19 May 2005

DECISION PAPER:

MAY 2005 DoD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

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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: BW ☑ 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: BW ☑ 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: BW ☑ 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: BW ☑ 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: BW ☑ 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 vardenafil on the Extended Core Formulary (ECF) (17 for, 0 opposed, 1 abstained, 1 absent). Because there are no other formulary PDE-5 inhibitors on the UF, MTFs are prohibited from adding additional PDE-5 inhibitor(s) to their local formularies. (See paragraph 8 E. on page 17 of P&T Committee minutes for rationale.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

9. ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITOR DRUG CLASS REVIEW

Portions of the clinical review were presented to the P&T Committee. The Committee provided expert opinion regarding clinical outcomes of importance for the purpose of developing an appropriate cost effectiveness model. Two ACE inhibitors, available as multisource generics for approximately two years, recently suspended manufacturing secondary to litigation results. The Committee will seek pricing information from the companies representing the name brand version of these products. Both the clinical and cost effectiveness analyses will be completed during the August 2005 meeting; no action necessary.

10. MULTIPLE SCLEROSIS DISEASE MODIFYING DRUG (MS-DMD) CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the four MS-DMDs: intramuscular interferon (IFN) beta-1a (Avonex), subcutaneous IFN beta-1a (Rebif), subcutaneous IFN beta-1b (Betaseron), and the subcutaneous polypeptide mixture glatiramer acetate (Copaxone). MS-DMDs have been available for the past 12 years and the class is currently ranked 33rd in MHS drug class expenditures. During a twelve-month period ending 31 January 2005, approximately 6,500 patients were prescribed a MS-DMD. In most cases MS-DMDs are prescribed by sub-specialists (neurologists).

A. COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to accept the conclusion that none of the MS-DMDs have a significant clinically meaningful therapeutic advantage in terms of safety, tolerability and effectiveness over the other MS-DMDs. (See paragraph 10 A. on pages 17-18 of P&T Committee minutes for rationale.) The P&T Committee also concluded that the overall average weighted cost per day of therapy for the MS-DMDs was lowest for Avonex. (See paragraph 10 B. on page 18 of P&T Committee minutes for rationale.) Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the MS-DMDs, and other relevant factors (i.e., relative uniqueness of each agent in patient therapy and the low expectation that patient behavior would be affected by formulary status), the P&T Committee voted (18 for, 0 opposed, 0 abstained) to recommend formulary status for all four MS-DMDs:

IFN beta-1a (Avonex), IFN beta-1a (Rebif), IFN beta-1b (Betaseron), and glatiramer (Copaxone) under the UF.

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing IFN beta-1a (Avonex) on the ECF (18 for, 0 opposed, 0 abstained). MTFs may add additional MS-DMDs to their local formularies if needed to meet the needs of their specific patient populations. (See paragraph 10 E. on page 19 of P&T Committee minutes for rationale.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

APPENDIX A – TABLE 1: PROCESSES AND RECOMMENDATION/APPROVAL AUTHORITIES

APPENDIX B – TABLE 2: NEWLY APPROVED DRUGS

APPENDIX C – DoD P&T COMMITTEE INTERIM MEETING: DERMATOLOGICAL TOPICAL ANTIFUNGAL DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost effectiveness of the 11 dermatological topical antifungals marketed in the U.S. by considering information regarding their safety, tolerability, effectiveness, and other factors, including marketed formulations, generic availability, chemical structures, existing MHS utilization patterns, and Food and Drug Administration (FDA)-approved labeling. The dermatological topical antifungal class was defined as the "azoles" clotrimazole (various generics), econazole (various generics), ketoconazole (various generics), miconazole (various generics), oxiconazole (Oxistat), sertaconazole (Ertaczo), and sulconazole (Exelderm); the "allylamines" butenafine (Mentax) and naftifine (Naftin); the "substituted pyridone" ciclopirox (Loprox); and the "polyene" nystatin. The topical formulation of terbinafine (Lamisil) was specifically excluded from the class, as it is now solely available in a non-prescription product.

A. COMMITTEE ACTION: The P&T Committee concluded that none of the topical antifungals have significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other topical antifungals. (See APPENDIX C, part A. on pages 23-24 of P&T Committee minutes for rationale). The P&T Committee concluded that econazole, sulconazole, ciclopirox, oxiconazole, and sertaconazole are not cost effective relative to nystatin, miconazole, clotrimazole, ketoconazole, butenafine, and naftifine. (See APPENDIX C, part B. on pages 24-26 of P&T Committee minutes for rationale). Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness analysis of the topical antifungal agents, the P&T Committee voted (11 for, 1 opposed, 1 abstained) to recommend formulary status for nystatin, miconazole, clotrimazole, ketoconazole, butenafine, and naftifine; and non-formulary status for econazole, sulconazole, ciclopirox, oxiconazole, and sertaconazole under the UF.

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluations of econazole, sulconazole, ciclopirox, oxiconazole, sertaconazole, 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 econazole, sulconazole, ciclopirox, oxiconazole, and sertaconazole (12 for, 0 opposed, 1 abstained). (See APPENDIX C, part C. on page 26 of P&T Committee minutes for criteria)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: Because topical antifungal products are used to treat acute (rather than chronic) infections, patients are unlikely to require a change in existing therapy. For this reason the P&T Committee recommended (12 for, 0 opposed, 1 abstained) 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. (See APPENDIX C, part D. on page 26 of P&T Committee minutes for rationale.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. *COMMITTEE ACTION:* Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing clotrimazole and nystatin on the BCF (12 for, 0 opposed, 1 abstained). MTFs may add additional UF topical antifungal agents to their local formularies if needed to meet the needs of their specific patient populations. (See APPENDIX C, part E. on pages 26-27 of P&T Committee minutes for rationale.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

William Winkenwerder, Jr., M.D.
Date: 14 July 2005

Department of Defense
Pharmacy and Therapeutics Committee Minutes

19 May 2005

1. CONVENING

The DoD P&T Committee convened at 0800 hours on 17, 18, and 19 May 2005 at the DoD Pharmacoeconomic Center, 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	Director, DoD Pharmacy Programs, TMA
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
Maj Nicholas Conger, MC	Air Force, Internal Medicine Physician
Maj Charlene Reith, BSC (for Col Philip Samples, BSC)	Air Force, Pharmacy Officer
LtCol Brian Crownover, MC	Air Force, Physician at Large
CDR William Hall, MC (via VTC)	Navy, Internal Medicine Physician
LCDR Roger Akins, MC (via VTC)	Navy, Pediatrics Physician
CDR Brian Alexander, MC (via VTC)	Navy, Physician at Large
LCDR Joseph Lawrence, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Barry Sheridan, MC (for COL Joel Schmidt, MC)	Army, Physician at Large
COL Kent Maneval, MS (for COL Isaiah Harper, MS)	Army, Pharmacy Officer (Defense Medical Standardization Board)
CDR Vernon Lew	Coast Guard, Pharmacy Officer
LTC Donald DeGroff, MS, USA	Contracting Officer Representative, TMOP
CDR Jill Pettit, MSC, USN	Contracting Officer Representative, TRRx
Joe Canzolino (present May 17th only)	Department of Veterans Affairs

B. Voting Members Absent

None	

C. Non-Voting Members Present

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

D. Non-Voting Members Absent

None	

E. Others Present

CDR William Blanche, MSC (present May 17th only)	Navy Pharmacy Specialty Leader
COL Gregory Wickern, MC	Air Force, Alternate for Pediatric Physician at Large
Mr. Dan Remund	DoD Pharmacoeconomic Center
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
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC , USA	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 (present May 19th only)	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Dave Flowers	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Col Nancy Misel, BSC, USAF	IMA, DoD Pharmacoeconomic Center
Mark Geraci (present May 18th only)	Department of Veterans Affairs
Paul Vasquez (present May 18th only)	Defense Supply Center Philadelphia

3. REVIEW MINUTES OF LAST MEETING

Dr. William Winkenwerder, Jr., M.D. approved the minutes of the DoD Pharmacy and Therapeutics (P&T) Committee held February 2005 on April 18, 2005.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

A. The February 2005 DoD Pharmacy and Therapeutics Committee Minutes (Table 1: Process and Recommendations/Approval Authorities) - The P&T Committee developed a comprehensive list of functions associated with formulary management and categorized each in one of three decision processes outlined in Table 1 (Appendix A). Under 10 U.S.C. § 1074g and 32 C.F.R. 199.21, recommendations to the Director, TMA, on formulary status, preauthorizations, and the effective date for a drug's change from formulary to non-formulary status must be reviewed by the Beneficiary Advisory Panel (BAP) before the Director may make a final decision. Establishment and changes to

medical necessity criteria are not required to be reviewed by the BAP before the Director makes a final decision. An administrative clarification was made to the table as follows:

- **Approval by Director, TMA required based on DoD P&T Committee recommendations and BAP Comments**
  - Bullet: "Changes to the existing prior authorizations and medical necessity criteria (e.g., due to the availability of new efficacy or safety data)"
  - Was changed to: "Changes to existing prior authorizations (e.g., due to the availability of new efficacy or safety data)"
- **Approval by Director, TMA required based on Committee recommendations**
  - Bullet: "Establishment of medical necessity criteria for non-formulary agents"
  - Was changed to: "Establishment and changes to existing medical necessity criteria for non-formulary agents"

B. DoD P&T Committee Charter – Legal counsel stated that the wording of the DoD P&T Committee Charter is silent regarding the ability of alternate DoD P&T members to vote in the absence of the primary member. CAPT Buss stated that the following change to the charter has been proposed: 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.

C. Quantity Limit for Azelastine (Astelin) – Quantity limits for azelastine were set at the February 2005 DoD P&T meeting as 1 bottle per 30 days (retail), and 3 bottles per 90 days (mail order). The intent of the previous quantity limit was to provide 30-day increments of the medication under standard dosing regimens. However, because of priming requirements for initial and intermittent use, one bottle will not last for 30 days if used continuously under the standard dosing regime. Administrative adjustment of the azelastine quantity limits are as follows: 2 bottles per 30 days, 3 bottles per 60 days, and 4 bottles per 90 days. (ESI standard is 4 bottles per 90 days).

5. ITEMS FOR INFORMATION

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

A. Angiotensin Receptor Blocker (ARB) Drug Class Review Clarification: The P&T Committee's Uniform Formulary (UF) recommendations documented in the February 2005 minutes and approved by Dr. Winkenwerder include each of the listed ARBs and their respective combinations with hydrochlorothiazide. As a result, both eprosartan (Teveten) and eprosartan / hydrochlorothiazide (Teveten HCT) were designated as non-formulary under the UF, and both telmisartan (Micardis) and telmisartan / hydrochlorothiazide (Micardis HCT) were placed on the Basic Core Formulary (BCF).

B. Beneficiary Advisory Panel (BAP) Briefing: TMA briefed the members of the DoD P&T committee regarding the March 23, 2005 BAP meeting. The Committee was briefed on BAP comments regarding DoD P&T Committee's UF and implementation recommendations.

C. Extension of Expiration Dates for Selected Agents Requiring Prior Authorization (PA): DoD PA criteria are currently established for agents within eight drug classes. These include: antifungals for onychomycosis [Lamisil (terbenafine), Penlac (ciclopirox), Sporanox (itraconazole)]; Enbrel (etanercept); fertility medications

(injectable gonadotropins); growth hormone (somatropin, somatrem); Humira (adalimumab); Kineret (anakinra); phosphodiesterase-5 (PDE-5) inhibitors [Cialis (tadalafil), Levitra (vardenafil), and Viagra (sildenafil)]; and Raptiva (efalizumab). When a PA is granted for any of these agents, the maximum duration of the PA is for one year.

Currently the contractor for TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy (TRRx) programs re-establishes the PA for each of these agents in these eight drug classes annually for the same fee that is negotiated for conducting the initial PA. Because the responses to the PA criteria established for some of these agents are not expected to change over time, re-establishing the PA for some of these agents annually will no longer be required, thus saving DoD the recurrent PA processing costs. As of June 1, 2005, these specific medications will no longer have a maximum one year expiration date and all existing PAs for them will have their current annual expiration date removed: Enbrel (etanercept); Humira (adalimumab); Kineret (anakinra); PDE-5 inhibitors (tadalafil, vardenafil, and sildenafil); and Raptiva (efalizumab).

D. Determining Medical Necessity for Non-Formulary Medications – PEC staff provided the DoD P&T Committee with an update concerning the medical necessity process for medications designated as non-formulary under the UF process. Important points included:

- Spouses, family members, and retirees do not need a medical necessity determination in order to fill prescriptions for non-formulary medications at the $22 non-formulary cost share through retail network pharmacies or mail order. They may fill prescriptions for non-formulary medications at the lower formulary cost share ($9) if the non-formulary medication is determined to be medically necessary.
- Active duty service members, who pay no cost shares, may not fill prescriptions for a non-formulary medication unless it is determined to be medically necessary. If the non-formulary medication is determined to be medically necessary, active duty service members may fill prescriptions at $0 cost share.
- Military Treatment Facilities (MTFs) will be able to fill non-formulary requests for non-formulary medications only if both of the following conditions are met: 1) a MTF provider writes the prescription, and 2) medical necessity is established for the non-formulary medication. MTFs may (but are not required to) fill a prescription for a non-formulary medication written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.
- Medical necessity criteria established by the DoD P&T Committee for medications designated as non-formulary under the UF apply to all three points of service (MTFs, mail order, retail). Medical necessity determinations are portable between the TMOP and the retail pharmacy network and have no expiration date.
- If an MTF fills a prescription for a medication designated as non-formulary under the UF process, the assumption is made that the MTF determined that it is medically necessary for the beneficiary to receive the non-formulary medication based on the criteria established by the DoD P&T Committee. An override is established in the patient's electronic medication profile and the beneficiary may then receive the non-formulary medication at the formulary cost share from either the retail pharmacy network or TMOP.
- According to the UF rule, information supporting medical necessity for use of a non-formulary medication may be provided at a later date (no later than 60 days

from the dispensing date), as an appeal to reduce the cost share for that prescription fill. Procedures are currently being developed to meet this requirement as of July 17, 2005, the effective date for the first medications designated as non-formulary under the UF process.

- More information, including medical necessity criteria and forms, is available on the TRICARE pharmacy website at: www.tricare.osd.mil/pharmacy/medical-nonformulary.cfm. Information on the formulary status and availability of specific medications is available by using the TRICARE Formulary Search Tool (www.tricareformularysearch.org).

E. PDE-5 Inhibitor PA Review – Mr. Dave Flowers presented a review of the status of the PDE-5 inhibitor PA with regard to frequency of requests, approval rate, and sentinel effect.

Frequency: At TRRx and TMOP, there were approximately 680 requests for PDE-5 PAs in the month of March 2005. This amount had been increasing slightly over the prior several months, gradually rising to this level from approximately 500 requests in the month of September 2004.

A significant reduction in the number of PA requests occurred beginning in mid-August 2004. From June 2004 through August 2004, an average of over 3,000 requests occurred each month. The reduction beginning in August was attributed to the automatic granting of PDE-5 inhibitor coverage to all males age 50 or over. This change was effective in Pharmacy Data Transaction Service (PDTS) on August 20, 2004, and as a result, no males age 50 or over have been required to follow the PA process in order to obtain these products.

***Approval* Rate:** Over the past ten months (June 2004 through March 2005), approximately 94% of all beneficiaries requesting PA for PDE-5 inhibitors were granted approval. When the PA requests were denied, there were three most commonly reported reasons. These reasons are presented below, in descending order of occurrence:

- PDE-5 is not being used for treatment of erectile dysfunction of organic origin
- PDE-5 is not being used for a male
- PDE-5 is not being used for the treatment of sexual dysfunction

Sentinel Effect: There are several measures that can be used to assess the impact of PA criteria. Frequency of occurrence, approval rate, and examining denial reasons are all common measures that represent components of a good approach to assess how many beneficiaries initiated the PA process, what was the eventual result, and why were these requests approved or denied.

An additional measure is assessing how many unique beneficiaries presented a prescription for a PDE-5 inhibitor in the TRRx and/or TMOP pharmacies, had this prescription rejected by PDTS at the point of service, and then chose not to initiate the formal PA approval process by submitting either the required forms, or having their provider contract the PA review team.

It was observed that there was a very large number of beneficiaries who elected to not initiate the necessary formal steps to obtain PA after receiving a rejection for a PDE-5 prescription at a TRRx or TMOP pharmacy.

The results for the first calendar quarter of 2005 (January through March 2005) are presented below:

- 5,176 = Beneficiaries with unique transaction rejects in PDTS requiring PA
- 1,829 = Beneficiaries entering the PA process
- 1,711 = Beneficiaries awarded a PA

6. REVIEW OF RECENTLY- APPROVED AGENTS

The PEC presented clinical information on three new medications approved by the FOOD AND DRUG ADMINISTRATION (FDA) and introduced to the U.S. market since February 2005 (Table 2 – Appendix B). Since none of the new medications fall into drug classes already reviewed by the P&T Committee, UF consideration was deferred until drug class reviews are completed.

The Committee discussed the potential need for a PA requirement for pramlintide (Symlin) subcutaneous injection, which 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. The Committee agreed (11 for, 6 opposed, 2 abstained) that a PA recommendation should be considered for pramlintide and requested that the PEC develop PA criteria to be reviewed at the next meeting.

The Committee also discussed concerns regarding availability of pramlintide through the TMOP given the black box warning and safety issues, but agreed (9 for, 7 opposed, 3 abstained) that it should be available through the TMOP. The Committee requested more complete information about the manufacturer's plan to target use to appropriate patients, which was not available at the time of the meeting.

7. BCF CLARIFICATION OF RECENTLY APPROVED DRUGS

The DoD 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 40 mg tablets, which are indicated only for the treatment of Paget's disease. Currently, the majority of use across DoD is 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. It is difficult to quantify this advantage, since many patients will also require supplemental calcium, which is readily available in combination with vitamin D. However, taking in account the manufacturer's offer to add alendronate plus D to the current BPA for alendronate without an increase in price and the fact that 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 clinical advantage to MTF patients at no additional cost.

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

B. Fluticasone Propionate HFA (Flovent HFA)

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 TMOP at the same price as the old CFC formulation.

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, as compared to insulin pens, cartridges, and dispensing syringes which represent 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.

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).

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

A. **PDE-5 UF Clinical Effectiveness:** The P&T Committee evaluated the relative clinical effectiveness of all the FDA-approved PDE-5 inhibitors available in the U.S. The PDE-5 inhibitor therapeutic class was defined as sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis). The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 C.F.R. 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

The P&T Committee agreed that in the Military Health System (MHS) PDE-5s are considered to be the gold standard for the treatment of erectile dysfunction (ED). During a twelve month period ending January 31, 2005, 142,333 patients were prescribed a PDE-5 Inhibitor. This class is now ranked 46th in MHS drug class expenditures.

1.) Efficacy: All PDE-5 inhibitors have FDA approved indications for the treatment of ED. There are no head-to-head trials comparing the three PDE-5 inhibitors. The available placebo controlled trials and meta-analyses were reviewed. Although all PDE-5s were found to be clinically effective when compared to placebo, variability in study design, demographics, and outcome measures precluded the ability to designate one PDE-5 as clinically superior. A difference in duration of action exists among these agents. There is no evidence to suggest clinical superiority based on these differences. In addition to its FDA-approved indication for ED, sildenafil has also

been proven safe and effective for the treatment of primary pulmonary hypertension. Another off-label use of sildenafil is in the setting of radical prostatectomy, but there is not currently reliable evidence supporting its effectiveness for this indication.

2.) *Safety/Tolerability:* The P&T Committee found that the PDE-5 inhibitors were not significantly different with respect to major contraindications, drug interactions, and adverse drug reactions. As of May 2005 all agents have similar alpha-blocker warnings and nitrate contraindications. Vardenafil has a drug interaction warning associated with patients taking Class IA or Class III antiarrhythmics. Sildenafil is associated with more visual side effects where tadalafil is associated with more back pain.

Conclusion: The P&T Committee concluded that all PDE-5 inhibitors have similar relative clinical effectiveness for treating erectile dysfunction. All three PDE-5 inhibitors have similar safety and tolerability profiles.

COMMITTEE ACTION: The P&T Committee voted (18 for, 0 opposed, 1 abstained) that for the purposes of the UF clinical review, 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.

B. PDE-5 Inhibitor 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 Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). Several analyses were used to determine the relative cost effectiveness of agents within the PDE-5 inhibitor therapeutic class. A pharmacoeconomic analysis using cost minimization techniques was used based on the clinical review conclusion that the efficacy, safety, and tolerability between all agents were roughly equivalent. A series of cost effectiveness analyses were then conducted to confirm the results of the cost-minimization analysis. Cost effectiveness analyses were also used to evaluate differences in the duration of action between the agents.

Results of the cost minimization and cost effectiveness analyses (CMA/CEA) showed vardenafil to be the most cost effective PDE-5 inhibitor across all points of service (MTF, TRRx, TMOP). This was true even when taking into consideration differences in the duration of action between the agents.

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 PDE-5 inhibitors within the UF. These factors included: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and switch costs. The results of the budget impact analysis further confirmed the results of the CMA/CEA. Sildenafil and tadalafil were found not to be cost effective relative to vardenafil.

Conclusion: The P&T 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 recommended that the status of sildenafil and tadalafil be changed from formulary to non-formulary on the UF, with vardenafil maintaining formulary status on the UF with the formulary cost share.

COMMITTEE ACTION: The P&T Committee agreed (18 for, 0 opposed, 1 abstained) with the relative cost effectiveness analysis of the PDE-5 inhibitors presented. 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 sildenafil and tadalafil, with vardenafil maintaining formulary status on the UF at the formulary cost share.

C. PDE-5 Inhibitor UF Medical Necessity Criteria: Based on the clinical evaluation 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 the following medical necessity criteria for these agents.

1.) Use of the formulary PDE-5 inhibitor (vardenafil) is contraindicated, and the use of either sildenafil or tadalafil is not contraindicated.

2.) The patient has experienced or is likely to experience significant adverse effects from the formulary PDE-5 inhibitor (vardenafil), and the patient is reasonably expected to tolerate either sildenafil or tadalafil.

3.) Use of the formulary PDE-5 inhibitor (vardenafil) resulted in therapeutic failure, and the patient is reasonably expected to respond to sildenafil or tadalafil [therapeutic failure as outlined on medical necessity form].

4.) The patient has previously responded to either sildenafil or tadalafil, and changing to vardenafil would incur unacceptable risk. This primarily pertains to patients requiring a PDE-5 inhibitor who have congenital or acquired QT prolongation or who are taking a Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarhrhythmic medication.

5.) Use of the PDE-5 inhibitor is for primary pulmonary hypertension and there is no alternative formulary agent.

COMMITTEE ACTION: The P&T Committee voted (18 for, 0 opposed, 0 abstained) to approve the medical necessity criteria.

D. PDE-5 inhibitor UF Implementation Plan: Because a substantial number of patients are currently receiving either sildenafil or tadalafil from one of the three MHS pharmacy points of service (128,007 patients, 90% of all patients receiving PDE-5 inhibitors) the P&T Committee proposed a 90-day transition period for implementation of the decision to change sildenafil and tadalafil to non-formulary drugs on the UF. Patients wishing to fill prescriptions for sildenafil or tadalafil at retail network pharmacies or the TMOP would then have to pay the non-formulary cost share unless medical necessity for these agents is established by the beneficiary or their provider.

MTFs will not be allowed to have sildenafil or tadalafil on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) the beneficiary provider must establish medical necessity for these agents. MTFs may (but are not required to) fill a prescription for sildenafil or tadalafil 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, 1 opposed, 1 abstention) 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. PDE-5 Inhibitor Extended Core Formulary (ECF) Review and Recommendations: The P&T Committee had previously determined that only one PDE-5 inhibitor would be added to the ECF based on the clinical and cost effective reviews. Since only one PDE-5 inhibitor, vardenafil, was selected for UF status, it was recommended that this agent also be added to the ECF.

Conclusion: Vardenafil was recommended for inclusion on the ECF.

COMMITTEE ACTION: The P&T Committee voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend that vardenafil be on the ECF.

9. ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITOR DRUG CLASS REVIEW

The DoD P&T Committee initiated the ACE inhibitor class review; however because price submissions were not complete, no action was taken. Two ACE inhibitors, available as multisource generics for approximately two years, recently suspended manufacturing secondary to litigation results. The Committee will seek pricing information from the companies representing the name brand version of these products. Continuation of the ACE inhibitor review will occur at the August 2005 DoD P&T Committee meeting.

10. MULTIPLE SCLEROSIS DISEASE MODIFYING DRUG (MS-DMD) CLASS REVIEW

A. MS-DMDs UF Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the four MS-DMDs in the U.S. by considering information regarding their safety, effectiveness and clinical outcomes. Currently, MS-DMDs have been approved for the treatment of relapsing-remitting (RR) MS. The therapeutic class includes three interferons (IFN): intramuscular (IM) IFN beta-1a (Avonex), subcutaneous (SC) IFN beta-1a (Rebif), SC IFN beta-1b (Betaseron); and one subcutaneous (SC) polypeptide mixture, glatiramer acetate (Copaxone). 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.

MS-DMDs have been available for the past 12 years and the class is currently ranked 33rd in MHS drug class expenditures. During a twelve-month period ending January 31, 2005, approximately 6,500 patients were prescribed a MS-DMD. In most cases MS-DMDs are prescribed by sub-specialists (neurologists).

1.) Efficacy for RR-MS: All the IFNs and glatiramer are indicated for the treatment of patients with relapsing forms of MS to decrease the frequency of clinical exacerbations. Avonex and Rebif also claim to delay accumulation of physical disability. A Cochrane systematic review of all the available trials through 2000 found only a modest reduction in exacerbations and disability following treatment of RR-MS with IFNs. A Cochrane systematic review of trials available through 2003 concluded that glatiramer had a modest reduction in exacerbations, but no beneficial

effect on disease progression. A decrease in exacerbations does not necessarily correlate to the progression of disease. There is no compelling evidence to support superiority of one agent over another. All beta IFNs and glatiramer have been shown to have a modest protective effect on disease exacerbations. IFN beta-1a agents (Rebif and Avonex) have shown to have a modest protective effect on disease disability; therefore they may have a marginal benefit over glatiramer.

2.) *Safety/Tolerability:* The P&T Committee agreed that there is no evidence that any one MS-DMD is preferable to the others with respect to safety or tolerability. These medications are generally well-tolerated and adverse events are dose-related. The most common side effects were local injection site reactions for the SQ drugs and flu-like symptoms for the IM drugs. Additionally, a self-limiting allergic-type reaction may be seen with glatiramer. All the MS-DMDs have similar safety and tolerability profiles with only rare incidences of true serious adverse effects.

Conclusion: The P&T Committee concluded that there is no compelling evidence to support superiority of one MS-DMD agent over another in the treatment of RR-MS. All MS-DMD agents have shown a modest effect in reducing exacerbations, with IFN beta-1a agents (Rebif and Avonex) demonstrating a modest reduction on disease disability. All the IFNs and glatiramer have similar safety and tolerability profiles.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (18 for, 0 opposed, 0 abstained) to accept the conclusion that none of the MS-DMDs have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over the other MS-DMDs.

B. MS-DMD 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).

Cost-minimization techniques determined that the overall average weighted cost per day of therapy for the MS-DMDs was lowest for Avonex, followed by Copaxone and Betaseron. Rebif was determined to have the highest average weighted cost per treatment day.

Conclusion: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the MS-DMDs, and other relevant factors (i.e., relative uniqueness of each agent in patient therapy and the low expectation that patient behavior would be affected by formulary status), the P&T Committee recommended that all MS-DMDs [IFN beta-1a (Avonex), IFN beta-1a (Rebif), IFN beta-1b (Betaseron), and glatiramer acetate (Copaxone)] maintain UF status with the formulary cost share.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (18 for, 0 opposed, 0 abstained) to recommend formulary status for IFN beta-1b (Betaseron), IFN beta-1a (Avonex), IFN beta-1a (Rebif), and glatiramer (Copaxone) under the UF.

C. MS-DMD UF Medical Necessity Criteria: Since no agents were selected for non-formulary status on the UF, establishment of medical necessity criteria is not applicable.

D. **MS-DMD UF Implementation Plan:** Since no agents were selected for non-formulary status on the UF, establishment of an implementation plan is not applicable

E. **MS-DMD ECF Review and Recommendations:** The P&T Committee had previously determined that this class of drugs is more suitable for ECF due to the subspecialty nature of the MS-DMD class. The P&T Committee reviewed the MS-DMDs recommended for inclusion on the UF to select one MS-DMD for inclusion on the ECF. Cost-minimization techniques determined that the overall average weighted cost per day of therapy for the MS-DMDs was lowest for Avonex. PDTS data collected from October 1, 2001 to March 30, 2005 showed that Avonex has maintained the highest percent of MTF market share of all MS-DMDs. Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing Avonex on the ECF.

Conclusion: The P&T Committee concurred with the recommendation to place Avonex on the ECF based on its high MTF utilization and cost effectiveness

COMMITTEE ACTION: The P&T Committee voted (18 for, 0 opposed, 0 abstained) to recommend Avonex as the ECF agent.

11. ADJOURNMENT

The third day of the meeting adjourned at 1100 hours on May 19, 2005. The dates of the next meeting are August 16–18, 2005.

Patricia Buss

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

List of Appendices

Appendix A – Table 1. Processes and Recommendation/Approval Authorities

Process	Function
Administrative (not part of DoD P&T Committee process, Beneficiary Advisory Panel (BAP) comments not required, Director, TMA, approval not required) Responsible parties include: TRICARE Mail Order Pharmacy and TRICARE Retail Pharmacy Contracting Officer Representatives (TMOP and TRRx CORs), TMA Pharmacy Program, TMA Office of General Counsel, and Pharmacoeconomic Center (PEC) staff	▪ Identification of new FDA-approved medications, formulations, strengths, package sizes, etc. ▪ If situation unclear, determination as to whether a new FDA-approved medication is covered by TRICARE ▪ If situation unclear, determination as to whether a new FDA-approved medication is part of the pharmacy benefit ▪ If situation unclear, determination as to whether a new FDA-approved medication is suitable for dispensing through the TRICARE Mail Order Pharmacy (TMOP) ▪ Calculating and implementing quantity limits if already established through the DoD P&T Committee process for a given medication or class of medications ▪ Making changes to quantity limits as needed based on non-clinical factors such as changes to packaging (e.g., medication previously available in boxes of 5 now only available packaged in boxes of 8) ▪ Establishing adjudication edits (PDTS limitations which are set well above the clinical maximum and are intended to prevent entry errors [e.g., entering a quantity of 17 for a 17-gram inhaler for which the actual unit of measure is 1 inhaler] or are intended to limit diversion) ▪ Implementing prior authorization requirements if already established through the DoD P&T Committee process for a given medication or class of medications ▪ Making minor changes to prior authorization forms NOT involving changes to underlying criteria, such as correcting contact information or rewording clinical questions ▪ Making changes to PA criteria, medical necessity criteria, quantity limits and any associated documents to accommodate new FDA-approved indications or respond to changes in FDA-recommended safety limitations (changes will be reviewed by DoD P&T Committee at next meeting) ▪ Removing medications withdrawn from the U.S. market from Basic Core Formulary (BCF) or Extended Core Formulary (ECF) listings and other documents ▪ Providing clarifications to existing listings on the BCF or ECF to specify specific brands/manufacturers when a joint DoD/VA mandatory source generic contract is awarded for a given product (i.e., clarifying an existing listing for "atenolol" to include the contractual requirement to use a specific manufacturer's products) ▪ As necessary to accomplish functions above: for example, making changes to PDTS coding for TMOP & TRRx, communicating status of medications as part of the pharmacy or medical benefit to Managed Care Support Contractors (MCSCs), making changes to the TMA Pharmacy website and the TRICARE Formulary Search Tool, and making changes to BCF and ECF listings on the PEC website.
Approval by Director, TMA, required based on DoD P&T Committee recommendations and BAP comments	▪ Classification of a medication as non-formulary on the Uniform Formulary (UF), and implementation plan (including effective date) ▪ Establishment of prior authorization requirement for a medication or class of medications, summary/outline of prior authorization criteria, and implementation plan (including effective date) ▪ Changes to existing prior authorization (e.g., due to the availability of new efficacy or safety data) ▪ Discontinuation of prior authorization requirements
Approval by Director, TMA, required based on DoD P&T Committee recommendations (not required to be submitted to BAP for comments)	▪ Establishment of quantity limits for a medication or class of medications; deletion of existing quantity limits; changes to existing quantity limits based on clinical factors (e.g., new clinical data or dosing regimens) ▪ Establishment and changes of medical necessity criteria for non-formulary agents ▪ Addition, deletion of medications listed on the Basic Core Formulary (BCF) or Extended Core Formulary (ECF)

Appendix B – Table 2. Newly Approved Drugs

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Pramlintide (Symlin; Amylin Pharm) injection; synthetic version of the neuro-endocrine hormone amylin, which complements the action of insulin by decreasing post-prandial glucose levels and slowing gastric emptying	Mar 05: *Type 1 DM*: as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy *Type 2 DM*: as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin Should be considered only for patients who have failed to achieve adequate glycemic control despite individualized insulin management and are receiving ongoing care under the guidance of a health care professional skilled in the use of insulin and supported by the services of a diabetes educator. Should NOT be considered for treatment of patients in the following categories: poor compliance with current insulin regimen; poor compliance with prescribed self-blood glucose monitoring; HbA1c >9%; recurrent severe hypoglycemia requiring assistance during the past 6 months; presence of hypoglycemia unawareness; confirmed diagnosis of gastroparesis; requirement for drugs that stimulate gastrointestinal motility; pediatric patients.	Prior authorization recommended due to safety concerns and the existing FDA requirements for risk minimization. Consideration of UF status deferred until drug class is reviewed.
Ibandronate Na (Boniva; Roche/GSK) 150 mg q month tabs; bisphosphonate; inhibits bone resorption	Mar 05: Treatment and prevention of osteoporosis in postmenopausal women	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.
Eszopiclone (Lunesta: Sepracor) tabs (control schedule IV); non-benzodiazepine sedative hypnotic	Dec 04: Treatment of insomnia. In controlled outpatient and sleep laboratory studies, Lunesta administered at bedtime decreased sleep latency and improved sleep maintenance	No UF recommendation at this meeting. Consideration of UF status deferred until drug class is reviewed.

Appendix C – DoD P&T Committee Interim Meeting: Topical Antifungal Drug Class Review

The P&T Committee held an interim electronic meeting during the period June 3, 2005 through June 6, 2005, during which it completed the class review that had been initiated during the May meeting of the Committee. A quorum of thirteen Committee voting members participated.

DERMATOLOGICAL TOPICAL ANTIFUNGAL DRUG CLASS REVIEW

A. **Topical Antifungal UF Relative Clinical Effectiveness:** The P&T Committee evaluated the relative clinical effectiveness of the 11 dermatological topical antifungals marketed in the US by considering information regarding their safety, tolerability, effectiveness, and other factors, including marketed formulations, generic availability, chemical structures, existing MHS utilization patterns, and FDA-approved labeling. The dermatological topical antifungal class was defined as the "azoles" clotrimazole (various generics), econazole (various generics), ketoconazole (various generics), miconazole (various generics), oxiconazole (Oxistat), sertaconazole (Ertaczo), and sulconazole (Exelderm); the "allylamines" butenafine (Mentax) and naftifine (Naftin); the "substituted pyridone" ciclopirox (Loprox); and the "polyene" nystatin. The topical formulation of terbinafine (Lamisil) was specifically excluded from the class, as it is now solely available in a non-prescription product. 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.

1.) *Other Factors: Structure/Mechanism of action:* The Committee agreed that it would be advantageous to include on the UF products that are available in more than one formulation, products that have differing mechanisms of action (e.g., an allylamine and an azole), products that have a wide number of FDA-approved indications, and products that are approved for use in the pediatric population.

2.) *Efficacy for tinea pedis:* A Cochrane systematic review for treatment of tinea pedis infections reported that allylamines were slightly more efficacious than the azoles; however, there was a language bias present, and the overall cure rates were similar (80% cure rates with the allylamines vs. 73% with the azoles). Ciclopirox showed similar efficacy as clotrimazole. There was no difference in cure rates when azoles were compared to azoles, or when allylamines were compared to allylamines. Three topical antifungals were not included in the Cochrane review: ketoconazole, oxiconazole and sertaconazole. The cure rates reported in clinical trials with use of ketoconazole for tinea pedis are similar to those reported with the other azoles. Head-to-head trials comparing ketoconazole shampoo to ciclopirox shampoo for treating seborrheic dermatitis reported no differences in efficacy. Head-to-head trials of oxiconazole to naftifine and terbinafine show similar efficacy. Cure rates reported

with sertaconazole were low (30%) in the clinical trials used to gain FDA approval; however the FDA now has more stringent requirements for definitions of mycological cure than were used previously. Overall, there is no evidence to support that one individual topical antifungal agent is superior to another for treating tinea pedis.

3.) *Efficacy for tinea cruris, tinea corporis, or pityriasis versicolor*: There are no systematic reviews and no head-to-head trials of individual topical antifungal agents for treating tinea cruris, tinea corporis or pityriasis versicolor. There is no evidence that any one topical antifungal agent is superior to another for treating these conditions.

4.) *Efficacy for cutaneous candidiasis*: There are no systematic reviews for the treatment of cutaneous candidiasis. Two head-to-head trials comparing nystatin to miconazole and nystatin to tolnaftate showed similar efficacy. There is no evidence that any one topical antifungal agent is superior to another for treating cutaneous candidiasis.

5.) *Safety/Tolerability*: The topical antifungals are recognized as safe therapeutic agents. Several of the products (clotrimazole, miconazole, butenafine) are available without a prescription in the same concentration and dosage form as the prescription product. Hypersensitivity is the only contraindication listed in the package inserts of the topical antifungals. Adverse reactions reported most commonly with the topical antifungals include itching, burning, and erythema, which are the common symptoms of fungal infections. Adverse event rates listed in the individual agents' product labeling range from 1-3%. Products containing propylene glycol may cause burning, but this varies with the dosage form and type of infection being treated.

Conclusion: The Committee concluded that the topical antifungals have similar safety and tolerability profiles. The individual topical antifungal agents appear to have similar efficacy and clinical outcomes for treating tinea pedis, tinea corporis, tinea cruris, pityriasis versicolor, and cutaneous candidiasis infections. Differences do exist in such factors as existing MHS utilization, available formulations, FDA-approved indications, pediatric labeling and dosing duration.

COMMITTEE ACTION: The Committee voted (12 for, 0 opposed, 1 abstained) to recommend that, for the purposes of the UF, none of the topical antifungals have significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other topical antifungals. The UF recommendation can be based on cost, current utilization patterns, available formulations, pediatric indications, and dosing duration. The Committee also recommended having agents with differing mechanisms of action (azoles and allylamines) on the UF. The FDA-approved indications, clinical use, and dosing duration of ciclopirox is more similar to that of the azoles, rather then the allylamines; thus for cost effectiveness determinations, ciclopirox was considered along with the azoles.

B. Topical Antifungal UF Relative Cost Effectiveness: The P&T Committee evaluated the relative cost effectiveness of the agents within the topical antifungal class in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). To determine the relative cost effectiveness of the agents within the topical antifungal therapeutic class, two separate

economic analyses were performed: A pharmacoeconomic analysis and budget impact analysis (BIA). From the preceding relative clinical effectiveness evaluation, the P&T Committee agreed that there was no compelling evidence to support clear superiority of one agent over another in terms of safety, effectiveness or clinical outcomes. For the UF, it would be advantageous to include products with differing mechanisms of action (e.g., an allylamine and an azole), those available in multiple dosage formulation, those approved for use in the pediatric setting, and those with existing high utilization in the MHS. The clinical characteristics of the substituted pyridone ciclopirox are more closely related to the azole topical antifungals than the allyalmines. For the purposes of the relative clinical effectiveness evaluation, topical antifungals with the azole and substituted pyridone (ciclopirox) structure were analyzed collectively; those agents with an allylamine structure were also analyzed separately from the azoles/substituted pyridone.

Given this conclusion, two cost-minimization analyses (CMAs) were conducted for each sub-class using two different measures of cost; the weighted average cost per gram and the weighted average annual cost of treatment per unique user. In general, the results of the CMAs revealed that: miconazole was the most cost effective agent in the azole/ substituted pyridone sub-class; naftifine and butenafine were similar in relative cost effectiveness in the allylamine sub-class; and nystatin was the most cost effective agent relative to all topical antifungals. More specifically, within the allylamine sub-class, naftifine was more cost effective than butenafine at the MTF and TMOP point of service (POS), whereas butenafine was more cost effective relative to naftifine at the TRRx POS. Examination of the cost continuum further suggested that a cluster of agents (nystatin, miconazole, clotrimazole, and ketoconazole) were more cost effective relative to the other agents within the therapeutic class (butenafine, ciclopirox, econazole, naftifine, oxiconazole, sertaconazole, and sulconazole). 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 topical antifungals 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 antifungal 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, given the DoD P&T Committee's decision to include on the UF at least one-agent from the azole/substituted pyridone sub-class, one agent from the allylamine sub-class, and nystatin. The BIA results revealed that a group of topical antifungals comprising nystatin, miconazole, clotrimazole, ketoconazole, butenafine, and naftifine best achieved this goal when compared to other combination groups of antifungals, and thus this group was determined to be more cost effective relative to other combination groups. The P&T Committee concluded that ciclopirox, econazole, oxiconazole, sertaconazole, and sulconazole were not cost effective relative to the other topical antifungals.

Conclusion: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the topical antifungals, the P&T Committee recommended that the status of econazole, sulconazole, ciclopirox, oxiconazole, and sertaconazole be changed from formulary to non-formulary, with

butenafine, clotrimazole, ketoconazole, miconazole, naftifine, and nystatin maintaining formulary status with the formulary cost share.

COMMITTEE ACTION: The P&T Committee agreed (12 for, 0 opposed, 1 abstained) with the relative cost effectiveness analysis of the topical antifungal agents presented. The P&T Committee, based upon its collective professional judgment, voted (11 for, 1 opposed, 1 abstained) to recommend formulary status for nystatin, miconazole, clotrimazole, ketoconazole, butenafine, and naftifine, and non-formulary status for ciclopirox, econazole, oxiconazole, sertaconazole, and sulconazole under the UF.

C. Medical Necessity Criteria: Based on the clinical evaluation of the topical antifungals and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the following medical necessity criteria were proposed for the non-formulary topical antifungals.

1.) Use of the formulary topical antifungals (clotrimazole, ketoconazole, miconazole, naftifine, butenafine and nystatin) is contraindicated, and the use of the non-formulary topical antifungal is not contraindicated.

2.) The patient has experienced or is likely to experience significant adverse effects from all the formulary topical antifungals (clotrimazole, ketoconazole, miconazole, naftifine, butenafine and nystatin), and the patient is reasonably expected to tolerate the non-formulary topical antifungal.

3) Use of the formulary topical antifungals (clotrimazole, ketoconazole, miconazole, naftifine, butenafine and nystatin) resulted in therapeutic failure following administration for the appropriate duration of therapy (2 weeks for an allylamine and 4 weeks for an azole), and the patient is reasonably expected to respond to the non-formulary topical antifungal.

4.) The criterion that "the patient has previously responded to a non-formulary topical antifungal, and changing to a formulary topical antifungal would incur unacceptable risk" does NOT apply to this class as there are few safety concerns with topical antifungals, treatment is usually well tolerated, and therapy is generally limited to single treatment courses.

5) The criterion that "there are no formulary alternatives" does NOT apply to this class, as six topical antifungals are recommended for inclusion on the UF.

COMMITTEE ACTION: The Committee voted (12 for, 0 opposed, 1 abstained) to recommend the medical necessity criteria for the non-formulary topical antifungals.

D. Implementation Plan: The Committee voted (12 for, 0 opposed, 1 abstained) to recommend an effective date of the first Wednesday after 30 days from the final decision date (the date that DoD P&T Committee minutes are signed by the Director, TMA, approving the Committee's recommendation). A 30-day implementation period is recommended, since the topical antifungal products are used to treat acute (rather than chronic) infections, thus patients are unlikely to require a change in existing therapy.

E. Topical Antifungal BCF Review and Recommendations: The P&T Committee reviewed the topical antifungals recommended for inclusion on the UF to select the BCF topical antifungals. It had previously been decided that at least two, but no more than

three topical antifungals, could be added to the BCF, based on the outcome of relative clinical effectiveness and relative cost effectiveness determinations.

There are currently no topical antifungal products on the BCF. Since no BCF prices were submitted for any of the topical antifungals, 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. Although the CMA revealed that miconazole (#4 in utilization at the MTF at 2,000 Rxs/month) was more cost effective than clotrimazole, the difference was determined to be negligible. From a clinical and economic standpoint, clotrimazole is a rational selection for the BCF due to its wide number of FDA-approved indications (tinea pedis, tinea cruris, tinea "pityriasis" versicolor, and cutaneous candidiasis), availability in several formulations (cream, lotion, topical solution), pediatric labeling in children older than 2 years of age, and high utilization in the MHS (#1 in utilization at the MTFs at 11,000 Rxs/month). Nystatin is also recommended for BCF selection due to its availability in several formulations (cream, ointment, powder), widespread usage for cutaneous candidiasis, rapid symptomatic relief, popularity of the powder dosage form, and high utilization (#3 in MTFS at 4,500 Rxs/month). Ketoconazole is #2 in MTF utilization, the CMA revealed it to be less cost effective than clotrimazole, and there is no therapeutic rationale to include two azoles on the BCF. Based on the relative clinical and cost effectiveness analyses, the P&T Committee recommended placing clotrimazole and nystatin on the BCF. MTFs can add additional UF topical antifungals 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 clotrimazole and nystatin on the BCF.

COMMITTEE ACTION: The P&T Committee voted (12 for, 0 opposed, 1 abstained) to recommend clotrimazole and nystatin as the BCF agents.