galantamine vs. placebo, and tacrine vs. placebo, all of the acetylcholinesterase inhibitors showed statistically significant differences in the primary outcome measures compared to placebo. Systematic reviews by Cochrane, the British National Institute for Clinical Excellence (NICE), the Canadian Coordinating Office of Health Technology Assessment (CCOHTA), and others have found that treatment with these drugs conferred a small clinical benefit when compared to placebo.

Moderate to severe Alzheimer's disease: Memantine is FDA-approved for treatment of moderate to severe Alzheimer's disease. Clinical trials comparing memantine to placebo used the ADAS-Cog and the Severe Impairment Battery (SIB) for primary outcome measures. In all of the trials, memantine showed a statistically and clinically significant improvement over placebo in the primary outcome measures.

Efficacy conclusion: All of the drugs used for Alzheimer's disease show statistically significant changes in cognition rating scores compared to baseline. Whether these results are clinically significant is debatable. There are no direct comparative trials available, but there is no evidence to suggest that any one Alzheimer's disease drug is more efficacious than another, when used according to FDA indications.

2.) *Safety/Tolerability:*

Serious effects – hepatotoxicity: Tacrine has been shown to cause elevated liver function tests (LFTs) in over 50% of patients, with 7% of patients experiencing LFT elevations greater than 10 times the upper limits of normal. In a major clinical trial, these LFT elevations led to an overall 72% discontinuation rate at the higher dosage range. The FDA requires a black box warning for the possibility of severe liver failure and death, and frequent monitoring of LFTs is mandated for patients using tacrine.

Side effects: Rivastigmine and galantamine are associated with a higher incidence of gastrointestinal (GI) side-effects and consequently require more complex titration than the other cholinesterase inhibitors or memantine. A complex titration schedule possibly affects

the likelihood that patients will adhere to these regimens. In clinical trials of memantine, the rate of patients discontinuing due to side effects was not statistically different from placebo.

Drug interactions: Donepezil and galantamine are metabolized by the CYP 450 enzyme system and thus may be prone to more drug interactions than other agents. However, it should be noted that interactions that increase levels of the Alzheimer's drugs are not generally considered to be clinically significant.

Safety/tolerability conclusion: The P&T Committee agreed that among the acetylcholinesterase inhibitors, tacrine differed significantly in terms of safety due to its potential to cause hepatic injury. While minor differences exist among the other acetylcholinesterase inhibitors and memantine, none were considered significantly different with respect to major contraindications, drug interactions, and adverse drug reactions.

3.) *Other Factors:*

Titration and dosing frequency: A difference in ease of dosing and dose titration schedules exists among these agents. Donepezil and galantamine extended release are dosed once daily, the other agents are dosed twice daily (galantamine immediate release, rivastigmine and memantine) or four times daily (tacrine). There are no well-designed randomized controlled trials that demonstrate improved outcomes with once daily dosing of these agents, however once daily products have the theoretical advantage of yielding a lower burden on caregivers.

DoD Provider Preferences: In a PEC survey of DoD providers (neurologists, geriatricians, internists, and family practitioners), the majority of respondents favored products with once daily dosing. Most respondents stated that they avoided tacrine because of hepatotoxicity; all expressed a preference for donepezil based on ease of titration and familiarity; most said that they add or switch to memantine when acetylcholinesterase inhibitors failed to provide expected benefit; and most felt that these medications should not be discontinued once they stopped arresting cognitive decline, since patients decline precipitously once these medications were stopped.

Other Factors Conclusion: There is no evidence to suggest clinical superiority of any one Alzheimer's agent based on differences in dosing and titration schedules or DoD provider opinion.

Overall Clinical Effectiveness Conclusion: The P&T Committee concluded that tacrine has less clinical utility than the other acetylcholinesterase inhibitors used in the treatment of the cognitive symptoms of Alzheimer's disease. Furthermore the safety concerns regarding the use of tacrine outweighed any cost benefit that might be obtained by keeping it on the UF. The P&T Committee further concluded that safety considerations for tacrine would support a PA; however, due to the extremely low number of unique utilizers (single digits) any potential problem was felt to be self-limiting. The P&T Committee concluded that all the remaining acetylcholinesterase inhibitors have similar relative clinical effectiveness for treating mild to moderate dementia associated with Alzheimer's disease. The P&T Committee agreed that memantine has a place in therapy for the treatment of moderate to severe dementia associated with Alzheimer's disease. With regard to safety and tolerability, memantine has an adverse event rate similar to placebo.

COMMITTEE ACTION. The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) that for the purposes of the UF clinical review, that tacrine possessed a safety disadvantage

relative to other available acetylcholinesterase inhibitors, but that all were similar in terms of effectiveness and clinical outcome, and that memantine has a place in therapy due to its indication for treatment of dementia in moderate to severe Alzheimer's disease.

B. Alzheimer's Drug UF Relative Cost Effectiveness: In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in the Code of Federal Regulations (32 C.F.R. 199.21(e)(2)).

The first step in determining the relative cost effectiveness of the selected agents in this class was to conduct a cost-analysis to calculate the total weighted average cost per day of treatment for each agent. The second step was to conduct the appropriate pharmacoeconomic analysis taking into account the conclusions of the clinical review. Because the clinical review concluded, with the exception of tacrine, that all of the agents within the Alzheimer's drug class had similar relative clinical effectiveness (efficacy, safety and tolerability), a cost-minimization analysis (CMA) was selected. To adjust for the safety issues associated with the use of tacrine, the cost of monitoring liver function tests was added to the drug cost of tacrine in the CMA.

The cost analysis only considered drug costs. The results showed tacrine to be the acetylcholinesterase inhibitor with the lowest total weighted average cost per day of treatment across all points of service (MTF, TRRx, TMOP). The CMA, which considered lab costs for monitoring tacrine, showed that donepezil was the most cost-effective agent when the additional requirement of multiple liver function tests was taken into account.

The results of the above analyses were then incorporated into a budget impact analysis (BIA), which accounted for other factors and costs associated with a potential decision regarding formulary status of Alzheimer's drugs within the UF. These factors included: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and switch costs. The results of the BIA further confirmed the results of the CMA. Donepezil was found to be the most cost-effective Alzheimer's drug overall.

Conclusion: The P&T Committee agreed (17 for, 0 against, 1 abstained, 1 absent) with the relative cost effectiveness analysis (CEA) of the Alzheimer's drugs presented. The P&T Committee concluded that the safety concerns regarding the use of tacrine outweighed any cost benefit that might be obtained by keeping it on the UF. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the Alzheimer's drugs, the P&T Committee recommended that the status of tacrine be changed from formulary to non-formulary on the UF, with donepezil, rivastigmine, galantamine, and memantine maintaining formulary status on the UF with the formulary cost share. To address the safety concerns of tacrine, a PA for tacrine was initially considered. However, due to the extremely low number of unique utilizers (single digits) currently being treated with tacrine across the MHS, the P&T Committee felt the medical community was adequately aware of the risks associated with tacrine use, and safety concerns were already being appropriately addressed.

COMMITTEE ACTION. The P&T Committee, based upon its collective professional judgment, voted (10 for, 6 against, 2 abstained, 1 absent) to recommend non-formulary status for tacrine, with donepezil, rivastigmine, galantamine, and memantine maintaining formulary status on the UF at the formulary cost share.

C. Alzheimer's Drug UF Medical Necessity Criteria: Based on the clinical evaluation of tacrine, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following medical necessity criteria for these agents.

- 1) Use of the formulary cholinesterase inhibitors (donepezil, galantamine, rivastigmine) is contraindicated, and the use of tacrine is not contraindicated.
- 2) The patient has experienced or is likely to experience significant adverse effects from the formulary acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine), and the patient is reasonably expected to tolerate tacrine.
- 3) Use of the formulary acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) resulted in therapeutic failure, and the patient is reasonably expected to respond to tacrine (therapeutic failure as outlined on medical necessity form).
- 4) The patient has previously responded to tacrine, and changing to the formulary acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) would incur unacceptable risk.
- 5) There is no alternative formulary agent.

COMMITTEE ACTION. The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to approve the medical necessity criteria.

D. Alzheimer's Drug UF Implementation Plan: Because of the low number of beneficiaries that would be affected by this formulary action (five patients known to be taking tacrine across the MHS), the P&T Committee recommended an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have tacrine on their local formularies. MTFs will be able to fill non-formulary requests for this agent only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) the beneficiary and/or provider must establish medical necessity for these agents. MTFs may (but are not required to) fill a prescription for tacrine written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION. The P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) an effective date no later than the first Wednesday following a 90 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

E. Alzheimer's Drug Extended Core Formulary (ECF) Review and Recommendations. The P&T Committee had previously determined that only one acetylcholinesterase inhibitor would be added to the ECF based on the clinical and cost effectiveness reviews. Additionally, the P&T Committee previously stated that one NMDA inhibitor (memantine) would be considered for addition to the ECF based on a favorable cost effectiveness evaluation. As a result of the economic evaluations presented, the P&T Committee recommended that donepezil be added to the ECF.

Conclusion: Donepezil was recommended for inclusion on the ECF.

COMMITTEE ACTION. The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to add donepezil to the ECF.

10. NASAL CORTICOSTEROIDS DRUG CLASS REVIEW

A. Nasal corticosteroid Relative Clinical Effectiveness Review: The Committee evaluated the relative clinical effectiveness of the six nasal corticosteroids marketed in the U.S.: beclomethasone dipropionate (Beconase AQ, Vancenase AQ and Vancenase AQ DS), budesonide (Rhinocort AQ), flunisolide (Nasarel), fluticasone propionate (Flonase), mometasone furoate (Nasonex), and triamcinolone acetonide (Nasacort AQ). 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) *Efficacy:* All of the nasal corticosteroids are FDA-approved for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). Endpoints used in clinical trials included patient scoring on the total nasal symptom score (nasal blockage, rhinorrhea, sneezing and nasal itching) or total symptom score (itchy/burning eyes, tearing, redness). Two clinical reviews of seventeen randomized controlled trials evaluating various nasal corticosteroids determined equal efficacy amongst the nasal corticosteroids. Twenty placebo-controlled/head-to-head trials also concluded that nasal corticosteroids were equally effective at equipotent doses at relieving allergic rhinitis symptoms. Possible differences may lie in individual physician/patient preferences and population specific safety concerns.

Efficacy Conclusion: Multiple clinical reviews over the past two decades suggest comparable efficacy between the nasal corticosteroids at relieving allergic rhinitis symptoms when used in equipotent doses.

2) *Safety and Tolerability:*

a. Local effects:

Transient local reactions, such as nasal irritation and stinging, sneezing, dryness, headaches, and occasional sore throat, are the common side effects seen with nasal corticosteroids. All of the aqueous nasal corticosteroid sprays can cause epistaxis, but in clinical trials, the placebo spray also had an appreciable rate of epistaxis. Other, rarely reported local adverse events include nasal septum ulceration and septal perforation. There is no evidence to suggest that one nasal corticosteroid is more likely to cause local adverse effects than another. According to package insert data, approximately 2-3% of patients discontinue a nasal corticosteroid treatment due to adverse events.

b. Systemic Adverse Events:

i. *Hypothalamic adrenal axis (HPA) suppression:* HPA-axis suppression is a concern with all corticosteroids (oral, inhaled, and nasal) as it can progress to acute adrenal crisis in all ages. Two separate review articles, one evaluating 19 randomized clinical trials and the other 7 additional randomized clinical trials, found no significant differences between the nasal corticosteroids in suppression of the HPA-axis. The true clinical relevance of nasal corticosteroid use and any resultant significant adrenal gland suppression/adrenal crisis is difficult to ascertain as the trials report changes in surrogate markers (e.g., urinary cortisol excretion, serum

cortisol, or adrenocorticotropin hormone concentration) and are not consistent across testing methods. Placebo-controlled trials show similar HPA-axis suppression between placebo and nasal corticosteroids, as evidenced by reductions in lab values, while comparisons with oral prednisone showed greater suppression than nasal corticosteroids. It is unlikely that the risks of HPA-axis suppression differ among nasal corticosteroids, although theoretically fluticasone propionate and mometasone furoate may confer lower risk due to lower bioavailability than the others.

- ii. *Growth retardation:* All inhaled and nasal corticosteroids are required by the FDA to have a warning label in their package inserts regarding the potential risk of growth suppression. Regular monitoring is especially necessary for children receiving multiple corticosteroid therapies, as excessive corticosteroid doses can lead to proven growth suppression. Head-to-head trials and placebo-controlled trials have shown conflicting results among the nasal corticosteroids in outcomes measuring lower leg growth velocity and standing height. Inconsistency across trials in growth measurement and study methodology make it difficult to interpret actual growth suppression and to determine the possible effects of nasal corticosteroids when predicting future pediatric growth velocity. In general, nasal corticosteroids should be used with care in children by titrating to the lowest effective dose so to keep growth suppression to a minimum.
- iii. *Cataracts:* A large retrospective evaluation from the UK compared the use of nasal corticosteroids in over 280,000 patients with and without diagnosed cataracts. Over 70% of the patients were solely receiving beclomethasone dipropionate. No increased association was found between nasal steroid use and cataract formation; however, patients receiving chronic oral corticosteroid therapy were found to have an increased frequency of cataract formation. Excessive doses of nasal corticosteroids can lead to rare effects of cataracts. There is insufficient evidence to predict whether one nasal corticosteroid is more likely to cause cataracts than the other.

Overall safety conclusion: Nasal irritation, epistaxis, and rhinorrhea are the most common local adverse events, and are equally likely to occur with any of the nasal corticosteroids. For systemic effects (HPA-axis suppression, growth suppression, and cataract formation), there is no definitive evidence that one nasal corticosteroid is more likely to cause these effects than another. Depending on the severity of allergic rhinitis symptoms, the benefits of nasal corticosteroids may outweigh the risks of systemic adverse effects. According to the package inserts, the risk of systemic effects is increased when higher than normal amounts of nasal corticosteroids are used.

3) *Other Factors:*

- a. *Dosing frequency:* Most of the nasal corticosteroid products are marketed for once daily administration. Budesonide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide are dosed once a day, while beclomethasone dipropionate and flunisolide require at least twice to three times daily dosing. Dosing may contribute to patient adherence or patient preference for an individual product. Theoretically, once daily dosing may result in improved patient compliance vs. products requiring multiple daily dosing.
- b. *Kinetics/dynamics:* Molecular weight, lipophilicity, and thixotropy are types of pharmacokinetic measures used to differentiate potency between the nasal

corticosteroids. When evaluating potency, varying results have been reported between nasal corticosteroids, as experimental set-ups in the laboratory setting do not conclusively correlate with what providers may witness in their patients. There is no evidence that differences in these kinetic/dynamic parameters are linked to differences in clinical outcomes.

- c. *Formulation:* The nasal aerosol formulations of Beconase (beclomethasone dipropionate), Vancenase (beclomethasone dipropionate), and Rhinocort (budesonide) have declined in popularity as physicians and patients have chosen the ease and convenience of use with the newer aqueous nasal formulations (Beconase AQ, Vancenase AQ, Vancenase AQ DS, Rhinocort AQ, Flonase, Nasonex, Nasacort AQ).
- d. *Pediatric Populations:* All the nasal corticosteroids are indicated for use in children six years of age or older, but fluticasone propionate is indicated for children down to the age of four years, and mometasone furoate is indicated for use in children as young as two years old.
- e. *Pregnancy:* The only nasal corticosteroid with a FDA Category B (low risk in humans) rating is budesonide. This indication was given primarily due to a retrospective epidemiological study reviewing data from three Swedish registries and a pregnancy outcome study (Steroid Treatment and Regular Therapy [START] study) of over 6,000 infants. All the other nasal corticosteroids are rated Category C (risk cannot be ruled out). There is one placebo-controlled human study that focused specifically on the safety and efficacy of maternal nasal corticosteroid (fluticasone propionate) use during pregnancy. There were no differences found between the treatment and placebo groups in pregnancy outcomes. Pregnant patients are still advised to discuss benefit versus risk ratios of nasal corticosteroid use with their OB/GYN provider.
- f. *Patient preference/tolerability:* Patient's attitudes toward features such as taste, odor, irritation, and moistness may attribute to adherence of certain nasal corticosteroids. Patient preference may play a role in differentiating between the nasal corticosteroids, but the available clinical data are poor, and no one nasal corticosteroid has proven superior to the others in patient preference trials. More well-designed, head-to-head randomized, controlled trials are needed to support a conclusion that one nasal corticosteroid is superior to another in tolerability or compliance.

Conclusion for Other Factors: Minor differences exist among the agents in terms of frequency of dosing, kinetic/dynamic parameters, pediatric labeling, and use in pregnancy.

Overall Clinical Effectiveness Conclusion: The DoD P&T Committee concluded that: 1) in equipotent doses, the nasal corticosteroids are equally effective at relieving symptoms of allergic rhinitis; 2) in equipotent doses the nasal corticosteroids have similar local side effect profiles; 3) there is a lower risk of systemic adverse effects (HPA-axis suppression, growth retardation, cataract formation) when nasal corticosteroids are used according to labeled dosing instructions; however, there is no evidence that systemic effects are likely to occur more frequently with one agent versus another; 4) products that are dosed once daily may have advantages in terms of patient preference over products requiring multiple daily dosing; 5) minor differences in pharmacokinetic/dynamic factors (thixotropy, molecular weight, lipophilicity) have not translated into differences in clinical outcomes; 6) mometasone furoate is indicated for use in pediatric patients as young as two years of age; 7) budesonide is rated pregnancy category B, while fluticasone propionate has evidence from one trial that pregnancy

outcomes were not adversely affected with use during pregnancy; and 8) there is no clear difference between the nasal corticosteroids in terms of patient preference and tolerability.

COMMITTEE ACTION. The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) that, for the purposes of the UF clinical review, none of the nasal corticosteroids have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other nasal corticosteroids.

B. Nasal Corticosteroids Relative Cost Effectiveness: The P&T Committee evaluated the relative cost effectiveness of the agents considering possible differences in safety, tolerability, and effectiveness in accordance with 32 CFR 199.21 (e)(2).

Two separate economic evaluations were performed, a pharmacoeconomic analysis and a BIA. From the proceeding relative clinical effectiveness evaluation, the P&T Committee determined that nasal corticosteroids have similar relative clinical efficacy, but some small differences in terms of dosing frequency, use in pregnancy, use in pediatric populations, and DoD provider preferences. The agents within the nasal corticosteroid therapeutic class were thus shown to differ slightly in relative clinical effectiveness.

The above stated differences in the nasal corticosteroids have not been evaluated in clinical trials for their effect on treatment outcomes. The PEC surveyed DoD medical providers to evaluate their opinion on these difference. The PEC conducted two cost analyses, one analysis with no effectiveness measure, and the second analysis incorporating the results of the survey as an effectiveness measure.

In the first cost analysis of the cost per day of therapy across DoD alone, the results showed that flunisolide was the most effective; budesonide, fluticasone propionate, mometasone furoate and triamcinolone acetonide (not in rank order) were less cost effective; and beclomethasone was not cost effective.

In the second cost analysis of the cost per day of therapy across DoD incorporating the effectiveness measure, the results showed that (all in alphabetical order) flunisolide, fluticasone propionate and mometasone furoate were the most cost effective, and beclomethasone dipropionate, budesonide and triamcinolone acetonide were not cost effective.

Both cost analyses were incorporated into a BIA, to analyze the cost to the DoD under various formulary status configurations, and to estimate the cost of formulary changes to the DoD. The results of the BIA revealed that the best combination of agents to meet DoD's clinical and cost effectiveness goals is the group of formulary agents that included flunisolide, fluticasone propionate, and mometasone furoate. These results matched the results from the cost analysis incorporating the effectiveness measure derived from the survey of DoD providers.

Conclusion: The P&T Committee, based on its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 3 absent) to accept the nasal corticosteroid CEA presented by the PEC. The P&T Committee concluded that flunisolide, fluticasone propionate, and mometasone furoate had similar cost effectiveness, and that they had greater cost effectiveness than beclomethasone dipropionate, budesonide, or triamcinolone acetonide.

Class Review Conclusion: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness evaluations, and other relevant factors, the P&T Committee recommended that beclomethasone dipropionate, budesonide, and triamcinolone acetonide be classified as non-formulary under the UF, and that flunisolide, fluticasone propionate, and mometasone furoate be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based on its collective professional judgment, voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend formulary status for flunisolide, fluticasone propionate, and mometasone furoate; and non-formulary status for beclomethasone dipropionate, budesonide, and triamcinolone acetonide under the UF.

C. Nasal Corticosteroids UF Medical Necessity Criteria: Based on the clinical evaluation of the nasal corticosteroids and the conditions for establishing medical necessity for non-formulary medications 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 all formulary nasal corticosteroids (flunisolide, fluticasone propionate, mometasone furoate) is contraindicated, and the use of a nonformulary nasal corticosteroid (beclomethasone dipropionate, budesonide, triamcinolone acetonide) is not contraindicated.
- 2) The patient has experienced or is likely to experience significant local adverse events (epistaxis, pharyngitis, nasal irritation) from all formulary nasal corticosteroids, and the patient is reasonably expected to tolerate a non-formulary nasal corticosteroid.
- 3) Use of all the formulary nasal corticosteroids resulted in therapeutic failure, and the patient is reasonably expected to respond to a non-formulary nasal corticosteroid (therapeutic failure as outlined on the medical necessity form).

COMMITTEE ACTION. The P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) to approve the medical necessity criteria.

D. Nasal corticosteroid UF Implementation Plan: Due to the relatively low number of patients that will be affected by this formulary action, the P&T Committee recommended an effective date no later than the first Wednesday following a 90-day implementation period.

COMMITTEE ACTION: The P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA

E. Nasal Corticosteroids Basic Core Formulary (BCF) Review and Recommendations.

The P&T Committee reviewed the nasal corticosteroids recommended for inclusion on the UF to select the BCF nasal corticosteroid(s). It had been previously decided that at least one, but no more than two, nasal corticosteroids would be added to the BCF, based on the outcome of a preliminary clinical effectiveness review and DoD needs assessment conducted at the August 2005 P&T Committee meeting.

A cost analysis was performed using prices submitted for BCF status. While flunisolide had a lower cost per day of therapy than fluticasone propionate and mometasone furoate, fluticasone propionate provided the best overall value to DoD, in terms of a competitive price, most preferred dosing frequency (once a day), and overwhelming preference by DoD providers in all but a small subpopulation of DoD patients. The Committee saw no compelling need to have a second agent on the BCF.

Conclusion: The P&T Committee recommended retaining fluticasone on the BCF.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend fluticasone as the BCF agent.

11. ANTIDEPRESSANTS GROUP 1 (AD1) DRUG CLASS REVIEW

A. AD1 UF Relative Clinical Effectiveness: The Committee evaluated the relative clinical effectiveness of antidepressant medications. The drug class reviewed included all U.S. marketed antidepressants, except monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), which will be reviewed separately. Individual medications are outlined in the table below. 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.

The Committee considered information concerning the safety, tolerability, efficacy, and clinical outcome of the AD1s. Like many medications, the AD1s have multiple potential uses in addition to the treatment of depression. The Committee's review focused most heavily on the use of these agents for depression, but also considered the clinical effectiveness of individual agents in the treatment of other psychiatric and non-psychiatric conditions. FDA-approved indications for the AD1s are outlined in the table below. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21.

Generic Name	Brand Name	FDA-Approved Indications (as of July 2005)
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Citalopram	Celexa, generics	MDD
Escitalopram	Lexapro	MDD, GAD
Fluoxetine	Prozac, generics	MDD, OCD, PD, bulimia (pediatric labeling MDD, OCD)
Fluoxetine 90 mg caps (weekly regimen)	Prozac Weekly	MDD (maintenance of response only)
Fluoxetine (special packaging)	Sarafem	PMDD
Fluvoxamine	Generics	OCD (pediatric labeling)*
Paroxetine HCl	Paxil, generics	MDD, GAD, OCD, PD, PTSD, SAD
Paroxetine HCl controlled release	Paxil CR	MDD, PD, PMDD, SAD
Paroxetine mesylate	Pexeva	MDD, OCD, PD
Sertraline	Zoloft	MDD, OCD, PD, PTSD, PMDD, SAD (pediatric labeling OCD)
Serotonin – Norepinephrine Reuptake Inhibitors (SNRIs)		
Duloxetine	Cymbalta	MDD, DPNP
Venlafaxine	Effexor, generics	MDD
Venlafaxine extended release	Effexor XR	MDD, GAD, SAD
Serotonin-2 Antagonist/Reuptake Inhibitors (SARIs)		
Nefazodone	Generics	MDD
Trazodone	Desyrel, generics	MDD
Norepinephrine and Dopamine Reuptake Inhibitors (NDRIs)		
Bupropion	Wellbutrin, generics	MDD
Bupropion sustained release	Wellbutrin SR, generics	MDD
Bupropion extended release	Wellbutrin XL	MDD
Alpha-2 Receptor Antagonists		
Mirtazapine	Remeron, generics	MDD

MDD = Major Depressive Disorder, GAD = Generalized Anxiety Disorder, OCD = Obsessive Compulsive Disorder, PD = Panic Disorder, PTSD = Posttraumatic Stress Disorder, PMDD = Premenstrual Dysphoric Disorder; SAD = Social Anxiety Disorder; DPNP = Diabetic Peripheral Neuropathic Pain

*Fluvoxamine is approved for depression in other countries, including Canada.

1) *Safety and Tolerability*: The Committee assessed the comparative safety and tolerability of the AD1s, including common adverse effects, rare but serious adverse effects, potential for drug interactions, safety of use in special populations, the risk of adverse effects when discontinuing use (discontinuation syndrome), and safety/tolerability issues with special formulations of paroxetine, fluoxetine, and bupropion.

a. Common Adverse Effects

- i. Adverse effect profiles of the AD1s are known to differ. A particular agent made be chosen to either avoid a known side effect, or to take advantage of a known side effect clinically (e.g., selecting an antidepressant likely to cause sedation for an elderly patient who is having difficulty sleeping).
- ii. Differences in clinical trials designs, patient populations, and methods of collecting adverse effect information make direct comparison of adverse effects difficult. Head-to-head trials comparing two or more AD1s are typically not powered to find significant differences in discontinuation rates due to adverse effects. Discontinuation rates in clinical trials are typically lower than in actual practice. In addition, many adverse effects tend to resolve with continued treatment and may or may not affect adherence to therapy or clinical outcomes. There are few long-term, prospective head-to-head trials under “real-world” conditions.
- iii. Overall, bupropion, fluoxetine, and paroxetine appear to be most associated with agitation/activation, while nefazodone, trazodone, and mirtazapine appear most likely to cause sedation. Anticholinergic effects have been reported with paroxetine and fluvoxamine. Gastrointestinal symptoms (e.g., nausea) are commonly reported with SSRIs, may be more common with venlafaxine, and may be less common with nefazodone, trazodone, bupropion, or mirtazapine. Diarrhea may occur more commonly with sertraline, compared to bupropion sustained release (SR), paroxetine, and mirtazapine.
- iv. Sexual dysfunction appears less likely to occur with bupropion, mirtazapine, trazodone, or nefazodone than with the SSRIs or SNRIs. There have been multiple trials supporting a lower risk of sexual dysfunction with bupropion compared to SSRIs.
- v. Elevations in blood pressure have been reported with the SNRIs (venlafaxine and duloxetine). This may be more frequent with venlafaxine than with duloxetine, although comparative data are lacking. There have also been reports of increases in blood pressure with bupropion and fluoxetine. Clinically relevant and statistically significant increases in cholesterol have been reported in a small percentage of patients treated with venlafaxine.
- vi. Most serotonergic antidepressants are associated with adverse effects when abruptly discontinued. This discontinuation syndrome appears to be related to elimination half-life, with symptoms occurring more frequently with medications with shorter half-lives (Propensity for syndrome among SSRIs): fluvoxamine > paroxetine > sertraline > escitalopram > citalopram > fluoxetine (half-life 6 days). Venlafaxine, which has a short half-life, may be associated with more discontinuation symptoms than the SSRIs. Comparative information with duloxetine is unavailable, but discontinuation symptoms have been reported. Little information is available concerning discontinuation symptoms with trazodone; there have been only anecdotal

reports with nefazodone and mirtazapine. Discontinuation symptoms from abrupt discontinuation of bupropion, which has little effect on the serotonergic system, appear uncommon.

b. Rare but Serious Adverse Effects/Use in Special Populations

- i. Abnormal bleeding, movement disorders, and hyponatremia have been reported rarely with SSRIs; there are insufficient data to determine if any one SSRI is associated with a higher risk.
- ii. The manufacturer of duloxetine issued a “Dear Doctor” letter in Oct 2005 expanding existing recommendations to avoid use of duloxetine in patients with substantial alcohol use to include patients with pre-existing liver disease, following reports of hepatic injury in patients receiving duloxetine. Duloxetine is not recommended in patients with any degree of hepatic insufficiency due to substantially reduced clearance. Duloxetine is contraindicated in patients with uncontrolled narrow-angle glaucoma because it can cause mydriasis, and should be used in caution in patients receiving medications or having medical conditions that slow gastric emptying.
- iii. Bupropion is contraindicated in patients with seizure disorder or conditions predisposing to seizure disorder or at increased seizure risk due to abrupt discontinuation of alcohol or sedatives. The risk of seizure in patients without predisposing factors appears low (0.1-0.4% at doses of 300-450 mg/d), but increases sharply at higher doses. Bupropion should be used with caution in hepatic impairment and extreme caution in severe hepatic cirrhosis.
- iv. Nefazodone has a black box warning stating that it should not be used in patients with active liver disease or pre-existing transaminase elevation.
- v. Trazodone should be used with caution in patients with cardiac disease. Priapism has been rarely reported with trazodone.
- vi. Agranulocytosis has been rarely reported with mirtazapine.
- vii. All ADIs are Pregnancy Category C except bupropion, which is Pregnancy Category B. Non-teratogenic adverse effects (e.g., respiratory distress) have been reported with serotonergic antidepressants when given in the third trimester. A recent epidemiological study cited in new labeling for paroxetine reported a greater than two fold increase in risk for birth defects in the first trimester with paroxetine compared to other SSRIs.
- viii. A recent FDA analysis showed a higher risk of suicidal ideation or suicidality during the first few months of treatment with antidepressants in children and adolescents (4% vs. 2% with placebo). The FDA has issued a Public Health Advisory urging particular caution in watching for signs of worsening depression or suicidal thoughts at the beginning of antidepressant therapy or whenever the dose is changed, and this information has been added to antidepressant labeling in general. Despite a number of meta-analyses and observational studies addressing the risk of suicidality with antidepressants, no one antidepressant appears to be consistently associated with a higher risk of suicidality. The FDA continues to analyze data; adult results are expected in 2006.

c. Potential for drug interactions

- i. Unlike fluoxetine, paroxetine, and fluvoxamine, which are metabolized by the cytochrome P450 system [fluoxetine and paroxetine inhibit P450 2D6 and fluvoxamine inhibits multiple P450 isoenzymes], sertraline, citalopram, and escitalopram are considered the least likely to result in significant drug interactions.
- ii. Of the SNRIs, venlafaxine is primarily eliminated renally and has minimal effect on P450 isoenzymes; clinically meaningful drug interactions appear unlikely. Duloxetine has a moderate inhibitory effect on P450 2D6, is metabolized by 2D6 and 1A2, and may have increased hepatotoxicity in patients with substantial alcohol use. In addition it has a potential interaction with drugs affecting gastric acidity.
- iii. Nefazodone, which inhibits 3A4, may interact with multiple medications. Information with trazodone is unclear. Bupropion does not appear to have substantial drug interactions, although it should not be used with drugs that lower the seizure threshold. Mirtazapine appears unlikely to cause substantial drug interactions, since it is metabolized by multiple pathways and does not appear to be a potent inhibitor of 2D6, 1A2, or 3A4.

d. Special Formulations

- i. *Paroxetine controlled release (CR)* - The CR formulation of paroxetine (Paxil CR) is designed to release its contents over 4-5 hours after the medication reaches the small intestine; the intent is to reduce the incidence of nausea and related GI symptoms compared to the immediate release (IR) product. Both products are given once daily.

Based on pooled data from two 12-week, double-blind, randomized, placebo-controlled MDD trials comparing paroxetine CR and IR at similar doses [Golden et al. *J Clin Psychiatry* 2002; 63:577-84], patients receiving paroxetine CR showed significantly lower rates of nausea in the first week compared to paroxetine IR (14% vs. 23%, $p \leq 0.05$). Nausea rates began to decline in both groups starting in week 2, with no significant differences after week 1, and no numerical advantage for the CR formulation after week 3. Discontinuations due to adverse effects occurred in 6% of patients in the placebo group, 10% of patients in the paroxetine CR group ($p=0.14$ vs. placebo), and 16% of patients in the paroxetine IR group ($p=0.0008$ vs. placebo). There was no statistically significant difference between the CR and IR group. Discontinuations due specifically to nausea occurred in 3% of patients in the CR group, 4% in the IR group, and 0.5% in the placebo group.

There are no head-to-head trials comparing paroxetine CR to other SSRIs, and thus no direct evidence comparing rates of nausea or discontinuation due to adverse effects.

- ii. *Fluoxetine 90-mg delayed release capsules (Prozac Weekly)* – Fluoxetine has a much longer half-life than other SSRIs, a fact that is exploited by the 90-mg weekly formulation. Fluoxetine weekly has an enteric coating that delays the onset of absorption by 1 to 2 hours relative to IR formulations, but does not otherwise extend the release of fluoxetine. It is FDA-approved only for maintenance of response in patients with MDD, not for initial therapy. The advantage of fluoxetine weekly is patient convenience and potentially increased adherence to treatment. This point has not been well-established, although one study reported greater compliance with the once-weekly regimen compared to 20 mg daily during a 3-month continuation phase [Claxton et al. *J Clin Psychiatry* 2000; 61:928-32]. Since compliance during a clinical

trial may be very different from compliance in practice, it is unclear whether this represents a real advantage for fluoxetine weekly. It is not clear whether fluoxetine 90 mg weekly is equivalent to fluoxetine 20 mg/d in maintaining response.

- iii. *Fluoxetine in special packaging for premenstrual dysphoric disorder (PMDD) (Sarafem)* – Fluoxetine 10 and 20 mg capsules are available in special packaging and with special labeling for the treatment of PMDD, under the name of Sarafem. Usual dosing is 20 mg/day; the product does not appear to differ from the other branded fluoxetine product (Prozac), except for differences in the color of the capsules. When Sarafem was first introduced, the manufacturer stated the intent was to allow patients with PMDD to avoid the stigma associated with use of antidepressants.
- iv. *Bupropion extended release (Wellbutrin XL)* – The main advantage offered by the extended release bupropion product (Wellbutrin XL) compared to sustained release bupropion is once-daily vs. twice-daily administration. This is not regarded as an overwhelming advantage for medications in most disease states, although there is some evidence that patients have poorer adherence to twice daily versus once daily regimens and that patients with depression have worse adherence to medication than non-depressed patients. In the case of bupropion sustained release, package labeling advises separating doses by 8 hours. Since patients are usually advised not to take bupropion late in the day due to its activating properties, bupropion sustained release is likely to be dosed in the morning and early afternoon, which may present more logistical problems than typical twice-daily regimens. Bupropion extended release may be taken as a single dose in the morning.

Safety/Tolerability Conclusion: The Committee concluded that adverse effect profiles differ across AD1s, but there are little data to support any substantial difference among AD1s with respect to tolerability. One possible exception is the SNRI venlafaxine, which appears to be associated with more adverse effects than the SSRIs. It is not clear whether duloxetine will prove to be better tolerated than venlafaxine. Bupropion, mirtazapine, nefazodone, and trazodone appear to have a lower risk of sexual dysfunction compared with SSRIs and SNRIs. The Committee agreed that fluvoxamine, fluoxetine, paroxetine, and duloxetine have a generally higher potential for drug interactions than citalopram, escitalopram, sertraline, and venlafaxine. Available evidence addressing the likelihood of discontinuation syndrome with SSRIs tends to correlate with a rank-order of risk based on half-life (greatest to least risk). fluvoxamine > paroxetine > sertraline > escitalopram > citalopram > fluoxetine. Venlafaxine has a short half-life, and may be associated with more discontinuation symptoms than SSRIs; duloxetine may be similar based on half-life. Discontinuation symptoms appear uncommon with bupropion; data are limited with trazodone, nefazodone, and mirtazapine. Rare but serious adverse effects appear to be associated with duloxetine (recent case reports of hepatotoxicity), bupropion (seizure), nefazodone (hepatotoxicity), mirtazapine (agranulocytosis), and trazodone (priapism). Drugs with issues of particular concern in specific patient populations include duloxetine (avoid in hepatic insufficiency, substantial alcohol use, liver disease, narrow angle glaucoma), paroxetine (recent epidemiological evidence of increased risk in pregnancy), and bupropion (avoid in patients with increased seizure risk).

2) *Efficacy/Clinical Outcomes*

a. *Major Depressive Disorder (MDD)*

- i. *SSRIs vs. SSRIs* – Of 23 head-to-head trials comparing SSRIs to other SSRIs, very few reported any significant differences between SSRIs. These trials were mostly of short

duration, with many lasting only 6-8 weeks. They typically assessed changes on the two most commonly used depression scales, the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery Asberg Depression Rating Scale (MADRS). Most of these trials reported response rates ($\geq 50\%$ decrease on the HAM-D or MADRS), with a few reporting remission rates (percent of patients achieving a certain HAM-D or MADRS score). A 9-month “real-world” effectiveness trial comparing paroxetine, sertraline, and fluoxetine in primary care patients with depression as determined by the primary care provider [Kroenke et al. *JAMA* 2001; 286:2947-55] found no significant differences in efficacy among these three SSRIs. Two meta-analyses of response rates performed by Oregon reviewers showed no differences between paroxetine and fluoxetine, and a very slight and probably clinically insignificant difference (RR 1.10, 95% CI 1.01-1.22) favoring sertraline over fluoxetine. Only two trials reported statistically significant differences in efficacy [Lepola et al. *Int Clin Psychopharmacol* 2003; 18(4):211-7; Moore et al. *Int Clin Psychopharmacol* 2005; 20(3):131-7]. Both of these trials reported greater efficacy with escitalopram compared to citalopram. A third trial comparing citalopram and escitalopram showed no significant differences [Burke et al. *J Clin Psychiatry* 2002; 53:331-6]. Results of an unpublished trial comparing escitalopram to sertraline supplied by the manufacturer of escitalopram showed no significant differences between these two SSRIs. There is no published data supporting greater efficacy for paroxetine CR or fluoxetine weekly, compared to the original formulations or to other SSRIs.

- ii. *Venlafaxine vs. SSRIs* – There are a number of head-to-head trials and meta-analyses comparing venlafaxine and various SSRIs, including paroxetine, fluoxetine, sertraline, and escitalopram. Overall, few of these trials reported significant differences between SSRIs and venlafaxine. Two meta-analyses comparing venlafaxine to fluoxetine showed a modest efficacy advantage for venlafaxine [Smith et al. *Br J Psychiatry* 2002; 180:364-404; Oregon reviewers], although venlafaxine was associated with more adverse effects. Two 8-week, randomized, controlled trials comparing venlafaxine extended release (venlafaxine XR) to escitalopram showed no differences in efficacy [Montgomery et al. *Neuropsychobiol* 2004; 50(1):57-64; Bielski et al. *J Clin Psychiatry* 2004; 65(9):1190-6].
- iii. *Duloxetine vs. SSRIs* – There are no published head-to-head trials designed to compare duloxetine with other AD1s, although limited comparative data are available from six 8-week duloxetine trials that included active control arms (fluoxetine or paroxetine). However, these trials were not powered to directly compare active treatments; fluoxetine or paroxetine doses were limited to 20 mg/d while duloxetine was dosed from 40 to 120 mg/d. Duloxetine 60 mg/d appeared generally comparable to escitalopram 10 mg/d based on results of an unpublished, randomized, placebo-controlled trial supplied by the manufacturer of duloxetine.

Based on *in vitro* data, duloxetine appears to bind more equally to serotonin and norepinephrine reuptake transporters than venlafaxine. This “more balanced” inhibition is theorized to have favorable effects on pain, since inhibitory modulation of pain signals in neural pathways occurs via release of both serotonin and norepinephrine. A complementary argument is that duloxetine may be a better treatment than other antidepressants for depressed patients presenting with “painful symptoms of depression.” Support for this argument is limited. Patients with depression commonly present with physical (somatic) symptoms, including pain,

which resolve along with mood symptoms following anti-depressant treatment. Brannan et al. [*J Psychiatric Res* 2005; 39:43-53] reported results of a randomized, placebo-controlled trial assessing the effects of duloxetine on pain in depressed patients with painful symptoms at baseline. The mean difference in Brief Pain Index (BPI) average pain scores (0=no pain; 10 = as bad as you can imagine) was consistently a little less than a point lower with duloxetine vs. placebo, starting at week 1. The difference reached statistical significance at weeks 1, 2, and 5, but was not significantly different at endpoint ($p=0.066$). Whether these results translate into a real advantage for duloxetine compared to other antidepressants in depressed patients presenting with somatic symptoms of pain is unclear.

- iv. *Venlafaxine vs. duloxetine* – There are no published head-to-head trials comparing venlafaxine and duloxetine for the treatment of depression. A 2005 meta-analysis [Vis et al. *Ann Pharmacother* 2005; 39:1789-807] comparing placebo-controlled trials with venlafaxine and duloxetine did not show a statistically significant difference between duloxetine and venlafaxine XR, although remission and response rates tended to favor venlafaxine XR. A summary of pooled results of two unpublished, double-blind, MDD randomized, controlled trials comparing duloxetine and venlafaxine supplied by the manufacturer of duloxetine showed no significant differences between venlafaxine and duloxetine based on Global Benefit-Risk assessment (a statistical method that weighs both efficacy and adverse effects), remission rate, or change from baseline in HAM-D total score.
 - v. *Bupropion* – Based on six head-to-head trials and one meta-analysis, bupropion appears similar in efficacy to SSRIs (fluoxetine, paroxetine, sertraline). There are no published data supporting greater efficacy for bupropion extended release, compared to the immediate or sustained release formulations of bupropion or to other SSRIs.
 - vi. *Mirtazapine* – Based on five head-to-head trials, mirtazapine appears similar in efficacy to SSRIs (fluoxetine, paroxetine, sertraline).
 - vii. *Nefazodone* – Based on three head-to-head trials, nefazodone appeared similar in efficacy to SSRIs (fluoxetine, paroxetine, and sertraline). One of these studies included pooled data from three trials with identical protocols focusing primarily on effects of nefazodone or fluoxetine on sleep quality; nefazodone appeared to significantly improve sleep quality compared to fluoxetine.
 - viii. *Trazodone* – Based on five 6-week trials, trazodone appeared similar in efficacy to fluoxetine and bupropion, and possibly less efficacious than venlafaxine, although insufficient evidence exists to draw any real conclusion. At present, the major role of trazodone in depressed patients appears to be as an adjunctive medication for the treatment of insomnia.
 - ix. *Treatment of depression in children and adolescents* – Fluoxetine is the only antidepressant FDA-approved for MDD in children and is used in most pediatric MDD trials. The FDA has concluded that only fluoxetine has been shown to have a favorable risk-benefit profile in pediatric patients, based on the fact that it is the only antidepressant that has demonstrated efficacy in a pediatric population.
- b. *Other Psychiatric Conditions:*
- i. *Generalized Anxiety Disorder (GAD)*. Venlafaxine, paroxetine, and escitalopram are FDA-approved for treatment of GAD. Sertraline appears to be efficacious for the

treatment of GAD based on results of a large published, placebo-controlled trial [Allgulander et al. *Am J Psychiatry* 2004; 161:1642-9]. Two head-to-head trials, one comparing paroxetine and sertraline and the other comparing paroxetine and escitalopram, reported no difference between active treatments based on reductions in anxiety (HAM-A) scores [Ball et al. *J Clin Psychiatry* 2005; 66:94-9; Bielski et al. *Ann Clin Psychiatry* 2005; 17:65-9].

- ii. *Obsessive Compulsive Disorder (OCD)*. Fluoxetine, fluvoxamine, paroxetine, and sertraline are FDA-approved for the treatment of OCD; fluoxetine, sertraline, and fluvoxamine are approved for use in children and adolescents. At least four separately conducted meta-analyses, one focusing on trials in pediatric patients, showed no significant difference between included SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline). Two head-to-head trials, one comparing sertraline and fluoxetine, and the other comparing paroxetine and venlafaxine XR, showed no difference in efficacy between active treatments [Bergeron et al. *J Clin Psychopharmacol* 2002; 22(2):148-54; Denys et al. *J Clin Psychopharmacol* 2003; 23(6):568-75]. Citalopram appears to be effective for the treatment of OCD based on results of a long-term (> 6 month) trial [Montgomery et al. *Int Clin Psychopharmacol* 2001; 16:75-86].
- iii. *Panic Disorder (PD)*. Fluoxetine, paroxetine, and sertraline are FDA-approved for panic disorder. A head-to-head trial comparing sertraline and paroxetine showed no significant differences in efficacy [Bandelow et al. *J Clin Psychiatry* 2004; 65:405-13]. Fluvoxamine and venlafaxine XR appear efficacious based on short-term, placebo-controlled trials. Citalopram appears to be efficacious for panic disorder based on results of a placebo-controlled trial with a 1-year extension [Wade et al. *Br J Psychiatry* 1997; 170:549-53; Lepola et al. *J Clin Psychiatry* 1998; 59:528-34]. A 10-week trial comparing both citalopram and escitalopram to placebo reported significant improvement with both active treatments on many measures, including quality of life, although only escitalopram significantly reduced the frequency of panic attacks compared to placebo [Stahl et al. *J Clin Psychiatry* 2003; 64:1322-7]. This trial was not designed to compare active medications
- iv. *Premenstrual Dysphoric Disorder (PMDD)*. Fluoxetine (as Sarafem), paroxetine, and sertraline are FDA-approved for the treatment of PMDD. Evidence supporting efficacy is also available for citalopram, fluvoxamine, and venlafaxine [Wyatt et al. *Cochrane Database Syst Rev* 2002; 4:CD001396; Freeman et al. *Obstet Gynecol* 2001; 98(5 Pt 1):737-44]. There are no head-to-head trials.
- v. *Post-Traumatic Stress Disorder (PTSD)*. Sertraline and paroxetine are FDA-approved for PTSD. Mirtazapine may be efficacious in PTSD based on a 6-week, head-to-head, open-label trial with sertraline which showed a higher percentage of responders with mirtazapine [Chung et al. *Human Psychopharmacol* 2004; 19:489-94]. Published data supporting efficacy of fluoxetine for PTSD include two small, placebo-controlled trials, one of which showed a significant effect on prevention of relapse over a 6-month period [Connor et al. *Br J Psychiatry* 1999; 175:17-22; Davidson et al. *J Clin Psychopharmacol* 2005; 25:166-9].
- vi. *Social Anxiety Disorder (SAD)*. Paroxetine, sertraline, and venlafaxine are FDA-approved for the treatment of SAD. Two placebo-controlled trials comparing venlafaxine XR and paroxetine showed no differences in efficacy between active treatments, although venlafaxine XR appeared to be associated with a faster onset of

action in one trial [Liebowitz et al. *Arch Gen Psychiatry* 2005; 62:190-8; Allgulander et al. *Human Psychopharmacol* 2004; 19:387-96]. Escitalopram appears efficacious for SAD based on results of a placebo- and paroxetine-controlled trial [Lader et al. *Depress Anxiety* 2004; 19:234-40], and an additional 12-week, placebo-controlled trial [Kaspar et al. *Br J Psychiatry* 2005; 186:222-6]. A small trial with fluvoxamine showed significant improvement in efficacy compared to placebo [Stein et al. *Am J Psychiatry* 1999; 156:756-60].

- vii. *Bulimia*. Fluoxetine is the only AD1 that is FDA-approved for treatment of bulimia. The majority of data (and all the larger trials) supporting efficacy of SSRIs for bulimia/binge eating disorder were done with fluoxetine. Although there are small trials with other AD1s, data are insufficient to draw conclusions about the efficacy of other AD1s for bulimia.

c. *Non-psychiatric conditions*

i. *Diabetic peripheral neuropathic pain (DPNP)*

A recent Cochrane systematic review [Saarto et al., *Cochrane Database System Rev.* 2005; (3):CD005454] addressed the use of antidepressants for the treatment of neuropathic pain in adult patients. The review included 50 trials of 29 antidepressants (total n=2515). The overall conclusion supported efficacy of TCAs for neuropathic pain, with amitriptyline having a number-needed-to-treat of 2 (95% CI 1.7-2.5) and a relative risk of 4.1 (95% CI 2.9-5.9) for obtaining at least moderate relief of pain. Researchers found limited evidence for the efficacy of SSRIs, and insufficient evidence for other antidepressants, including venlafaxine.

In addition to antidepressants, a number of anticonvulsants are used to treat DPNP. After excluding non-diabetic etiologies and stabilizing glycemic control, the American Diabetes Association advises starting treatment of DPNP with a TCA, (e.g., amitriptyline 25-150 mg at bedtime), or an anticonvulsant (e.g., gabapentin 1800 mg daily) [Boulton et al. *Diabetes Care* 2005; 28:956].

Duloxetine is FDA-approved for the treatment of DPNP. Safety and efficacy of duloxetine for the treatment of DPNP were established in two 12-week randomized controlled studies (total n=1074), one of which is published [Goldstein et al. *Pain* 2005; 116(1-2):109-18.]. Based on the published trial, the percent of patients achieving a $\geq 50\%$ reduction in 24h Average Pain Score was 49% for patients receiving duloxetine 60 mg/d and 52% with 120 mg/d, compared to 26% of patients receiving placebo. The 60 mg/d dose of duloxetine was better tolerated.

Venlafaxine also appears to be efficacious and safe in DPNP. Rowbotham et al. [*Pain* 2004; 110:697-706] evaluated low dose (75mg) and high dose venlafaxine (150-225 mg) versus placebo in patients with painful diabetic neuropathy. The multicenter, double blind, randomized, placebo-controlled study included 244 adult outpatients with stable type 1 or 2 diabetes. At week 6, the percentage of patients achieving a 50% reduction in Visual Analog Pain Intensity score from baseline was 27% for placebo, 32% for 75mg, and 50% for 150-225mg, $p < 0.001$ v. placebo.

Overall, there is insufficient evidence to determine the relative effectiveness of TCAs, SNRIs, or anticonvulsants for the treatment of DPNP or non-diabetic neuropathic pain. The AD1s and the newly introduced anticonvulsant pregabalin are not yet

represented in clinical practice guidelines for DPNP and comparative evidence versus more established therapies is largely unavailable.

ii. *Other Non-Psychiatric Conditions*

The Committee did not attempt to review all non-psychiatric conditions in which one or more of the AD1s may have a beneficial effect. Some of these apply only to very limited populations (e.g., neurocardiogenic syncope/recurrent idiopathic dizziness), to predictably exploit side effects of the medications (e.g., treatment of premature ejaculation with SSRIs), or to be only an additional option among multiple possible options (e.g., migraine prophylaxis). The Committee noted the following:

- Duloxetine is approved for the treatment of stress urinary incontinence in Europe, under the name of Yentreve. The manufacturer of duloxetine has rescinded its new drug application for U.S. approval for stress urinary incontinence (SUI). It is unclear whether clinical evidence was felt to be insufficient, or whether the FDA is further investigating reports of suicide attempts and suicidal ideation occurring during clinical trials of duloxetine for SUI. The FDA's information sheet on duloxetine currently suggests that physicians consider the data on suicidality before prescribing duloxetine for SUI. Increases in suicidality have not been reported in trials of duloxetine for depression or DPNP.
- There are several clinical trials assessing use of AD1s for the treatment of hot flashes, of particular interest because of the scarcity of effective options for women unwilling or unable to take estrogens. Short-term trials with several AD1s, including venlafaxine, paroxetine, and fluoxetine, have shown efficacy; however, a 9-month, placebo-controlled trial with citalopram and fluoxetine failed to show a significant decrease in hot flashes with either medication, compared with placebo. There are insufficient data to support greater efficacy for any one AD1.
- Duloxetine was shown to be efficacious for the treatment of fibromyalgia in female patients with or without MDD in a 10-week, randomized, double-blind, placebo-controlled trial [Arnold et al., *Am J Med* 2002; 112:191-7], based on significantly greater improvement with duloxetine on the Fibromyalgia Impact Questionnaire (FIQ) total score (mean difference -5.5 points; score range 0-80, 0 = no impact). Response rates, based on patients achieving a $\geq 50\%$ reduction in FIQ pain score (score range 0-10, 0 = no impact), were 28% for duloxetine vs. 17% for placebo ($p=0.06$).

Efficacy / Clinical Outcome Conclusion: The Committee concluded that the AD1s offer similar efficacy in treating MDD with the exception of data supporting slightly greater efficacy with venlafaxine compared to the SSRIs and with escitalopram compared to citalopram. Fluoxetine has a unique advantage for the treatment of MDD in children.

The Committee noted that efficacy in other psychiatric conditions (GAD, OCD, PD, PMDD, PTSD, SAD, and bulimia) contributes to the overall usefulness of the AD1s. The Committee agreed that the existence of published clinical evidence supporting efficacy in these disease states should be taken into account in addition to FDA-approved indications. By this measure, paroxetine and sertraline appear to be the most broadly useful SSRIs. Bupropion, mirtazapine, trazodone, and nefazodone are indicated only for MDD. With regard to the SNRIs, venlafaxine has FDA-approved indications for GAD and SAD, in addition to MDD.

Duloxetine is the only AD1 with an FDA-approved indication for a non-psychiatric condition, DPNP. It is not clear whether duloxetine offers advantages over other agents used for the treatment of DPNP.

3) *Provider Opinion*

The Committee reviewed results of a survey sent to the Army, Navy, and Air Force specialty consultants, and distributed by them to MTF internal medicine, family practice, and psychiatry providers. The survey was also posted on the PEC's webforum, RxNet, to facilitate discussion. Providers were asked to identify clinical situations and differences in safety and tolerability among agents that would lead them to favor one antidepressant over another, and which antidepressants they rarely prescribed and could theoretically live without.

Of 42 responses, 21 were from psychiatrists and 21 from primary care practitioners including internal medicine and family practice. Overall, providers agreed that SSRIs as a class were more useful than SNRIs, followed by bupropion, trazodone, and mirtazapine.

Providers found sertraline to be most useful, followed by escitalopram, fluoxetine, citalopram, paroxetine, and fluvoxamine. About half of the responders perceived escitalopram to offer an efficacy or tolerability advantage over citalopram; the other half saw little or no difference. Provider comments indicated definite niches in therapy for sertraline (many indications; lower risk of adverse effects and drug interactions); fluoxetine (can be used in children, activating); venlafaxine (may be more effective than SSRIs but also has more adverse effects); bupropion (low risk of sexual adverse effects, can be used to treat sexual adverse effects from SSRIs; may be useful in smokers and ADHD patients); trazodone (treatment of sleep symptoms); and mirtazapine (sedating; may be useful to stimulate weight gain in elderly or oncology patients or in HIV wasting).

4) *Overall Clinical Effectiveness Conclusion*

- The Committee concluded that the AD1s offer similar efficacy in treating MDD with the exception of data supporting slightly greater efficacy with venlafaxine compared to the SSRIs and with escitalopram compared to citalopram. Fluoxetine has a unique advantage for the treatment of MDD in children. With respect to other psychiatric conditions, paroxetine and sertraline appear to be the most broadly useful AD1s based on FDA-approved indications and published clinical evidence. Duloxetine is the only AD1 with an FDA-approved indication for a non-psychiatric condition, DPNP; it is not clear whether duloxetine offers advantages over other agents used for the treatment of DPNP.
- The Committee concluded that adverse effects differ across AD1s, but there are little data to support any substantial difference among AD1s with respect to tolerability. One possible exception is the SNRI venlafaxine, which appears to be associated with more adverse effects than the SSRIs. It is not clear whether duloxetine will prove to be better tolerated than venlafaxine. The difference in adverse effects between agents may affect the choice of agent in individual patients, creates specific niches in which adverse effects become useful therapeutic effects (e.g., mirtazapine), and increases the number of AD1s necessary to provide adequate clinical coverage.
- Bupropion, mirtazapine, nefazodone, and trazodone appear to have a lower risk of sexual dysfunction compared with SSRIs and SNRIs. Fluvoxamine, fluoxetine, paroxetine, and duloxetine have a generally higher potential for drug interactions than

citalopram, escitalopram, sertraline, and venlafaxine. The likelihood of discontinuation syndrome with the SSRIs appears to correlate with half-life. Venlafaxine may be associated with more discontinuation symptoms than SSRIs; duloxetine may be similar, although data are lacking. Discontinuation symptoms appear to be rare with bupropion, which has little serotonergic effect.

- Rare but serious adverse effects include recent case reports of hepatotoxicity with duloxetine, increased seizure risk with bupropion, hepatotoxicity with nefazodone, agranulocytosis with mirtazapine, and priapism with trazodone. Drugs with issues of particular concern in specific patient populations include duloxetine (avoid in hepatic insufficiency, substantial alcohol use, liver disease, narrow angle glaucoma), paroxetine (recent epidemiological evidence of increased risk in pregnancy), and bupropion (avoid in patients with increased seizure risk). All AD1s are Pregnancy Category C except for bupropion, which is Pregnancy Category B.

COMMITTEE ACTION: The Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to accept the clinical effectiveness conclusion as stated above.

B. AD1 UF Relative Cost Effectiveness. The P&T Committee evaluated the relative cost effectiveness of the AD1s in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e) (2).

To determine the relative cost effectiveness of the AD1s, two separate economic analyses were performed a pharmacoeconomic analysis and BIA. From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that AD1s differed in regards to efficacy, safety, and tolerability in the treatment of MDD and other psychiatric illness. To account for the difference in relative clinical effectiveness in this therapeutic class, two cost effectiveness analyses (CEAs) were performed a CEA based on the results obtained via a multi-attribute utility theory (MAUT) analysis, and a CEA based on the findings reported in *Drug Class Review on Second Generation Antidepressants* by the Oregon Health & Science University Drug Effectiveness Review Project (OHSU-DERP). In a CEA, the agents within a therapeutic class are competed on two dimensions, cost and effect (outcomes). In both CEAs, the drug cost used in the analysis was the point of service adjusted total weighted average cost per day of treatment (for all three points of service).

The CEA-MAUT was presented first. For this analysis, the effectiveness measure used for each agent was the composite score derived from the MAUT analysis that ranked the agents based on clinical outcome evidence. The MAUT accounted for the differences in clinical outcome evidence; FDA indication supporting an agent's use for psychiatric and non-psychiatric conditions other than MDD, such as GAD, PTSD, DPNP, etc.; evidence supporting efficacy and safety in the pediatric population; differences in safety (e.g., drug interactions, use in pregnancy, contraindications, potential for cardiovascular adverse events, and potential for rare but serious adverse events); and differences in tolerability (e.g., sexual dysfunction).

Overall, the results of the CEA-MAUT were as follows:

- Trazodone was determined to be the most cost-effective agent;
- Fluoxetine and sertraline were determined to be more cost effective and more costly compared to trazodone;

- Other agents were shown to be less effective and more costly, compared to trazodone, fluoxetine, and sertraline.

With respect to the SSRIs:

- Fluoxetine was most-effective, followed by citalopram, paroxetine IR, escitalopram, and paroxetine CR, in that order.

With respect to the SNRIs:

- Venlafaxine was shown to be more cost-effective compared to duloxetine.

With respect to the other AD1s:

- Trazodone was the most cost effective agent followed by mirtazapine, nefazodone, bupropion SR, and bupropion XL, in that order.
- (Note: Although trazodone was determined to be the most cost-effective agent, and nefazodone was shown to be more cost-effective compared to bupropion SR and bupropion XL, neither trazodone nor nefazodone was considered a viable first-line monotherapy treatment alternative for MDD).

The second cost effectiveness analysis (CEA-Response) was based on the OHSU-DERP report for MDD. This report examined 49 head-to-head randomized controlled clinical trials and one systematic review. The overall conclusion of the report was that “effectiveness and efficacy were similar and the majority of trials did not identify substantial differences among drugs. Studies were often small and relatively underpowered to detect significant differences in efficacy.” However, both the OHSU-DERP report and the PEC clinical review did acknowledge that there was some evidence to suggest that escitalopram is more effective compared to citalopram; venlafaxine has a modest but statistically significant additional treatment effect compared to fluoxetine; and that escitalopram and venlafaxine are equally effective. However, one of two studies reported significantly greater discontinuations due to adverse effects in the venlafaxine group than in the escitalopram group. To account for these potential differences in clinical outcomes, a CEA-Response model was constructed. This model examined the costs and outcomes of treatment for MDD during the acute phase of treatment (8-weeks). In addition to drug costs, other direct medical costs included provider costs and costs associated with the treatment of adverse events. The effectiveness measure was reported response rate at 8-weeks.

Overall, the results from the CEA-Response analysis revealed that:

- Fluoxetine was the most cost-effective agent;
- Escitalopram was more effective and more costly;
- Venlafaxine was equivalent in effectiveness compared to escitalopram, but was significantly more costly;
- Other agents were equivalent in effectiveness compared to fluoxetine but were more costly.

A summary analysis was then conducted based on the CEA-MAUT and CEA-Response results. The summary analysis focused on comparisons either between the most cost-effective agent and

the more costly agents within a sub-class or between a generic agent and its branded product extension (e.g., paroxetine IR and paroxetine CR). This analysis focused on the:

- SSRIs – fluoxetine in special packaging for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly), sertraline, escitalopram, and paroxetine CR;
- SNRIs – venlafaxine versus duloxetine;
- Bupropion XL versus Bupropion SR.

The results of the summary analysis showed:

For the SSRIs:

- Fluoxetine branded product extensions - Sarafem and Prozac Weekly were > 7-fold more costly and had similar relative clinical effectiveness compared to generic fluoxetine;
- Sertraline had equal (CEA-Response) or slightly greater (CEA-MAUT) relative clinical effectiveness but was significantly more costly compared to fluoxetine;
 - (Note. sertraline is projected to go generic in June 2006)
- Escitalopram was shown to have lower overall relative clinical effectiveness (CEA-MAUT) compared to fluoxetine but potentially greater relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to citalopram, however at a significantly greater cost;
- The CEA-MAUT and CEA-Response both showed the paroxetine IR and paroxetine CR had similar relative clinical effectiveness, but paroxetine CR was significantly more costly compared to paroxetine IR.

For the SNRIs:

- Venlafaxine was shown to have greater overall relative clinical effectiveness (CEA-MAUT) and greater relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to duloxetine for a similar cost;
- Bupropion XL was shown to have greater overall relative clinical effectiveness (CEA-MAUT) but similar relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to bupropion SR at a significantly greater cost.

The results of the CEAs were subsequently incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of AD1s best meets the clinical needs of the DoD population at the lowest cost to the MHS. Based on the BIA results and other clinical considerations (e.g., the need to make a broad array of antidepressants available to meet the clinical coverage needs), the Committee agreed that a group of AD1s that included bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine IR, sertraline, trazodone, and venlafaxine best achieved this goal when compared to other combination groups of AD1s, 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 (12 for, 5 opposed, 1 abstention, 1 absent) to accept the AD1 cost-analysis presented by the PEC. The P&T Committee concluded that: fluoxetine in special packaging for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly), escitalopram, and paroxetine CR were not cost-effective relative to the other agents within the SSRI sub-class; duloxetine was not cost-effective compared to venlafaxine; bupropion XL was not cost-effective compared to bupropion. Ultimately, the P&T committee did not value escitalopram's potentially greater relative clinical effectiveness in the treatment of MDD (based on clinical trial evidence supporting a clinical efficacy advantage over citalopram) or bupropion XL's greater overall relative clinical effectiveness (based on its once-daily dosing regimen) enough to overcome the agents' significantly higher cost. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the AD1s, and other relevant factors, the P&T Committee recommended that fluoxetine in special packaging for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly), escitalopram, and paroxetine CR, duloxetine, and bupropion XL be classified as non-formulary under the UF and that bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine (HCl and mesylate formulations), sertraline, trazodone, venlafaxine and venlafaxine extended release be classified as formulary on the UF. The P&T Committee recommended that existing quantity limits for fluoxetine 90-mg delayed release capsules (Prozac Weekly) of 4 capsules per 30 days, 12 capsules per 90 days be continued, since there is little new information to support the safety and efficacy of weekly doses exceeding 90 mg.

COMMITTEE ACTION. The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 1 abstention, 1 absent) to recommend that fluoxetine in special packaging for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly) escitalopram, and paroxetine CR, duloxetine, and bupropion XL be classified as non-formulary under the UF, with bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, venlafaxine and venlafaxine extended release remaining on the UF. In addition, the P&T Committee recommended that existing quantity limits for fluoxetine 90-mg delayed release capsules (Prozac Weekly) of 4 capsules per 30 days, 12 capsules per 90 days be continued.

C. AD1 UF Medical Necessity Criteria: Based on the clinical evaluation of the AD1s 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 formulary agents is contraindicated, and the use of a non-formulary agent is not contraindicated.
- 2.) The patient has experienced or is likely to experience significant adverse effects from the formulary agents, and the patient is reasonably expected to tolerate a non-formulary agent.
- 3.) Use of the formulary agent resulted in therapeutic failure, and the patient is reasonably expected to respond to a non-formulary agent.
- 4.) The patient has previously responded to a non-formulary agent and changing to a formulary agent would incur unacceptable risk.
- 5.) There is no alternative pharmaceutical agent on the formulary.

With respect to criteria 2 and 3, the Committee noted the following:

Adverse effect profiles are known to differ among the AD1s and other factors may play a part in selecting an agent for a particular patient (e.g., symptoms of sedation or agitation, family history of efficacy). Clinical practice guidelines support SSRIs as the first choice in most patients, and support trying a second SSRI in patients who have failed a first SSRI due to lack of efficacy, but they do not support trying all available SSRIs before being treated with an antidepressant with a different mechanism of action.

- For escitalopram, the Committee supported medical necessity in the following cases:
 - The patient has previously failed adequate trials of at least two other SSRIs (at least 8 weeks each), without response or remission, and other formulary medications (such as venlafaxine and bupropion) are not appropriate for treatment.
 - The patient has previously tried at least two other SSRIs and could not tolerate the adverse effects, and other formulary medications (such as venlafaxine and bupropion) are not appropriate for treatment.
- For duloxetine, the Committee supported medical necessity in patients who have tried and failed, or were unable to tolerate, venlafaxine, and in whom other formulary medications (e.g., SSRIs and bupropion) are not appropriate for treatment.
- The Committee had difficulty envisioning circumstances in which paroxetine controlled release (Paxil CR), bupropion extended release (Wellbutrin XL), fluoxetine 90 mg extended release capsules (Prozac Weekly), and specially packaged fluoxetine for PMDD (Sarafem) would be considered medically necessary, since all of these medications would be available on the UF in other formulations. With respect to paroxetine CR, which has data supporting a significantly lower incidence of nausea in the first week after starting therapy compared to the IR formulation, the Committee agreed that one circumstance in which paroxetine CR could be considered medically necessary might be in a patient who had previously responded to paroxetine and who had other predisposing factors for nausea (e.g., chemotherapy or a GI disorder).

With respect to criterion 5, the Committee agreed that medical necessity criteria for duloxetine in DPNP should be based on national clinical practice guideline recommendations for treatment of DPNP. The Committee also agreed that duloxetine could be considered medically necessary in other types of neuropathic pain (e.g., phantom limb syndrome) under criterion #5 if reliable evidence exists for safety and efficacy and more accepted therapies are not clinically appropriate.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 1 abstained, 2 absent) to accept the AD1s medical necessity criteria.

D. AD1 UF Implementation Plan: Because a substantial number of patients is currently receiving non-formulary AD1s and the need to carefully assess and monitor patients taking this class of medication, the P&T Committee recommended an effective date no later than the first Wednesday following a 180-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, 1 abstained, 2 absent) to recommend an implementation period of 180 days.

E. AD1 Basic Core Formulary (BCF) Review and Recommendations: The P&T Committee reviewed the AD1s recommended for inclusion on the UF to select recommended

agents for the BCF. Based on the outcome of relative clinical effectiveness determinations, the Committee decided that three or four SSRIs, zero or one SNRIs, and zero to two other agents (bupropion, mirtazapine, nefazodone, or trazodone) would be added to the BCF. AD1s currently on the BCF include: citalopram, fluoxetine (excluding Sarafem and Prozac Weekly), paroxetine (excluding Paxil CR), sertraline, venlafaxine extended release, bupropion sustained release (but not Wellbutrin XL), and trazodone.

With respect to the SSRIs, the Committee agreed that it was reasonable to add fluoxetine (excluding Prozac Weekly and Sarafem) and citalopram to the BCF, based on cost effectiveness and clinical effectiveness considerations. In addition, the Committee agreed that sertraline should be added to the BCF despite its significantly higher cost compared to fluoxetine and citalopram. Sertraline is the most commonly used SSRI in MTFs and its relative clinical effectiveness based on the CEA-MAUT was slightly greater than other SSRIs, primarily as a result of its FDA-approved indications and evidence supporting efficacy in a large number of psychiatric conditions in addition to MDD, as well as its relatively low risk of drug interactions and adverse effects. Sertraline is expected to become generically available in June of 2006. Given the inclusion of fluoxetine, citalopram, and sertraline, the Committee agreed that paroxetine IR should not be added to the BCF. Reasons for not adding paroxetine to the BCF include: 1) it's not as cost effective as fluoxetine and citalopram, 2) it has declining use in MTFs, 3) it was ranked lower by providers compared to other SSRIs, 4) it has a relatively high risk of drug interactions and adverse effects, 5) a high risk of discontinuation syndrome; and 6) a recent labeling change regarding use in pregnancy.

With respect to the SNRIs, the Committee concluded that venlafaxine should not be added to the BCF. Although venlafaxine may be slightly more efficacious than SSRIs, it is also associated with more adverse effects, including the potential for increases in blood pressure. It is typically not used for initial treatment. The cost of venlafaxine is at least two-fold higher than treatment with any SSRI and several times higher than treatment with the most cost-effective SSRI. While SNRIs have a definite place in therapy, the Committee agreed that it was not necessary to retain an SNRI on the BCF.

With respect to the other AD1s, the Committee agreed that trazodone and bupropion sustained release should be added to the BCF. Trazodone is relatively commonly used in MTFs (about 12,000 prescriptions per month), is available at low cost, and its use as an adjunctive medication for insomnia in depressed patients was supported by provider opinion. Bupropion sustained release is also commonly used in MTFs, and has a definite and well-supported role in treatment of patients who have experienced or are concerned about sexual dysfunction with SSRIs.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend the following as the BCF agents: fluoxetine (excluding Prozac Weekly and Sarafem, which are non-formulary), citalopram, sertraline, trazodone, and bupropion SR.

12. MACROLIDES/KETOLIDE DRUG CLASS REVIEW

A. Macrolide/Ketolide Relative Clinical Effectiveness: The DoD P&T Committee evaluated the relative clinical effectiveness of the macrolides: azithromycin (Zithromax), azithromycin 2 gram extended release suspension (Zmax), clarithromycin IR (Biaxin and various generics), clarithromycin extended release (ER) (Biaxin XL), all erythromycin salts and esters as well as erythromycin/sulfisoxazole combination suspension (various generics); and the ketolide, telithromycin (Ketek). Information regarding the safety, effectiveness, and clinical outcomes

for the treatment of various infections was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21.

1) *Spectrum of Activity/Resistance*: Increasing use of macrolides has resulted in increased rates of macrolide resistant *S. pneumoniae*. Macrolide resistance to *S. pneumoniae* appears to be a class effect. *In-vitro*, telithromycin remains active against macrolide and penicillin resistant *Streptococcus*, and is the only agent in the class with an FDA indication for multi-drug resistant *S. pneumoniae* (MDRSP). However, telithromycin's ability to overcome MDRSP has not resulted in higher cure rates. *H. influenzae* is commonly resistant to erythromycin, whereas azithromycin, clarithromycin and telithromycin are active against *H. influenzae*

2) *Efficacy*

a) *Endpoints*: Endpoints in the clinical trials included clinical cure rate, bacteriologic eradication, and antibiotic failure rates. Any applicable trials evaluating clinical outcomes, such as mortality, hospital admission rates, or length of hospitalization, were also evaluated.

b) *Efficacy for Community Acquired Pneumonia (CAP)*

Place in Therapy: The American Thoracic Society (ATS), the Infectious Diseases Society of America (IDSA), and the Canadian Infectious Diseases Society/Canadian Thoracic Society (CIDS/CTS) guidelines do not give a preference for azithromycin or clarithromycin for treating CAP, but state that erythromycin is not preferred due to poor tolerability and limited spectrum of activity. There are no specific recommendations yet for telithromycin, although an update in ATS/IDSA guidelines is expected soon.

Efficacy of Macrolides/Ketolide: The Committee reviewed 17 head-to-head trials comparing one macrolide/telithromycin to another macrolide/telithromycin, or one macrolide/telithromycin versus another antimicrobial agent. Sixteen trials showed similar cure rates and/or bacteriological eradication rates. One poor quality trial comparing azithromycin to clarithromycin found a significant decrease in length of hospitalization and mortality with azithromycin. Another trial examined healthcare utilization from two pooled trials comparing clarithromycin IR to telithromycin. Despite equivalent cure rates in the individual trials, telithromycin was associated with significantly fewer CAP-related hospitalizations than clarithromycin IR in the pooled analysis. The original studies in the pooled analysis were not designed to analyze healthcare utilization; therefore, results were interpreted with caution.

CAP Conclusion: The Committee concluded there was no evidence of a difference in clinical cure rates/bacterial eradication rates between azithromycin, Zmax, clarithromycin IR/ER, erythromycin, and telithromycin when treating CAP. Erythromycin may have limited clinical utility in treating CAP caused by *H. influenzae*, due to its inactivity against the microorganism.

c) *Efficacy for Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)*:

Place in Therapy: Guidelines from the American College of Physicians (ACP), American Society of Internal Medicine (ASIM), and American College of Chest Physicians do not give specific recommendations for the treatment of ABECB. Other recommendations from noted infectious disease physicians state azithromycin and clarithromycin are recommended in patients with uncomplicated ABECB (< 65 years of age; < 4 exacerbation per year, no co-morbidities, and minimal or no impairment in pulmonary function). Erythromycin was not recommended due to limited activity

against *H. influenzae*. No guidelines or recommendations have addressed the use of telithromycin for ABECB.

Efficacy of Macrolides/Ketolide: The Committee reviewed six double-blind, head-to-head trials comparing one macrolide/telithromycin to another macrolide, or another antimicrobial agent. All six trials showed similar cure rates and/or bacteriological eradication rates for the treatment of ABECB. One trial evaluated healthcare utilization, and found telithromycin was associated with significantly fewer respiratory-related hospitalizations, all-cause hospitalizations, and emergency room visits than clarithromycin IR, despite similar clinical cure rates. Healthcare utilization was a secondary endpoint to this study, and results should be interpreted with caution.

ABECB Conclusions: The Committee concluded there is no evidence of a difference in clinical cure rates/bacterial eradication rates between azithromycin, Zmax, clarithromycin IR/ER, erythromycin, and telithromycin when treating ABECB. Erythromycin may have limited clinical utility in treating ABECB caused by *H. influenzae*, due to its inactivity against the microorganism

d) *Efficacy for Acute Bacterial Sinusitis (ABS):*

Place in Therapy: Treatment guidelines from the American Academy of Pediatrics (AAP) and the Sinus and Allergy Health Partnership (SAHP) recommend clarithromycin and azithromycin in patients with mild uncomplicated ABS who have a type I hypersensitivity to penicillin. The AAP guidelines no longer recommend erythromycin for ABS due to the increasing resistance. However, the SAHP guidelines do not give preference to any macrolide, and include telithromycin in the same treatment category as the other macrolides for ABS.

Efficacy of Macrolides/Ketolides: Six double-blind, head-to-head trials comparing a macrolide/telithromycin to another macrolide or another antimicrobial showed similar cure rates and/or bacteriological eradication rates for the treatment of ABS. A retrospective cohort study of 29,102 patients with ABS concluded that newer broad spectrum antibiotics (azithromycin clarithromycin and amoxicillin-clavulanate) were no better than amoxicillin, trimethoprim-sulfamethoxazole, or erythromycin.

ABS Conclusions: The Committee agreed that all the macrolides (azithromycin, Zmax, clarithromycin IR/ER, and erythromycin) and telithromycin have shown efficacy for the treatment of ABS, and there is no evidence of a difference in clinical cure rates/bacterial eradication rates between the products when treating ABS.

e) *Efficacy for Acute Pharyngitis:*

Place in Therapy: The IDSA guidelines and a position paper by the ACP/ASIM for the treatment of group A β -hemolytic streptococcus pharyngitis (GABHS) recommend erythromycin only in patients with a history of a penicillin allergy. Erythromycin is recommended due to its narrow spectrum of activity compared to azithromycin and clarithromycin. Azithromycin, clarithromycin, or telithromycin are recommended in patients who cannot tolerate erythromycin.

Efficacy of Macrolides/Ketolide: Three trials comparing clarithromycin IR to azithromycin or telithromycin, as well as one trial comparing azithromycin to erythromycin showed similar clinical cure rates. Six trials comparing all the products,

(except Zmax, which has not been studied) have shown similar cure rates to penicillin, the gold standard for the initial treatment of acute pharyngitis.

Acute Pharyngitis Conclusions: The Committee agreed that azithromycin, clarithromycin IR/ER, erythromycin, and telithromycin have shown efficacy for the treatment of pharyngitis, and there is no evidence of a difference in clinical cure rates/bacterial eradication rates between the products. Currently there are no published trials evaluating Zmax for the treatment of acute pharyngitis.

f) *Efficacy for Acute Otitis Media (AOM):*

Place in Therapy. The AAP and the American Academy of Family Physicians (AAFP) guidelines recommended macrolides as third-line agents, with use reserved for patients with a history of a type I reaction to penicillins and cephalosporins. The guidelines state that azithromycin, clarithromycin, and erythromycin/sulfisoxazole are all considered preferred macrolides. Erythromycin alone is not recommended due to its lack of activity against *H. influenzae*.

Efficacy of Macrolides: Two head-to-head trials comparing azithromycin to clarithromycin showed similar clinical cure rates. In addition, trials comparing azithromycin, clarithromycin IR, erythromycin-sulfisoxazole and erythromycin to either standard dose amoxicillin or amoxicillin-clavulanate showed similar cure rates. There were no clinical trials found evaluating clarithromycin ER, Zmax, and telithromycin for the treatment of AOM, and these agents do not have an FDA indication for the treatment of AOM.

AOM Conclusions: The Committee agreed that azithromycin, clarithromycin IR, erythromycin-sulfisoxazole and erythromycin have shown efficacy against AOM versus amoxicillin or amoxicillin-clavulanate, and there is no evidence of a difference in clinical cure rates/bacterial eradication rates between the products. Erythromycin alone may not be as effective for AOM compared to the other macrolides due to its inactivity against *H. influenzae*. There were no clinical trials found evaluating clarithromycin ER, Zmax and telithromycin for the treatment of AOM.

g) *Efficacy for H. pylori infections and Mycobacterium avium complex (MAC):*

Macrolides/ketolides are also used to treat infections cause by mycobacterium avium complex in the immunocompromised population and *H. pylori*-associated peptic ulcer disease. These infections occur with less frequency in DoD than respiratory infections. Thus, the Committee briefly reviewed the data and concluded the following: 1) For *H. pylori* eradication, clarithromycin-based regimens appear to be superior to azithromycin-based regimens; and 2) other macrolide/ketolides have not been adequately evaluated. For the prevention of MAC, either azithromycin or clarithromycin IR is recommended; there is insufficient data from the other macrolides/ketolides to recommend their use. For treatment of MAC, clarithromycin IR may be superior to azithromycin at clearing MAC from the blood, but trials have shown no mortality difference between the two drugs.

3) *Safety and Tolerability:*

Rare but Serious Adverse Drug Reactions (ADRs): All the macrolides/ketolides have the propensity, based on case reports and clinical trials, to cause pseudomembranous colitis, hepatotoxicity, and to prolong the QTc interval. Erythromycin and telithromycin

may cause exacerbation of myasthenia gravis, and should be used with caution in these patients.

Other ADRs: All the macrolide/ketolide products can cause taste perversion/abnormal taste, dizziness, rash, headache, and transient hearing loss. Cases of visual disturbances have been reported with telithromycin.

GI ADRs: Erythromycin has the highest incidence of GI adverse effects (abdominal pain, diarrhea, nausea/vomiting) compared to the other products. Package insert data suggest that Zmax and telithromycin cause more GI related adverse effects than clarithromycin IR/ER or azithromycin.

Special Populations. Pregnancy and Pediatric: Azithromycin and erythromycin are rated pregnancy category B rating whereas clarithromycin and telithromycin are rated pregnancy category C. Azithromycin, clarithromycin IR, and erythromycin are the only agents that have been evaluated in pediatric patients.

Drug Interactions: Azithromycin and Zmax are not metabolized via hepatic cytochrome P450 3A4 mechanisms, and are associated with fewer drug interactions than clarithromycin IR/ER, erythromycin, or telithromycin.

Overall Safety and Tolerability Conclusion: The Committee concluded that azithromycin and Zmax have the most favorable safety/tolerability profile, followed by clarithromycin and telithromycin, with erythromycin having the least favorable safety/tolerability profile.

4) *Other Factors:*

Pharmacokinetics: Erythromycin stearate and base need to be given on an empty stomach, whereas erythromycin ethylsuccinate and estolate can be given without regard to meals. Zmax bioavailability increases greater than two-fold when administered with food, but should be given on an empty stomach due the possibility of increasing the risk of adverse effects. Azithromycin, clarithromycin and telithromycin can be given without regard to meals. Azithromycin and Zmax are not interchangeable, due to differences in absorption and the time to reach peak serum concentration. Both clarithromycin and telithromycin require dosage adjustment for renal dysfunction; telithromycin requires dosage adjustment for liver dysfunction with concomitant renal dysfunction.

Dosing: The following agents can be given daily. Azithromycin, clarithromycin ER, and telithromycin. Clarithromycin IR is dosed twice daily, whereas erythromycin can be dosed between two to four times daily. Zmax is the only agent that is administered as a one-time dose.

Palatability of Oral Suspensions: Clinical studies evaluating taste preferences of antibiotic suspensions showed that pediatric patients preferred the taste of azithromycin over clarithromycin or erythromycin/sulfisoxazole.

Provider Opinion: A survey of DoD providers revealed that MDRSP was not considered a problem when treating CAP in the outpatient setting; there was not an advantage of Zmax's one time dosing versus other azithromycin products; azithromycin was preferred over the other agents in the class; and telithromycin and Zmax were thought to confer no additional benefit over the other members in the drug class.

Conclusions for Other Factors: There are minor differences in the pharmacokinetic profiles, dosing frequency, and palatability of the macrolides/ketolides that can affect individual patient preferences.

Overall Clinical Effectiveness Conclusion: The Committee concluded: (1) telithromycin *in vitro* shows activity against MDRSP, but this has not translated into superior clinical cure/improvement/bacteriological eradication rates in clinical trials; (2) erythromycin may have a limited role in treating many common types of upper and lower respiratory tract infections due to inactivity against *H. influenzae*; (3) clinical cure rates/bacterial eradication rates are similar between the macrolides/ketolides when used for treating CAP, ABECB, ABS, and acute pharyngitis; (4) for AOM, there is no clinical trial experience with clarithromycin ER or Zmax; clinical cure rates are similar with the other products; (5) clarithromycin IR has the best evidence for the treatment of *H. pylori* infections; (6) either azithromycin or clarithromycin can be used for prevention of MAC infection and clarithromycin IR is preferred over azithromycin for the treatment of MAC infections; (7) azithromycin is preferred relative to other macrolides and telithromycin in terms of safety and tolerability; and (8) there are minor differences amongst the agents in terms of other factors. Overall, the Committee concluded that azithromycin has increased overall clinical effectiveness relative to Zmax, clarithromycin IR/ER, erythromycin, and telithromycin.

COMMITTEE ACTION: The DoD P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to accept the clinical effectiveness conclusion as stated above.

B. Macrolide Antibiotic UF Relative Cost Effectiveness: In considering the relative cost effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 C.F.R. 199.21(e)(2).

The macrolide cost effectiveness review was conducted as two discreet analyses. The first analysis considered only the erythromycin salts and base, while the second analysis compared the newer macrolides [azithromycin, Zmax (brand), clarithromycin, and telithromycin]. The first step for each evaluation utilized a cost-analysis to calculate the total weighted average cost per course of therapy for each agent. The second step was to conduct the appropriate pharmacoeconomic analysis taking into account the conclusions of the clinical review. Because the clinical review suggested minimal differences in clinical effectiveness (efficacy, safety, and tolerability) between the erythromycin salts and base, the appropriate pharmacoeconomic analysis for these agents was determined to be cost-minimization. However, a CEA was used to evaluate Zmax, azithromycin, clarithromycin, and telithromycin, because the clinical review suggested differences in clinical effectiveness (efficacy, safety, and tolerability) between these agents. Effectiveness differences between the agents were quantified through the use of a MAUT table.

Although the results of the erythromycin cost analysis (salts and base) determined erythromycin base to have the lowest total weighted average cost per course of therapy across all points of service (MTF, TRRx, TMOP), the cost effectiveness profiles for all the erythromycin agents were considered favorable.

The cost-analysis evaluation between azithromycin, Zmax, clarithromycin, and telithromycin determined azithromycin to have the lowest total weighted average cost per course of therapy across all points of service, followed by Zmax, clarithromycin, and telithromycin, respectively.

The CEA produced results with the same rank order, i.e, azithromycin being the most cost-effective followed by Zmax, clarithromycin and telithromycin.

The results of the above analyses were then incorporated into a BIA, which accounted for other factors and costs associated with a potential decision regarding formulary status of macrolide antibiotics within the UF. These factors included market share migration (due to changing provider prescribing practices), cost reduction associated with non-formulary status, and medical necessity processing fees. Switch costs were not included, because the macrolides were assumed to be used acutely rather than on a chronic basis. The results of the BIA confirmed the results of the preliminary analyses. Erythromycin and azithromycin (other than the Z-max formulation) were found to be the most cost-effective macrolide antibiotics overall. A sensitivity analysis conducted around the uncertainty of azithromycin prices due to its generic availability suggested that, as the price of generic azithromycin falls: 1), azithromycin becomes even more cost effective compared to other second generation macrolides; and 2) scenarios placing the branded Z-max formulation into the non-formulary tier become increasingly more cost beneficial to DoD.

Conclusion: The P&T Committee agreed (17 for, 0 against, 1 abstained, 1 absent) with the relative-cost effectiveness analyses presented for the macrolide antibiotics. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the macrolide antibiotics, the P&T Committee recommended that the status of telithromycin and the Zmax formulation of azithromycin be changed from formulary to non-formulary on the UF, with erythromycin (base and salts), clarithromycin immediate and extended release, and non-Zmax formulations of azithromycin maintaining formulary status on the UF with the formulary cost share.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend non-formulary status on the UF for telithromycin and the Zmax formulation of azithromycin, with erythromycin salts and base, all forms of clarithromycin, and non-Zmax formulations of azithromycin maintaining formulary status on the UF at the formulary cost share.

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

- 1) Use of a formulary macrolide (azithromycin, clarithromycin IR/ER, and erythromycin) is contraindicated, and the use of a non-formulary agent (Zmax and telithromycin) is not contraindicated.
- 2) The patient has experienced or is likely to experience significant adverse effects from formulary macrolides, and the patient is reasonably expected to tolerate a non-formulary agent.
- 3) Treatment with a formulary macrolide has resulted in a therapeutic failure, and the patient is reasonably expected to respond to a non-formulary agent. [Note: "Therapeutic failure" to be outlined on the medical necessity form].
- 4) There is no alternative formulary agent available. The patient may receive telithromycin if he/she has a recent history of documented MDRS, and cannot be treated with agents from other formulary antibiotic classes (e.g., quinolone antibiotics).

COMMITTEE ACTION: The DoD P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to accept the macrolide/ketolide medical necessity criteria.

D. Macrolide/ketolide UF: Because of the low utilization of Zmax and telithromycin at the MTFs, and the fact that these agents, for the most part, are not used chronically, the Committee recommended an effective date no later than the first Wednesday following a 60-day implementation.

COMMITTEE ACTION: The DoD P&T Committee voted (16 for, 1 opposed, 1 abstained, 1 absent) to recommend an implementation period of 60 days.

E. Macrolide/Ketolide BCF Review and Recommendations: The P&T Committee reviewed the macrolides recommended for inclusion on the UF to select the BCF macrolide.

There are currently two macrolides on the BCF: azithromycin 250 mg tablet, and all formulations of erythromycin with the exception of erythromycin particles in tablets (PCE Dispertab) and erythromycin base delayed release capsule. From a clinical and economic standpoint, azithromycin 250 mg tablets and at least one erythromycin salt/ester are rational selections for the BCF. Azithromycin is the highest utilized macrolide in the entire MHS (MTF, TRRx, and TMOP), has a wide range of FDA indications, and is now generically available. Erythromycin has a wide variety of FDA indications, is efficacious for many different types of infections, has a niche in the treatment certain types of disorders/infections, is relatively low in cost compared to the other macrolides and telithromycin, and is generically available. Because of the large number of erythromycin formulations (base and salts), and no one erythromycin formulation has shown to have superior clinical efficacy over another, the individual MTFs can decide what erythromycin formulation should be added to their local formulary.

Conclusion: The Committee concurred with the recommendation to place azithromycin 250 mg tablet and one erythromycin salt/ester on the BCF.

COMMITTEE ACTION: The DoD P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend azithromycin 250 mg tablet, and one erythromycin (base or salt) as the BCF agent(s).

13. ANTI-MUSCARINIC OVER ACTIVE BLADDER MEDICATIONS

PEC staff presented a clinical review of the medications used for the treatment of overactive bladder disease. The agents in this class include oxybutynin chloride immediate release (Ditropan), extended release (Ditropan XL), and transdermal patches (Oxytrol); tolterodine tartrate immediate release (Detrol) and extended release (Detrol LA); trospium chloride (Sanctura); solifenacin succinate (VESIcare); and darifenacin hydrobromide (Enablex). The current BCF agents for this class are oxybutynin chloride immediate release and tolterodine tartrate extended release (Detrol LA). The BCF specifically excludes oxybutynin chloride extended release (Ditropan XL).

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 February 2006 meeting; no action necessary.

13. ADJOURNMENT

The third day of the meeting adjourned at 1130 hours on November 18, 2005. The dates of the next meeting are February 14 – 16, 2006.

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

List of Appendices

Appendix A – Table 1. Implementation Status of UF Decisions

Appendix B – Table 2. Newly Approved Drugs

Appendix C – Table 3. Abbreviations

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

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Decision	Comments
Aug 05	Alpha Blockers for BPH	tamsulosin (Flomax)	BCF	terazosin alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05; MTFs must have terazosin and alfuzosin on formulary.
Aug 05	CCBs	amlodipine (Norvasc) isradipine IR (Dynacirc) isradipine ER (Dynacirc CR) nicardipine IR (Cardene, generics) nicardipine SR (Cardene SR) verapamil ER (Verelan) verapamil ER for bedtime dosing (Verelan PM, Covera HS) diltiazem ER for bedtime dosing (Cardizem LA)	BCF	nifedipine ER (Adalat CC) verapamil SR diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150-day implementation period)	BCF selection effective 13 Oct 05; MTFs must have the CC formulation of nifedipine ER (Adalat CC or its generic equivalent) verapamil SR, and the Tiazac formulation of diltiazem ER on formulary.
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	moexipril (Univasc), moexipril / HCTZ (Uniretic) perindopril (Aceon) quinapril (Accupril) quinapril / HCTZ (Accuretic) ramipril (Altace)	BCF	captopril lisinopril lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05; MTFs must have captopril, lisinopril, and lisinopril HCTZ on formulary.
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.

Meeting	Drug Class	Non-Formulary Medications	BCF/ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Decision	Comments
Feb 05	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; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy;

TRRx = TRICARE Retail Pharmacy program; UF = UF

ER = extended release; IR = immediate release; SR = sustained release

ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs Nov 2005 DoD P&T Committee Meeting

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Pregabalin (Lyrica; Pfizer) capsules; GABA Analogue	Dec 04 (not launched until Sept 05): Lyrica is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. Lyrica is indicated as adjunctive therapy for adult patients with partial onset seizures	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Ramelteon tablets (Rozerem; Takeda); Selective melatonin receptor agonist (Non-benzodiazepine sedative hypnotic)	Jul 05 (launched in Sept 05); Ramelteon is indicated for the treatment of both chronic and transient insomnia characterized by difficulty with sleep onset.	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Mecasermin injection (Increlex; Tercica Pharmaceuticals); Recombinant human insulin-like growth factor-1 (IGF-1)	Aug 05 (anticipated launch in Jan 06); growth deficiency; Mecasermin is indicated for the long-term treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion and have developed neutralizing antibodies to GH.	Prior Authorization recommended due to safety concerns (hypoglycemia) and the potential for misuse in patients with short stature. Consideration of UF status deferred until drug class is reviewed.
Mometasone furoate oral inhaler (Asmanex Twisthaler; Schering Plough); Oral inhaled corticosteroids	Mar 05 (launched in Jul 05); Asmanex Twisthaler is indicated for the maintenance of asthma as prophylactic therapy in patients 12 years of age or older. The Asmanex Twisthaler is also indicated for asthma patients who require oral corticosteroid therapy, where adding Asmanex Twisthaler therapy may reduce or eliminate the need for oral corticosteroids.	Quantity limits recommended due to existing precedence in the class. Consideration of UF status deferred until drug class is reviewed.
Omega 3 acid ethyl esters capsules (Omacor; Reliant Pharmaceuticals); Fish oil supplement	Nov 04 (launched Sep 05); Omacor is indicated as an adjunct to diet to reduce very high (>500 mg/dL) triglyceride levels in adults.	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Nepafenac ophthalmic solution 0.1% (Nevanac; Alcon); Ophthalmic NSAID	Aug 05 (launched Sept 05); Nevenac is indicated for the treatment of postoperative inflammation associated with cataract surgery.	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.

Appendix C – Table 3. Table of Abbreviations

AAP	American Academy of Pediatrics
ABECB	acute bacterial exacerbation of chronic bronchitis
ABS	acute bacterial sinusitis
ACP	American College of Physicians
AD1(s)	Antidepressants-1 (Group of antidepressants considered in Nov 2005 P&T antidepressant review)
ADAS	Alzheimer's Disease Assessment Scale
ADAS-Cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AOM	acute otitis media
ASIM	American Society of Internal Medicine
ATS	American Thoracic Society
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BPI	Brief Pain Inventory
CAP	community acquired pneumonia
CCOHTA	Canadian Coordinating Office of Health Technology Assessment
CEA	cost effectiveness analysis
CFR	Code of Federal Regulations
CIBIC-Plus	Clinician's Interview Based Assessment of Change - Plus
CIDS/CTS	Canadian Infectious Diseases Society/Canadian Thoracic Society
CMA	cost-minimization analysis
CR	controlled release
DHP	Defense Health Program
DM	diabetes mellitus
DoD	Department of Defense
DPNP	diabetic peripheral neuropathic pain
ECF	Extended Core Formulary
ER	extended release
FDA	Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
GAD	generalized anxiety disorder
GH	growth hormone
GHR	growth hormone receptor
GI	gastrointestinal
HAM-D	Hamilton Rating Scale for Depression
HPA	hypothalamic adrenal axis
IDSA	Infectious Diseases Society of America
IGF	insulin growth factor
IGFD	insulin growth factor-1 deficiency
IR	immediate release
LFT	liver function test
MAC	<i>M. avium</i> complex
MADRS	Montgomery Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MAUT	multi-attribute utility theory
MDD	major depressive disorder
MDRSP	multi-drug resistant <i>S. pneumoniae</i>
MHS	Military Health System
MTF	military treatment facility
NDRI	norepinephrine dopamine reuptake inhibitor

NICE	(British) National Institute for Clinical Excellence
NMDA	N-methyl D-aspartate
OCD	obsessive compulsive disorder
OHSU-DERP	Oregon Health & Science University Drug Effectiveness Review Project
P&T	Pharmacy and Therapeutics
PA	prior authorization
PAR	perennial allergic rhinitis
PD	panic disorder
PEC	Pharmacoeconomic Center
PMDD	premenstrual dysphoric disorder
PTSD	posttraumatic stress disorder
RA	rheumatoid arthritis
SAD	social anxiety disorder
SAHP	Sinus and Allergy Health Partnership
SAR	seasonal allergic rhinitis
SIB	Severe Impairment Battery
SNRI	serotonin norepinephrine reuptake inhibitor
SR	sustained release
SSRI	selective serotonin reuptake inhibitor
SUI	stress urinary incontinence
TCA	tricyclic antidepressant
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
UF	Uniform Formulary
XR	extended release

AAP	American Academy of Pediatrics
ABECB	acute bacterial exacerbation of chronic bronchitis
ABS	acute bacterial sinusitis
ACP	American College of Physicians
AD1	Antidepressants Group 1 (group of antidepressants considered in the November 2005 P&T antidepressant drug class review – see page 26 for listing)
ADAS	Alzheimer's Disease Assessment Scale
ADAS-Cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AOM	acute otitis media
ASIM	American Society of Internal Medicine
ATS	American Thoracic Society
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BPI	Brief Pain Inventory
CAP	community acquired pneumonia
CCOHTA	Canadian Coordinating Office of Health Technology Assessment
CEA	cost effectiveness analysis
CFR	Code of Federal Regulations
CIBIC-Plus	Clinician's Interview Based Assessment of Change – Plus
CIDS/CTS	Canadian Infectious Diseases Society/Canadian Thoracic Society
CMA	cost-minimization analysis
CR	controlled release
DHP	Defense Health Program
DM	diabetes mellitus
DoD	Department of Defense
DPNP	diabetic peripheral neuropathic pain

ECF	Extended Core Formulary
ER	extended release
FDA	Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
GAD	generalized anxiety disorder
GH	growth hormone
GHR	growth hormone receptor
GI	Gastrointestinal
HAM-D	Hamilton Rating Scale for Depression
HPA	hypothalamic adrenal axis
IDSA	Infectious Diseases Society of America
IGF	insulin growth factor
IGFD	insulin growth factor-1 deficiency
IR	immediate release
LFT	liver function test
MAC	<i>M. avium</i> complex
MADRS	Montgomery Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MAUT	multi-attribute utility theory
MDD	major depressive disorder
MDRSP	multi-drug resistant <i>S. pneumoniae</i>
MHS	Military Health System
MTF	military treatment facility

NDRI	norepinephrine dopamine reuptake inhibitor
NICE	(British) National Institute for Clinical Excellence
NMDA	N-methyl D-aspartate
OCD	obsessive compulsive disorder
OHSU-DERP	Oregon Health & Science University Drug Effectiveness Review Project
P&T	Pharmacy and Therapeutics
PA	prior authorization
PAR	perennial allergic rhinitis
PD	panic disorder
PEC	Pharmacoeconomic Center
PMDD	premenstrual dysphoric disorder
PTSD	posttraumatic stress disorder
RA	rheumatoid arthritis
SAD	social anxiety disorder
SAHP	Sinus and Allergy Health Partnership
SAR	seasonal allergic rhinitis
SIB	Severe Impairment Battery
SNRI	serotonin norepinephrine reuptake inhibitor
SR	sustained release
SSRI	selective serotonin reuptake inhibitor
SUI	stress urinary incontinence
TCA	tricyclic antidepressant
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
UF	Uniform Formulary
XR	extended release

19 August 2005

DECISION PAPER:**AUGUST 2005 DoD PHARMACY AND THERAPEUTICS COMMITTEE
RECOMMENDATIONS**

- 1. CONVENING**
- 2. ATTENDANCE**
- 3. REVIEW MINUTES OF LAST MEETING**
- 4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES**
- 5. ITEMS FOR INFORMATION**
- 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

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

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

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: 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

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

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

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

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 nifedipine 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:

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:

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:

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

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

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

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

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
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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, treprostini, 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, 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, nifedipine, 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, nifedipine, 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, nifedipine, 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, felodipine, 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, felodipine, 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 release.

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

List of Appendices

Appendix A – Table 1: Implementation Status of UF Decisions

Appendix B – Table 2: Newly Approved Drugs

Appendix C – Table 3: Calcium Channel Blockers

Appendix D – Table 4: Abbreviations

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

19 May 2005

DECISION PAPER:**MAY 2005 DoD PHARMACY AND THERAPEUTICS COMMITTEE
RECOMMENDATIONS**

- 1. CONVENING**
- 2. ATTENDANCE**
- 3. REVIEW MINUTES OF LAST MEETING**
- 4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES**
- 5. ITEMS FOR INFORMATION**
- 6. REVIEW OF RECENTLY APPROVED AGENTS**
- 7. BASIC CORE FORMULARY (BCF) CLARIFICATION OF RECENTLY APPROVED DRUGS**

The DoD Pharmacy and Therapeutics (P&T) Committee reviewed the relative clinical and cost effectiveness of the following recently approved formulations of medications already listed on the BCF.

A. Alendronate 70 mg / cholecalciferol (vitamin D) 2800 IU (Fosamax Plus D)

The current BCF listing for alendronate includes all oral strengths except for 40 mg tablets, which are indicated only for the treatment of Paget's disease. Currently, the majority of use across DoD is of the weekly formulations of alendronate (35- and 70-mg tablets). Addition of vitamin D, which is required for normal bone formation, to alendronate may provide a clinical advantage for patients who have inadequate dietary intake of vitamin D and insufficient exposure to sunlight. Taking into account the manufacturer's offer to add alendronate plus D to the current BPA for alendronate without an increase in price, and because the product is not expected to delay the availability of generic versions of alendronate or alendronate plus vitamin D, the Committee agreed that the product offers a small clinical advantage to military treatment facility (MTF) patients at no additional cost. (See paragraph 7 A. on page 13 of P&T Committee minutes.)

COMMITTEE ACTION: The Committee recommended adding alendronate plus D to the BCF (17 for, 1 abstained, 1 absent).

Director, TMA, Decision:

■ Approved □ Disapproved

Approved, but modified as follows:

B. Fluticasone Propionate HFA (Flovent HCA)

The current BCF listing is for fluticasone oral inhaler. The manufacturer is no longer manufacturing the chlorofluorocarbon (CFC)-containing product (Flovent) and is replacing it with a hydrofluoroalkane (HFA)-containing product (Flovent HFA). Since the product is now the only fluticasone metered dose inhaler available and since the HFA product does not appear to offer any clinical disadvantages compared to the CFC product, the Committee agreed that there was no need to clarify the current BCF listing. As of May 2005, the Flovent HFA metered dose inhaler was available to MTFs and the mail order program at the same price as the old CFC formulation. (See paragraph 7 B. on pages 13-14 of P&T Committee minutes.) No action taken.

C. Insulin Glargine (Lantus) 100 u/mL 3 mL cartridges

The current BCF listing is for insulin glargine injection (Lantus), which was previously available only as a 10 mL vial. The 3 mL cartridges are designed for use with the manufacturer's OptiClik device. The Committee agreed that while this device may benefit some patients (e.g., patients who are needle-phobic or visually impaired), the number of patients who would benefit represents only a small percentage of patients using insulin glargine. The Committee noted that, overall, about 92% of insulin use in DoD is vials, with insulin pens, cartridges, and dispensing syringes representing only 8% of use. The Federal Supply Schedule (FSS) price (as of May 2005) for Lantus was \$25.70 for the 10 mL vial (\$2.67 per mL) vs. \$79.09 for a box of five 3 mL cartridges (\$5.27 per mL). The Committee agreed that the potential clinical benefit associated with use of the cartridges was not sufficient to justify the additional cost. (See paragraph 7 C. on page 14 of P&T Committee minutes.)

COMMITTEE ACTION: The Committee recommended clarifying the current BCF listing for insulin glargine injection to exclude the 100 u/mL 3 mL cartridges (18 for, 1 abstained).

Director, TMA, Decision:

■ Approved □ Disapproved

Approved, but modified as follows:

8. PHOSPHODIESTERASE-5 (PDE-5) INHIBITOR DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the three PDE-5 inhibitors: sildenafil (Viagra), vardenafil (Levitra); and tadalafil (Cialis). There has been an increase in the use of PDE-5s over the past five years, placing this class in the top 50 of Military Health System (MHS) drug class expenditures.

A. COMMITTEE ACTION: The P&T Committee concluded that none of the PDE-5 inhibitors have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other PDE-5 inhibitors. (See paragraph 8 A. on pages 14-15 of P&T Committee minutes.) The Committee concluded that sildenafil and

tadalafil were not cost effective relative to vardenafil. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PDE-5 inhibitors, the P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend formulary status for vardenafil and non-formulary status for sildenafil and tadalafil under the Uniform Formulary (UF). (See paragraph 8 B. on pages 15-16 of P&T Committee minutes) Under 32 C.F.R. 199.21(g)(3), no pharmaceutical agent may be designated as non-formulary on the UF unless preceded by such recommendation by the P&T Committee.

Director, TMA, Decision:

■ Approved □ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of sildenafil and tadalafil, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended medical necessity criteria for the sildenafil and tadalafil (18 for, 0 opposed, 0 abstained). (See paragraph 8 C. on page 16 of P&T Committee minutes for criteria)

Director, TMA, Decision:

■ Approved □ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Because a substantial number of patients are currently receiving either sildenafil or tadalafil (128,007 patients, 90% of all patients receiving PDE-5 inhibitors), the P&T Committee recommended (17 for, 1 opposed, 1 abstained) an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 8 D. on pages 16-17 of P&T Committee minutes for rationale.)

Director, TMA, Decision:

■ Approved □ Disapproved

Approved, but modified as follows: