DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

May 2007

1. **CONVENING**
2. **ATTENDING**
3. **REVIEW MINUTES OF LAST MEETING**
4. **ITEMS FOR INFORMATION**
5. **REVIEW OF RECENTLY APPROVED AGENTS**

A. **Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF)** – The Pharmacy and Therapeutics (P&T) Committee was briefed on three new drugs which were approved by the Food and Drug Administration (FDA) (see Appendix B). The P&T Committee determined that these three new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed. The P&T Committee discussed the need for quantity limit (QL) or prior authorization (PA) requirements for the drugs (see paragraph 5A on pages 19-20 of the P&T Committee minutes).

COMMITTEE ACTION: QL RECOMMENDATIONS

- Arformoterol (Brovana) –The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend QLs for arformoterol of 60 unit dose vials per 30 days, 180 unit dose vials per 90 days.
- Lapatinib (Tykerb) – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for lapatinib as follows: 150 tablets per 30 days at retail network pharmacies, with a days supply limit of 30 days (no multiple fills for multiple co-pays); and 225 tablets per 45 days at mail order, with a days supply limit of 45 days.
- Vorinostat (Zolinza) – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for vorinostat as follows: 120 tablets per 30 days at retail network pharmacies, with a days supply limit of 30 days (no multiple fills for multiple co-pays); and 180 tablets per 45 days at mail order, with a days supply limit of 45 days.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. Over-the-Counter Terbinafine 1% Cream (Lamisil AT) – The John Warner National Defense Authorization Act for FY 2007 directs the Secretary of Defense to conduct a demonstration project to assess the impact of authorizing TRICARE coverage for over-the-counter (OTC) agents recommended for inclusion on the UF. The DoD P&T Committee must find that the OTC drug is cost effective and therapeutically equivalent to a prescription drug. The P&T Committee, after consultation with the TRICARE Management Activity (TMA) Pharmacy Program Office, selected the topical antifungal terbinafine 1% cream OTC (Lamisil AT) as the second OTC product for the demonstration.

The P&T Committee reviewed the topical antifungal drug class in May 2005. Topical antifungals on the UF include clotrimazole (Lotrimin, generics), nystatin (Mycostatin, generics), miconazole (Monistat Derm, generics), ketoconazole (Nizoral, generics), butenafine (Mentax), and naftifine (Naftin). Clotrimazole (Lotrimin, generics) and nystatin (Mycostatin, generics) are classified as Basic Core Formulary (BCF) agents. Topical antifungal agents classified as non-formulary under the UF are econazole (Spectazole, generics), sertaconazole (Ertaczo), sulconazole (Exelderm), ciclopirox (Loprox, generics; excludes ciclopirox topical solution (Penlac) for onychomycosis), oxiconazole (Oxistat) and 0.25% miconazole/15% zinc oxide (Vusion).

Relative Clinical Effectiveness – The P&T Committee concluded (14 for, 0 opposed, 1 abstained, 2 absent) that terbinafine 1% cream OTC has no clinically significant differences with respect to safety, efficacy, or tolerability, when compared to other allylamines included on the UF (butenafine and naftifine). The P&T Committee also concluded that it was unlikely that clinically significant differences exist between OTC terbinafine and the other prescription allylamines for the treatment of common dermatologic infections.

Relative Cost Effectiveness – Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) that terbinafine 1% cream OTC is more cost effective than other allylamines in the topical antifungal class (butenafine and naftifine) across all three points of service.

COMMITTEE ACTION: UF RECOMMENDATION –Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that terbinafine 1% cream OTC be classified as formulary on the UF (see paragraph 5B on pages 20-22 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

6. DRUG CLASS REVIEW – ANTILIPIDEMIC II AGENTS (LIP-2s)

The P&T Committee evaluated the relative clinical effectiveness of the Antilipidemic II (LIP-2) agents. This class is divided into three subclasses: fibric acid derivatives, omega-3 fatty acids, and bile acid sequestrants (BAS). The fibric acid derivatives available commercially include gemfibrozil (Lopid, generics) and several formulations of fenofibrate (Tricor, Lofibra, Antara, and Triglide). Omega-3 fatty acid ("fish oil") products include the prescription product Omacor, along with a number of nutritional supplement products available OTC. Of these, only Omacor is eligible for inclusion on the UF. The BAS class consists of cholestyramine/sucrose (Questran, generics), cholestyramine/aspartame (Questran Light, generics), colestipol (Colestid, generics), and the newest agent, colesevelam (Welchol).

The LIP-2 drug class accounted for $63 million in Military Health System (MHS) expenditures in FY 2006, ranking in the top 20 in terms of total expenditures.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the following clinical effectiveness conclusion:

1) Fibric acid derivatives

   a) Both gemfibrozil and fenofibrate reduce triglycerides (TG) by 20-50% and raise high density lipoprotein (HDL) by 10-20%. There is insufficient evidence to conclude that gemfibrozil and fenofibrate differ in their ability to reduce TG and raise HDL.

   b) Two placebo-controlled trials with gemfibrozil have shown a benefit in reducing the risk of cardiovascular events in a primary prevention setting and the risk of nonfatal myocardial infarction (MI) and coronary heart disease (CHD) death in a secondary prevention setting. Mixed results were demonstrated with fenofibrate in a large outcomes trial in a primary/secondary prevention setting; fenofibrate did not result in a statistically significant benefit in reducing the composite of CHD death or nonfatal MI, but was associated with significant reductions in nonfatal MI ($p=0.01$) and coronary revascularization ($p=0.035$).

   c) Although gastrointestinal (GI) adverse effects occurred in fewer than 5% of patients taking fibric acid derivatives, they appeared to occur more frequently in patients taking gemfibrozil than those taking fenofibrate, based on pooled data from product labeling. Gemfibrozil must be taken twice daily prior to meals.

   d) Monotherapy with either fibric acid derivatives or statins has been associated with an increased risk of myalgia, myositis, and rhabdomyolysis. This risk appears to be increased with gemfibrozil/statin combination therapy, based on spontaneous adverse event reporting data from the FDA. These data showed a higher reporting rate of rhabdomyolysis with a statin plus gemfibrozil (8.6) compared to a statin plus fenofibrate (0.58), based on the number of spontaneous case reports per 1 million U.S. prescriptions from 1998 to 2002. This study excluded cerivastatin, which has now been withdrawn from the market. Limitations include varying definitions of myotoxicity, lack of verification of data, and the use of spontaneous reporting rates, which are subject to reporting bias and do not establish a causal relationship. It is unclear whether combination therapy with fenofibrate and a

statin increases the risk of myotoxicity more than either agent given alone. One trial comparing statin monotherapy vs. combination therapy with fenofibrate plus a statin reported similar rates of myalgia.

e) Pharmacokinetic differences in glucuronidation pathways between gemfibrozil and fenofibrate are postulated to account for potential differences in the risk of developing myotoxicity when used in combination with a statin. However, there are no head-to-head trials supporting a lower risk of myotoxicity with gemfibrozil than with fenofibrate, either alone or in combination with a statin, and professional organizations have not favored one fibric acid derivative over the other. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the National Heart Lung and Blood Institute conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

f) Fenofibrate formulations include nanocrystallized fenofibrate (Tricor), micronized fenofibrate (Antara), insoluble drug delivery microparticle (IDD-P) fenofibrate (Triglide) and generic formulations of non-micronized and micronized fenofibrate (Lofibra). These newer formulations, regardless of dosage strength or particle size, are bioequivalent to 200 mg of the original fenofibrate formulation. Changes in particle size are designed to address bioavailability issues, allowing the most recent products (Tricor, Antara and Triglide) to offer once daily dosing and be taken without regard to meals. There is insufficient evidence to conclude that newer formulations offer improved efficacy, safety, or tolerability compared to each other or to older formulations.

2) Omega-3 Fatty Acids (Omacor)

a) Omacor is the only prescription omega-3 fatty acid product approved by the FDA. FDA oversight of the manufacturing process for Omacor offers increased assurance of its omega-3 fatty acid content and purity, in contrast to some fish oil supplements.

b) Overall, Omacor decreases TG by 20-45%. However, Omacor has also been associated with increases in low density lipoprotein (LDL), which may offset beneficial reductions in TG.

c) The TG-lowering effects of Omacor are slightly lower than those achieved with fibric acid derivatives or niacin. Omacor is associated with similar increases in HDL compared to fibric acid derivatives and niacin. Niacin and gemfibrozil both have clinical trial evidence supporting long-term benefits on cardiovascular outcomes.

d) The omega-3 fatty acid formulation found in Omacor does not have outcomes studies that demonstrate beneficial cardiovascular effects (e.g., reductions in cardiovascular death, MI or stroke).

3) Bile Acid Sequestrants

a) The BAS agents reduce LDL by 15 to 30%. This subclass has largely been replaced by the statins, which reduce LDL by 18% to 55%. There is insufficient evidence to conclude that BAS differ in their ability to lower LDL.

Cholestyramine is the only BAS to show beneficial effects on cardiovascular outcomes.

b) Colesevelam has no major efficacy advantages compared to cholestyramine or colestipol, despite manufacturer claims of enhanced bile acid binding capacity. It has a more favorable pregnancy category rating than the older products (B vs. C) and may cause less constipation, which may be clinically relevant in patients with a previous history of GI obstruction.

c) Issues with palatability of powder formulations and/or large daily tablet burdens are a concern with the class as a whole and may affect compliance.

d) The BAS agents have a high degree of therapeutic interchangeability.

Overall Clinical Effectiveness Conclusion – Based on clinical issues alone, there are no compelling reasons to classify any of the LIP-2 agents as non-formulary under the UF.

Relative Cost Effectiveness Conclusion: Based on the results of the pharmacoeconomic analyses and other clinical and cost considerations, the DoD P&T Committee voted (15 for, 0 opposed, 0 abstained, and 2 absent) that:

1) Gemfibrozil was the most cost-effective fibric acid derivative evaluated. Of the various fenofibrate formulations, IDD-P fenofibrate demonstrated the best cost effectiveness profile.

2) Colesevelam was recognized as not cost effective in the treatment of hyperlipidemia compared to other BAS.

3) In the management of hypertriglyceridemia, Omacor was identified as not cost-effective compared to gemfibrozil, fenofibrate, and niacin.

4) The UF scenario that maintained fenofibrate, IDD-P fenofibrate, cholestyramine/ aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil on the UF was the most cost effective UF scenario.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the LIP-2s, and other relevant factors, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) that: 1) fenofibrate, IDD-P fenofibrate, cholestyramine/aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil be maintained as formulary on the UF; 2) micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and Omacor be classified as non-formulary under the UF; and 3) the normal brand formulary cost-share of $9.00 for IDD-P fenofibrate (Triglide) be lowered to the generic formulary cost-share of $3.00 (see paragraphs 6A, 6B, and 6C on pages 22-37 of the P&T Committee minutes).

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate." The objective is to maximize use of IDD-P fenofibrate in the retail network and mail

order, given its significantly lower cost relative to other fenofibrate products. Lowering the cost-share for brand name IDD-P fenofibrate will provide a greater incentive for beneficiaries to use the most cost effective fenofibrate formulation in the purchased care arena.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. *COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA* – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) general MN criteria for micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and Omacor (see paragraph 6D on page 37 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. *COMMITTEE ACTION: IMPLEMENTATION PERIOD* – The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 6E on pages 37-38 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved (for mod.) ☐ Disapproved

Approved, but modified as follows:

D. *COMMITTEE ACTION: BCF RECOMMENDATION* – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that gemfibrozil and IDD-P fenofibrate (Triglide) be designated as the BCF selections in this class (see paragraph 6F on page 38 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

7. DRUG CLASS REVIEW – 5-ALPHA REDUCTASE INHIBITORS (5-ARIs)

The P&T Committee evaluated the relative clinical effectiveness of the 5-alpha reductase inhibitor agents (5-ARIs). The 5-ARI drug class includes finasteride (Proscar, generics) and dutasteride (Avodart). Both have been approved by the FDA for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate.

The 5-ARI drug class accounted for $31.2 million in MHS expenditures for FY 2006 and is ranked #50 in terms of total expenditures. More than 281,000 prescriptions for 5-ARIs

were filled in the MHS during a one-year period (January 2006 to December 2006). Of these, 59% were for finasteride and 41% were for dutasteride.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the following clinical effectiveness conclusion:

1) There is insufficient evidence to conclude that there are significant differences in efficacy between finasteride and dutasteride. Indirect comparisons from long-term efficacy trials suggest similar decreases in total prostate volume, increases in urinary flow rate, improvement in symptoms, and similar reductions in the risk of acute urinary retention and BPH-related surgery.
2) The only fully published head-to-head trial suggests that dutasteride therapy reduces serum dihydrotestosterone levels by 95%, compared to 71% with finasteride. The clinical significance of this finding has yet to be determined. This 24-week trial contributes no useful comparative data concerning long-term efficacy. A large but as yet unpublished head-to-head trial (the Enlarged Prostate International Comparator Study) reported no differences in efficacy outcomes with finasteride vs. dutasteride after one year of treatment.
3) There is insufficient evidence to compare the two agents when used in combination with alpha blockers. More data are available with finasteride than with dutasteride, including a long-term trial with finasteride and doxazosin (the Medical Therapy of Prostatic Symptoms trial); there are no published long-term combination trials with dutasteride.
4) The overall effect of 5-ARIs on prostate cancer prevention is unclear.
5) There appear to be few differences in the incidence of adverse effects with finasteride or dutasteride, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated. The most common adverse effects are related to sexual dysfunction; they diminish with chronic dosing.
6) Reported withdrawal rates due to adverse effects are low in clinical trials of finasteride and dutasteride, similar during the first year of therapy, and decrease further with both agents during continued treatment.
7) There are no major differences between finasteride and dutasteride with regard to use in special populations or drug interactions.
8) Neither agent appears to interfere with prostate cancer detection.
9) Finasteride and dutasteride appear to have a high degree of therapeutic interchangeability; either could be expected to meet the needs of the majority of DoD BPH patients.

Relative Cost Effectiveness Conclusion: Based on the results of the cost minimization analysis (CMA) and other clinical and cost considerations, the DoD P&T Committee voted (15 for, 0 opposed, 0 abstained, and 2 absent) that:

1) Finasteride was the most cost effective agent, with a lower cost per day of treatment than dutasteride across all condition sets evaluated.

2) A cost-effectiveness analysis that evaluated the cost per BPH surgery averted showed that finasteride was the preferred choice with a lower expected cost per surgery averted than dutasteride.

3) The UF scenario that placed finasteride as the sole 5-ARI on the UF was the most cost effective scenario.

A. ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the 5-ARIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that: 1) finasteride be classified as formulary on the UF, and 2) that dutasteride be classified as non-formulary under the UF (see paragraphs 7A, 7B, and 7C on pages 38-44 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation for dutasteride and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for dutasteride (see paragraph 7D on page 44 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 7E on pages 44-45 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. ***COMMITTEE ACTION: BCF RECOMMENDATION*** – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend designating finasteride as the BCF selection in this class (see paragraph 7F on page 45 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

8. DRUG CLASS REVIEW – PROTON PUMP INHIBITORS (PPIs)

The P&T Committee evaluated the relative clinical effectiveness of the PPIs. The PPI drug class includes the following agents: esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec and generics), omeprazole/sodium bicarbonate (Zegerid), omeprazole magnesium (Prilosec OTC), pantoprazole (Protonix), and rabeprazole (Aciphex). Omeprazole magnesium (Prilosec OTC) was added to the UF for purposes of the OTC Demonstration Project as a result of the February 2007 P&T Committee meeting.

PPIs have become the standard of care for treatment of acid-related gastrointestinal disorders. As of March 07, about 350,000 MHS prescriptions for PPIs are filled per month. This drug class has now taken over the #1 spot in terms of MHS expenditures: more than $485 million over the 12 months from April 2006 to March 2007, compared to about $350 million in FY 2005. Military treatment facility (MTF) pharmacies dispense 47% of all PPI tablets, compared to 36% dispensed by retail network pharmacies and 17% dispensed by the TRICARE Mail Order Pharmacy (TMOP). Across the MHS, rabeprazole is the most commonly prescribed PPI, due mainly to its favorable formulary status and high utilization at MTFs. The next four most-prescribed PPIs – lansoprazole, esomeprazole, pantoprazole, and omeprazole – have similar utilization patterns. Of the PPIs, only prescription omeprazole is generically available.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the following clinical effectiveness conclusion:

1) Based on head-to-head and other controlled trials, PPIs have similar efficacy in a wide range of acid related disorders and are highly therapeutically interchangeable.

2) Although some trials appear to demonstrate superior efficacy for healing of erosive esophagitis (EE) with esomeprazole, actual differences are small and inconsistent among trials. Evidence for clinical efficacy is similar enough to consider all agents equally effective in healing of EE.

3) There is sufficient evidence to support the use of PPIs for maintenance of initial healing and symptomatic relief of EE for as long as five years. However, the evidence is insufficient to conclude that one PPI is superior to the others for maintenance of EE healing.

4) There appear to be no comparative differences among PPIs for healing, maintenance of healing, or symptom improvement in peptic ulcer disease and/or non-steroidal anti-inflammatory drug (NSAID) induced ulcers.

5) Based on available clinical trials, PPIs appear to be similarly efficacious in the short-term treatment of endoscopy-negative reflux disease (ENRD); there are insufficient data to draw conclusions regarding efficacy for long-term or on-demand treatment.

6) *H. pylori* eradication rates appear similar among PPIs when differing doses of antibiotics and treatment duration are taken into account.

7) There are insufficient data to suggest superiority of one PPI over the others for treatment of pediatric patients; omeprazole, lansoprazole, and esomeprazole have FDA indications for use in pediatric patients.

8) The class as a whole is well-tolerated, with an adverse effect profile similar to placebo; most drug interactions are minor in nature. In general, PPIs appear very similar with respect to safety and tolerability.

9) Minor differences include the lack of a requirement to adjust the dose of pantoprazole (Protonix) in patients with severe hepatic disease (unlike other PPIs); a less favorable pregnancy category rating for omeprazole than the more recently introduced PPIs (C vs. B); and the availability of liquid dosage forms for esomeprazole, lansoprazole, and omeprazole/sodium bicarbonate.

Relative Cost Effectiveness Conclusion: Based on the results of the CMAs and other clinical and cost considerations, the P&T Committee voted (14 for, 0 opposed, 0 abstained, 3 absent) that:

1) The CMA of each potential UF scenario showed that, as expected, the more restrictive the UF scenario, the lower the cost per day of treatment.

2) Among UF scenarios with two agents on the UF, omeprazole and esomeprazole were the most cost effective option.

3) Among UF scenarios with three to four agents on the UF, omeprazole, esomeprazole, pantoprazole, and rabeprazole were the most cost effective agents.

4) The UF scenario that maintained omeprazole and esomeprazole as the only two agents on the UF in conjunction with a PA requiring a trial of either agent for new patients was the most cost effective scenario.

A. ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that: 1) omeprazole and esomeprazole be maintained as formulary on the UF with a PA requiring a trial of either agent for new patients; 2) that rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate be classified as non-formulary under the UF with a PA requiring a trial of either omeprazole or esomeprazole for new patients; and 3) that the normal brand formulary cost-share of $9.00 for esomeprazole be lowered to the generic formulary cost-share of $3.00.

   The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T may also designate that the drug be cost-shared at the generic rate." Lowering the cost-share for brand name esomeprazole will provide a greater incentive for beneficiaries to use esomeprazole rather than the less cost effective branded products – rabeprazole, lansoprazole, pantoprazole, or omeprazole/sodium bicarbonate – in the

purchased care arena (see paragraphs 8A, 8B, and 8C on pages 46-53 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: PA CRITERIA

The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) that the following PA criteria should apply to PPIs other than omeprazole or esomeprazole. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:
   a) The patient has received a prescription for any PPI agent at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.
2) PA criteria if automated criteria are not met:
   a) The patient has tried omeprazole or esomeprazole and had an inadequate response or was unable to tolerate treatment due to adverse effects.
   b) Treatment with omeprazole or esomeprazole is contraindicated.

(See paragraph 8D on pages 53-54 of the P&T Committee minutes.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate (see paragraph 8E on page 54 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA (see paragraph 8F on page 54 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend designating generic omeprazole (Prilosec 40 mg specifically omitted) and esomeprazole as the BCF selections in this class (see paragraph 8G on page 55 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

9. DRUG CLASS REVIEW – ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

The P&T Committee evaluated the relative clinical effectiveness of the seven angiotensin receptor blockers (ARBs) marketed in the U.S. The ARB drug class is comprised of losartan (Cozaar), irbesartan (Avapro), valsartan (Diovan), candesartan (Atacand), telmisartan (Micardis), eprosartan (Teveten), olmesartan (Benicar) and their respective combinations with hydrochlorothiazide (HCTZ).

Utilization of the ARBs has been steadily increasing in the MHS. The ARB drug class accounted for $137 million in MHS expenditures in FY 2006, and is ranked #10 in terms of total expenditures during that time period.

The P&T Committee focused on efficacy differences with respect to labeled indications, particularly in those areas where a benefit in clinical outcomes (e.g., death, hospitalization for heart failure, decreased need for dialysis or renal transplantation) was demonstrated. The primary areas evaluated were efficacy for hypertension, chronic heart failure, and type 2 diabetic nephropathy.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the following clinical effectiveness conclusion:

1) There is no evidence that any one ARB is more efficacious than the others for lowering blood pressure.
2) Although losartan is labeled to reduce the risk of stroke in patients with left ventricular hypertrophy (LVH), Joint National Commission (JNC) guidelines support use of other antihypertensive drugs (e.g., angiotensin converting enzyme (ACE) inhibitors, diuretics) in this setting. Differences in blood pressure reduction largely account for differences in cardiovascular outcomes seen in trials comparing ARBs to other antihypertensives.
3) There is no evidence to support clinically significant differences in efficacy between candesartan and valsartan in reducing heart failure (HF) hospitalizations in patients with chronic HF.
4) There is no evidence to support clinically significant differences in efficacy between irbesartan and losartan in improving clinical outcomes (e.g., reducing the risk of doubling of serum creatinine, death, or development of end stage renal disease) in patients with type 2 diabetic nephropathy.
5) Valsartan is the only ARB labeled to reduce death and development of heart failure in post-MI patients with left ventricular systolic dysfunction (LVSD).

However, ACE inhibitors have a larger body of evidence supporting a mortality benefit in post-MI patients with LVSD than valsartan. The aldosterone antagonists spironolactone (Aldactone, generics) and eplerenone (Inspra) are also labeled for use or have shown efficacy in the post-MI setting.

6) There is no evidence that the ARBs differ significantly with regard to safety and tolerability profiles.

7) Based on clinical issues alone, there are no compelling reasons to classify any of the ARBs as nonformulary under the UF.

Relative Cost Effectiveness Conclusion: Based on the results of the CMAs and other clinical and cost considerations, the Committee voted (15 for, 0 opposed, 0 abstained, and 2 absent) that:

1) A UF scenario with three or fewer agents on the UF was more cost effective than scenarios that included additional agents on the UF.

2) Telmisartan was the most cost effective agent for the management of hypertension; candesartan was more cost effective for management of chronic HF than valsartan; losartan and irbesartan had similar cost effectiveness profiles for treatment of type 2 diabetic nephropathy.

3) The UF scenario that included candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ was the most cost effective UF scenario evaluated.

A. COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ARBs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ be maintained as formulary on the UF and that eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ be classified as non-formulary under the UF (see paragraphs 9A, 9B, and 9C on pages 55-61 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) general MN criteria for eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ (see paragraph 9D on pages 61-62 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA (see paragraph 9E on pages 62 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

D. ***COMMITTEE ACTION: BCF RECOMMENDATION*** – Based on the results of the clinical and economic evaluations, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that telmisartan and telmisartan/HCTZ remain on the BCF (see paragraph 9F on page 62 of the P&T Committee minutes).

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows

10. QUANTITY LIMITS

The P&T Committee agreed that current QLs for two nasal inhalers should be increased, based on daily maximum doses recommended in product labeling and increases in QL override requests based on higher dosing consistent with labeling (see paragraph 10 on pages 63-64 of the P&T Committee minutes).

COMMITTEE ACTION: QL RECOMMENDATIONS

- Mometasone nasal spray (Nasonex) – The Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that the QL for mometasone nasal spray (Nasonex) be increased to 34 gm (2 inhalers) per 30 days (retail network pharmacies), 102 gm (6 inhalers) per 90 days (mail order), based on daily maximum dosing recommended in product labeling.
- Ipratropium nasal spray (Atrovent) – The Committee voted (13 for, 0 opposed, 2 abstained, and 2 absent) to recommend that 1) the QL for ipratropium nasal spray (Atrovent) be changed from a collective limit to a QL by strength; 2) the QL for the 0.03% strength be increased to 2 inhalers (60 mL) per 30 days (retail network pharmacies), 6 inhalers (180 mL) per 90 days (mail order); and 3) the QL for the 0.06% strength be increased to 3 inhalers (45 mL) per 30 days (retail network pharmacies), 9 inhalers (135 mL) per 90 days (mail order), based on daily maximum dosing recommended in product labeling.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

11. RE-EVALUATION OF NON-FORMULARY AGENTS

Amlodipine (Norvasc) was designated non-formulary at the August 2005 P&T Committee meeting. In early 2007, the FDA approved Mylan Pharmaceutical's first-time generic for Norvasc (amlodipine, Pfizer). The price of amlodipine remains high enough that the Committee felt that even the generic was not cost effective relative to other drugs in the calcium channel blocker class. However, as part of its re-evaluation of the non-formulary UF status of amlodipine, the P&T Committee recognized that there will be situations in the future in which it would be helpful if a procedure were in place that allowed reclassification of such a drug from non-formulary to generic in a more expeditious manner than can be accomplished through the normal quarterly P&T Committee cycle. Such a procedure would be advantageous for both the MHS and its beneficiaries. The P&T Committee proposed the following process to more expeditiously reclassify non-formulary agents:

1) For each drug class in which such a reclassification is a possibility, the P&T Committee will recommend criteria under which non-formulary agents will be reclassified as generic agents on the UF. These criteria will be reviewed and adopted as a recommendation of the committee. The recommendation will be subject to comment by the Beneficiary Advisory Panel (BAP), and final decision by the Director, TMA (see recommended criteria below).
2) When the pre-established criteria for reclassification are met, the Chairperson of the P&T Committee will call for an electronic vote by the members of the P&T Committee on the matter.
3) Upon a majority vote affirming that the non-formulary drug should be reclassified as generic, that agent will be changed from non-formulary status to formulary status as a generic.
4) Committee members will be briefed on any reclassification of a non-formulary agent at the next meeting of the P&T Committee. This information will be recorded as an information-only item in the meeting minutes. The item will be included in information provided for the BAP's next meeting; however, since the BAP will have already made any comments on the subject, it is not expected the item will normally generate further BAP comment.

The DoD P&T Committee recommended the following criteria for the re-evaluation of non-formulary agents for UF status. These criteria would apply only to drug classes in which UF status was NOT awarded based on condition sets that specified the number of similar agents on the UF (i.e., agents in the same class or subclass). All three criteria must be met for the reclassification of a non-formulary agent.

1) The P&T Committee had concluded previously that the non-formulary agent had similar relative clinical effectiveness (i.e., similar efficacy, safety, and tolerability) compared to similar agents on the UF, and the drug had not been excluded from the UF based on clinical issues alone.
2) The non-formulary agent becomes generically available and:
    a) The generic product is "A-rated" as therapeutically equivalent to the brand name product according to the FDA's classification system

b) The generic market supply is stable and sufficient to meet DoD MHS supply demands.

3) The non-formulary agent is cost effective relative to similar agents on the UF. A non-formulary agent becomes cost-effective when:

a) The non-formulary agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the UF class to which they were compared.

b) The non-formulary agent's total weighted average cost based on an alternate measure used during the previous review is less than or equal to that for the UF class to which they were compared. For example, antibiotics may be compared on the cost per course of therapy used to treat a particular condition.

(See paragraph 11 on pages 64-65 of the P&T Committee minutes).

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 against, 3 absent) that the process and criteria described above should be adopted.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

Appendix A – TABLE 1. Implementation Status of UF Recommendations/Decisions
Appendix B – TABLE 2. Newly Approved Drugs
Appendix C – TABLE 3. Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

(CASSCELLS) 24 July 07

May 2007 DoD P&T Committee Meeting
Uniform Formulary Drug Classes Reviewed and Summary of Recommendations

Antilipidemic Agents (Part 2)

May 2007 P&T Cmte meeting

LIP-2 Agent		Multiple Sources Available	P&T Cmte Recommendations		
Chemical Name	Brand Name		UF Status	Implementation	BCF/ECF
Fibric Acid Derivatives					
gemfibrozil	**Lopid**	**Yes**	**Generic**	**N/A**	**BCF**
fenofirate IDD-P[1] (micronized)	**Triglide**	**No**	**Formulary[2]**	**N/A**	**BCF**
fenofibrate	Lofibra	Yes	Generic	N/A	–
fenofibrate micronized	Antara	No	Non-formulary	90 days	–
fenofibrate nanocrystallized	Tricor	No	Non-formulary	90 days	–
Omega-3 Fatty Acids					
omega-3 fatty acid	Omacor	No	Non-formulary	90 days	–
Bile Acid Sequestrants					
cholestyramine/sucrose	Questran	Yes	Generic	N/A	–
cholestyramine/ aspartame	Questran Light, Prevalite	Yes	Generic	N/A	–
colestipol	Colestid	Yes	Generic	N/A	–
colesevelam	Welchol	No	Non-formulary	90 days	–

[1] IDD-P – Insoluble Drug Delivery-microParticle
[2] Although a brand-name drug, $3 co-pay recommended by the DoD P&T Committee

5-Alpha Reductase Inhibitors (5-ARIs)

May 2007 P&T Cmte meeting

5-ARI		Multiple Sources Available	P&T Cmte Recommendations		
Chemical Name	Brand Name		UF Status	Implementation	BCF/ECF
finasteride	**Proscar**	**Yes**	**Generic**	**N/A**	**BCF**
dutasteride	Avodart	No	Non-formulary	90 days	–

Proton Pump Inhibitors (PPIs)

May 2007 P&T Cmte meeting

PPI		Multiple Sources Available	P&T Cmte Recommendations		
Chemical Name	Brand Name		UF Status	Implementation	BCF/ECF
omeprazole	**Prilosec**	**Yes**	**Generic**	**N/A**	**BCF**
esomeprazole	**Nexium**	**No**	**Formulary[1]**	**N/A**	**BCF**
lansoprazole	Prevacid	No	Non-formulary	90 days	–
omeprazole / sodium bicarbonate	Zegerid	No	Non-formulary	90 days	–
pantoprazole	Protonix	No	Non-formulary	90 days	–
rabeprazole	Aciphex	No	Non-formulary	90 days	–

[1] Although a brand-name drug, $3 co-pay recommended by the DoD P&T Committee

Prepared by: CAPT Patricia Buss, MC, USN; OASD(HA)/TMA/OCMO; (703) 681-0064; 27 June 2007, #123968, 132983, 132992.

Angiotensin II Receptor Blockers (ARBs)

May 2007 5 P&T Cmte meeting

ARB		Multiple Sources Available	P&T Cmte Recommendations		
Chemical Name	**Brand Name**		**UF Status**	**Implementation**	**BCF/ECF**
telmisartan	**Micardis**	**No**	**Formulary**[1]	**N/A**	**BCF**
telmisartan/HCTZ[1]	**Micardis HCT**	**No**	**Formulary**	**N/A**	**BCF**
candesartan	Atacand	No	Formulary	N/A	–
candesartan/HCTZ	Atacand HCT	No	Formulary	N/A	–
losartan	Cozaar	No	Formulary	N/A	–
losartan/HCTZ	Hyzaar	No	Formulary	N/A	–
irbesartan	Avapro	No	Non-formulary	120 days	–
irbesartan/HCTZ	Avalide	No	Non-formulary	120 days	–
olmesartan	Benicar	No	Non-formulary	120 days	–
olmesartan/HCTZ	Benicar HCT	No	Non-formulary	120 days	–
valsartan	Diovan	No	Non-formulary	120 days	–
valsartan/HCTZ	Diovan HCT	No	Non-formulary	120 days	–
eprosartan	Teveten	No	Non-formulary	120 days	–
eprosartan/HCTZ	Teveten HCT	No	Non-formulary	120 days	–

[1] HCTZ – hydrochlorothiazide

Prepared by: CAPT Patricia Buss, MC, USN; OASD(HA)/TMA/OCMO; (703) 681-0064; 27 June 2007, #123968, 132983, 132992.

Additional Information: Impact of Non-formulary Selections

Impact on MTFs

In accordance with 32 C.F.R. 199.21, on the effective date noted above for each drug class, MTFs may not have any of these non-formulary drugs 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. An MTF provider writes the prescription, and
2. Medical necessity is established for the non-formulary medication.

In accordance with HA Policy 004-32, 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 by the MTF, as long as medical necessity has been established. Establishing medical necessity at an MTF does not, however, carry over to the TRICARE Retail Network Pharmacy (TRRx) or TRICARE Mail Order Pharmacy (TMOP).

Impact on Beneficiaries

Beginning on the implementation dates noted above, non-active duty beneficiaries who fill scripts for any of these medications outside the MTF will pay $22 for up to a 30 or 90-day supply, depending on whether they fill the prescription through TRRx or TMOP. If medical necessity is established for using one of the non-formulary drugs listed above, patients may qualify for the $9 cost share for up to a 30-day TRRx supply or up to a 90-day TMOP supply. Active duty service members' cost share is $0 in all points of service for all three tiers (formulary generic, formulary brand-name, non-formulary); however, active duty service members may not fill prescriptions for a non-formulary medication at the $0 cost share unless it is determined to be medically necessary.

Forms and specific procedures for establishing medical necessity will be available on the TRICARE Pharmacy website shortly. In general, for medical necessity to be established, one or more of the following criteria must be met for **all** of the available formulary alternatives:

1. Use of formulary pharmaceutical agents is contraindicated;
2. The patient experiences or is likely to experience significant adverse effects from formulary pharmaceutical agents;
3. Formulary pharmaceutical agents result or are likely to result in therapeutic failure;
4. The patient previously responded to the non-formulary pharmaceutical agent, and changing to a formulary pharmaceutical agent would incur unacceptable clinical risk;
5. There is no alternative pharmaceutical agent on the formulary

Resources

Further information about the new TRICARE Uniform Formulary is available at:
"What's New? Uniform Formulary Update" at http://www.tricare.osd.mil/pharmacy/

Prepared by: CAPT Patricia Buss, MC, USN; OASD(HA)/TMA/OCMO; (703) 681-0064; 27 June 2007, #123968, 132983, 132992.

Department of Defense
Pharmacy and Therapeutics Committee Minutes
May 2007

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on May 15-16, 2007 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
LTC Brett Kelly, MSC, USA	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Lt Col Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
Capt Jeremy King, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
LCDR Ronnie Garcia, MC *for* LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician
CDR David Tanen, 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 David Estroff, MC *for* COL Ted Cieslak, MC	Army, Physician at Large
LTC Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino, RPh.	Department of Veterans Affairs

B. Voting Members Absent

Col Everett McAllister, BSC	Air Force, Pharmacy Officer
LCDR Scott Akins, MC	Navy, Pediatrics Physician

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CPT Alvin Blackmon, MSC, USA	Defense Supply Center Philadelphia
Mr. Lynn T. Burleson	Assistant General Counsel, TMA

D. Non-Voting Members Absent

LT Thomas Jenkins, MSC, USN	TMA Aurora
Martha Taft	Health Plans Operations, TMA

E. Others Present

Col Nancy Misel, BSC, USAF	IMA DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
LCDR Joe Lawrence, MSC, USN	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
Shana Trice, Pharm.D.	DoD Pharmacoeconomic Center
David Bretzke, Pharm.D.	DoD Pharmacoeconomic Center
Angela Allerman, Pharm.D.	DoD Pharmacoeconomic Center
Eugene Moore, Pharm.D.	DoD Pharmacoeconomic Center
Julie Liss, Pharm.D.	DoD Pharmacoeconomic Center
Elizabeth Hearin, Pharm.D.	DoD Pharmacoeconomic Center
David Meade, Pharm.D.	DoD Pharmacoeconomic Center
Harsha Mistry, Pharm.D.	DoD Pharmacoeconomic Center
Lisa Longo, Pharm.D.	VAPBM
Lisa McNair	TMA
LCDR Rob Hayes	DHHS, Indian Health Service

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – February 2007 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. Approval of February Minutes – MG Elder Granger, USA, MC, Deputy Director, TMA, approved the minutes of the February 2007 DoD P&T Committee meeting on May 2, 2007.

4. 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 – CAPT Buss briefed the members of the P&T Committee regarding the March 2007 BAP meeting. The P&T Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions – The PEC briefed the members of the P&T Committee on the progress of implementation for drug classes reviewed for UF status since February 2005.

C. Administrative Action – Modification of Modafinil (Provigil) Prior Authorization (PA) Criteria – A PA for modafinil (Provigil) was recommended by the P&T Committee at the November 2006 meeting and subsequently approved by the Director, TMA, with an effective date of April 18, 2007. The PEC briefed the members of the P&T Committee on an administrative action to omit the PA criterion addressing use for cocaine dependence from PA criteria posted on the TRICARE Pharmacy website and incorporated into PA forms. The criterion provided for coverage of modafinil for cocaine dependence, based on two randomized trials supporting the use of modafinil for the treatment of cocaine dependency. (One trial reported decreased euphoria with cocaine use, the other an increased abstinence rate; modafinil is thought to counteract the glutamate-depleting effect of cocaine, possibly reducing craving.) The criterion was administratively omitted because coverage of substance abuse treatment in settings other than authorized institutional providers falls under another TRICARE approval process and is affected by other TRICARE regulations, not because of clinical considerations. The P&T Committee concurred with the change.

5. REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on three new drugs which were approved by the Food and Drug Administration (FDA) (see Appendix B). The P&T Committee determined that these three new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed. The P&T Committee discussed the need for quantity limit (QL) or PA requirements for the drugs.

The P&T Committee agreed that the three new drugs required QLs, based on existing QLs for similar agents (oral cancer agents and products for oral inhalation) and recommendations for use in product labeling.

COMMITTEE ACTION: QLs

- Arformoterol (Brovana) – The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend QLs for arformoterol (Brovana) of 60 unit dose vials per 30 days, 180 unit dose vials per 90 days.

- Lapatinib (Tykerb) – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for lapatinib (Tykerb) as follows: 150 tablets per 30 days at retail network pharmacies, with a days supply limit of 30 days (no multiple fills for multiple co-pays); and 225 tablets per 45 days at mail order, with a days supply limit of 45 days.
- Vorinostat (Zolinza) – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for vorinostat (Zolinza) as follows: 120 tablets per 30 days at retail network pharmacies, with a days supply limit of 30 days (no multiple fills for multiple co-pays); and 180 tablets per 45 days at mail order, with a days supply limit of 45 days.

B. Over-the-Counter (OTC) terbinafine 1% Cream (Lamisil AT)

Section 705 of the John Warner National Defense Authorization Act for Fiscal Year 2007 directs the Secretary of Defense to conduct a demonstration project under section 1092 of title 10, U.S. Code, to allow particular OTC drugs to be included on the UF under section 1074g of such title. The purpose is to assess the impact of authorizing TRICARE coverage for OTC agents recommended for inclusion on the UF. For an OTC drug to be included as part of the OTC Demonstration Project, the P&T Committee must find that the OTC drug is cost effective and therapeutically equivalent to a prescription drug. Beneficiaries will be required to have a prescription for the OTC product. OTC drugs provided under the demonstration project shall be made available through military treatment facilities (MTFs) and the TRICARE Mail Order Pharmacy (TMOP).

The P&T Committee, after consultation with the TMA Pharmacy Program office, selected the topical antifungal terbinafine 1% cream OTC (Lamisil AT) as the second OTC product for the project. Since this is the first opportunity for terbinafine 1% cream OTC to be considered for UF inclusion, it was reviewed as a new drug in a class previously reviewed.

The P&T Committee reviewed the topical antifungal drug class in May 2005. Topical antifungals on the UF include clotrimazole (Lotrimin, generics), nystatin (Mycostatin, generics), miconazole (Monistat Derm, generics), ketoconazole (Nizoral, generics), butenafine (Mentax), and naftifine (Naftin). Clotrimazole and nystatin are classified as Basic Core Formulary (BCF) agents. Topical antifungal agents classified as non-formulary under the UF are econazole (Spectazole, generics), sertaconazole (Ertaczo), sulconazole (Exelderm), ciclopirox (Loprox, generics; excludes ciclopirox topical solution (Penlac) for onychomycosis), oxiconazole (Oxistat) and 0.25% miconazole/15% zinc oxide (Vusion).

1) *Relative Clinical Effectiveness* – Terbinafine is a synthetic allylamine derivative that interferes with synthesis of the fungal cell wall. Terbinafine was originally available as a prescription product in 1992, but as of 1999 is solely available OTC. FDA-approved indications for terbinafine include tinea pedis, tinea cruris, and tinea corporis. Terbinafine is also effective for treating tinea versicolor, although it is not labeled for this indication. Dosing and administration vary with the indication; for tinea pedis, terbinafine is applied twice daily for seven days, or once daily for four weeks. For tinea versicolor, tinea corporis, or tinea cruris, the

recommended dosing is once daily for 14 days. Terbinafine 1% OTC is available in several different formulations, including cream, spray, and gel; only the cream is under consideration for UF inclusion.

Allylamines on the UF include butenafine (Mentax) and naftifine (Naftin). The allylamines, including terbinafine, appear to be slightly more efficacious than azoles for treatment of tinea pedis. A Cochrane analysis evaluated efficacy of the allylamines (terbinafine, naftifine) and azoles (clotrimazole, econazole, miconazole, and sulconazole) for treating tinea pedis. Pooled analyses of trials comparing azoles with allylamines yielded cure rates of 73% with the azoles vs. 80% with the allylamines. There were no detectable differences in efficacy between individual allylamines or individual azoles.

In general, topical antifungals are recognized as safe and well-tolerated, allowing for the switch from prescription to OTC status for terbinafine. Common adverse events reported with terbinafine include burning, stinging, peeling or other local reactions, which are commonly attributed to the vehicle or the condition itself; terbinafine does not appear to be any more likely to cause these adverse reactions than the other allylamine products on the UF.

Conclusion: The P&T Committee concluded that terbinafine 1% cream OTC has no clinically significant differences with respect to safety, efficacy, or tolerability, when compared to other allylamines included on the UF. The P&T Committee also concluded that it was unlikely that clinically significant differences exist between OTC terbinafine and the prescription allylamines for the treatment of common dermatologic infections.

2) *Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of terbinafine 1% cream OTC in relation to efficacy, safety, tolerability, and clinical outcomes of the other allylamines in the topical antifungal 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).

   Based on the information reported from the relative clinical effectiveness evaluation, there was evidence to suggest that terbinafine 1% cream OTC has similar efficacy, safety, tolerability, and clinical outcomes compared to the other allylamines in the topical antifungal class.

   The cost review for terbinafine 1% cream OTC compared the Federal Supply Schedule cost per 30 grams to the other allylamines, naftifine and butenafine.

   Conclusion: The results of the cost review showed that terbinafine 1% cream OTC is more cost effective than other allylamines in the topical antifungal class (butenafine and naftifine) across all three points of service.

3) *Clinical and Cost Effectiveness Conclusions* – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to accept the clinical and cost effectiveness conclusions stated above.

   COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional

judgment, voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend that terbinafine 1% cream OTC be classified as formulary on the UF for the OTC Demonstration Project.

4) *Medical Necessity (MN) Criteria* – Since terbinafine 1% cream OTC was not recommended for non-formulary status under the UF, establishment of MN criteria is not applicable.

5) *UF Implementation Period* – Since terbinafine 1% cream OTC was not recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

6. DRUG CLASS REVIEW – ANTILIPIDEMIC AGENTS II (LIP-2s)

The P&T Committee evaluated the relative clinical effectiveness of the Antilipidemic Agents II (LIP-2) agents. This class is divided into three subclasses: fibric acid derivatives, omega-3 fatty acids, and bile acid sequestrants. Omega-3 fatty acid ("fish oil") products include the prescription product Omacor, along with a number of nutritional supplement products available OTC. Of these, only Omacor is eligible for inclusion on the UF.

The LIP-2 drug class accounted for $63 million in Military Health System (MHS) expenditures in FY 2006, ranking in the top 20 in terms of total expenditures. By comparison, the LIP-1 drug class reviewed in August 2006 (statins, ezetimibe, niacin, and combinations) accounted for $500 million in MHS expenditures and was ranked #1.

A. LIP-2s – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the LIP-2 agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes 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(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.

Table 1: Antilipidemic II Agents Available in the U.S.

Subclass	Generic Name	Brand Name
Fibric Acid Derivatives	Gemfibrozil	Lopid, generics
	Fenofibrate	
	Nanocrystallized	Tricor
	Non-micronized/micronized	Lofibra (generic to innovator Tricor)
	Micronized	Antara
	IDD-P (micronized)	Triglide
Omega-3 fatty acids	Omega-3 fatty acid	Omacor
Bile Acid Sequestrants	Cholestyramine/aspartame	Questran Light, Prevalite, generics
	Cholestyramine/sucrose	Questran, generics
	Colestipol	Colestid, generics
	Colesevelam	Welchol

IDD-P = Insoluble Drug Delivery - microParticle

1) Formulations

a) Fibric Acid Derivatives

i) Products

The fibric acid derivatives available commercially include gemfibrozil (Lopid, generics) and several formulations of fenofibrate. Fenofibrate is a prodrug that is metabolized to its active ingredient, fenofibric acid. The innovator fenofibrate product launched in 1998 under the trade name Tricor by Abbott Laboratories was very insoluble in water, thus was poorly absorbed and required administration with food. Drug particle size has been reduced in newer fenofibrate formulations to enhance absorption compared to the original fenofibrate product. As products are re-formulated, previous versions are typically removed from the market.

The most recent fenofibrate formulations are micronized fenofibrate (Antara), insoluble drug delivery microparticle (IDD-P) fenofibrate (Triglide), and nanocrystallized fenofibrate (Tricor). Antara, Triglide, and Tricor can be taken without regard to meals.

The innovator fenofibrate formulation has been discontinued by Abbott, along with a later version. The current Tricor product (nanocrystallized) is the third version on the market. Lofibra is a branded generic to the two earlier Tricor formulations, and is available in both a micronized and non-micronized version.

ii) FDA approval process

The newer fenofibrate formulations received FDA approval via a 505b(2) application. Under this process, newer products are approved by demonstrating bioequivalence to the original new drug application of the innovator fenofibrate 200 mg product. The newer formulations are marketed in varying dosage strengths lower than 200 mg. However, bioequivalence is similar between innovator fenofibrate 200 mg, IDD-P micronized fenofibrate (Triglide) 160 mg, nanocrystallized fenofibrate 145 mg, and micronized fenofibrate (Antara) 130 mg.

b) Omega-3 Fatty Acids

i) Products

Fish oil Supplements – The omega-3 fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Several formulations of omega-3 fatty acids (fish oils) are available as dietary supplements. Dietary products do not undergo the rigorous approval process required for prescription products.

Prescription omega-3 fatty acids (Omacor) – Omacor is a marine-derived omega-3 polyunsaturated fatty acid product that was approved by the FDA in 2004. It is the first and only prescription fish oil product available. Each 1-gram Omacor capsule contains 90% omega-3 acid esters,

consisting of 465 mg (46%) EPA, 375 mg (38%) DHA), 6% other omega-3 acid esters, and 10% omega-6 fatty acids.

ii) FDA indication

Fish Oil Supplements – The FDA allows a qualified health claim for dietary supplements and conventional foods containing EPA and DHA omega-3 fatty acids to reduce the risk of coronary heart disease (CHD).

Omacor – Omacor is currently approved only as an adjunct to diet in patients with very high triglyceride (TG) levels (>500 mg/dL).

iii) Off-label uses

Prevention of CHD – In Europe, fish oil supplements are approved by regulatory authorities for secondary prevention of CHD. The U.S. FDA has not approved use of the Omacor product for CHD prevention, as it considers the data incomplete. In February 2007, the manufacturer added wording to the labeling stating that Omacor has not been shown to prevent myocardial infarction (MI) or strokes. However, Omacor is likely to be used off-label for CHD prevention.

c) Bile Acid Sequestrants

i) Products – The bile acid sequestrants (BAS) have been marketed since the 1960s and are still utilized for lowering low density lipoprotein (LDL). The class consists of cholestyramine/sucrose (Questran, generics), cholestyramine/aspartame (Questran Light, generics), colestipol (Colestid, generics), and the newest agent, colesevelam (Welchol).

ii) Indications – The BAS are all indicated for use as either monotherapy or in combination with statins to reduce LDL.

iii) Pharmacokinetics – The BAS are not absorbed and are not hydrolyzed by digestive enzymes. The older agents preferably bind to dihydroxy bile acids over trihydroxy bile acids. Colesevelam binds to both dihydroxy and trihydroxy bile acids equally, thus removing both types of bile acids from the circulation. *In vitro* lab data suggests that colesevelam is 4 to 6 times more potent than the older BAS in regard to lower total cholesterol and LDL levels, possible due to enhanced binding of trihydroxy bile acids. However, this difference in *in vitro* binding has not translated into enhanced efficacy of colesevelam in clinical trials assessing lipid parameters.

2) Efficacy

a) Efficacy Measures

The primary efficacy measures used to assess efficacy of the LIP-2 agents are reduction in LDL, TG, and total cholesterol levels (TC), and increases in high-density lipoprotein (HDL). The fibric acid derivatives and omega-3 fatty acids primarily reduce elevated TG levels and raise HDL. The BAS primarily reduce LDL.

When available, clinical outcomes data (reduction of CHD risk, including MI, mortality (all-cause or CHD), need for revascularization, and stroke) were also evaluated to assess differences between agents.

b) Fibric Acid Derivatives

i) Lipoprotein efficacy

Package inserts – The majority of clinical trials evaluating lipid effects have compared gemfibrozil or fenofibrate (Tricor, Antara, Triglide, Lofibra) with placebo. Both fenofibrate and gemfibrozil reduce TG levels by 20 to 50% and increase HDL by 10 to 20%. Varying effects on LDL concentrations are seen, ranging from reductions to increases of 5 to 20%.

Head-to-head trial – One small comparative trial with the fibric acid derivatives is available. Micronized fenofibrate 200 mg (an earlier Tricor formulation) was compared to gemfibrozil in 21 patients with type IIa and IIb hyperlipidemia. After six weeks, similar reductions in triglycerides were seen between the two agents (54% with fenofibrate vs. 46.5% with gemfibrozil; not statistically significant). However, micronized fenofibrate resulted in greater reductions in LDL and TC than gemfibrozil. The differences in LDL effects were likely attributed to the fact that a gemfibrozil dose of 900 mg QD was used, rather than the FDA-approved 600 mg BID dosage.

ii) Clinical outcomes

Three placebo-controlled trials are available that assessed clinical outcomes for gemfibrozil (HHS, VA-HIT) and fenofibrate (FIELD). There are no published head-to-head trials available that assess clinical outcomes (e.g. all-cause mortality, CHD mortality, MI, etc).

- *Helsinki Heart Study 1987 (HHS)* – HHS was a double-blind, placebo-controlled study conducted in 4,000 Finnish men (average age 47 years) who did not have CHD (primary prevention trial). After five years, gemfibrozil 600 mg BID resulted in a significant reduction (34%) in nonfatal MI and CHD death, compared to placebo. There was no difference between gemfibrozil and placebo in all-cause mortality.
- *Veteran Affairs High density lipoprotein cholesterol Intervention Trial 2001 (VA-HIT)* – VA-HIT was a secondary prevention trial conducted in over 2,000 male VA patients who had a history of CHD (average age 64 years). After five years, compared to placebo, treatment with gemfibrozil 600 mg BID resulted in a significant reduction (22%) in the risk of nonfatal MI or CHD death. There was no difference in death due to any cause. Thirty percent of the study participants were diabetic, and when this subpopulation was analyzed, significant reductions in the composite of nonfatal MI, stroke and CHD death were seen.

- *Fenofibrate Intervention and Event Lowering in Diabetes 2005 (FIELD)* – The FIELD trial was a randomized double-blinded placebo-controlled trial which included 9,975 type 2 diabetic participants, 2,131 of whom had cardiovascular disease. Patients were treated with fenofibrate 200 mg QD or placebo for 5 years. Patients were not receiving statins at the start of the study, but could start antilipidemic therapy, including statins, during the trial.

  After five years, there was no statistically significant difference between fenofibrate and placebo in the primary composite endpoint of nonfatal MI and CHD death (5.9% vs. 5.2%, respectively, hazard ratio 0.89, 95% CI 0.75-1.05). However, statistically significant reductions in nonfatal MI (4% vs. 3%) and total cardiovascular events (14% vs. 13%) were seen with fenofibrate. Reductions in total cardiovascular events were primarily due to a significant reduction in the need for coronary revascularization (7% vs. 6%). The concomitant use of statins in 17% of the placebo group vs. only 8% of the fenofibrate group may have accounted for the modest effect of fenofibrate in reducing cardiovascular events.

  An unexpected finding was a 19% (p=0.22) increase in CHD death with fenofibrate compared to placebo, reflecting an increase in sudden deaths in the fenofibrate group.

iii) Efficacy conclusion

Clinically the fibric acid derivatives are useful in reducing elevated TG concentrations and raising HDL. There are no major clinical differences between gemfibrozil and fenofibrate in terms of changes in lipid parameters as shown in the HHS, VA-HIT and FIELD clinical trials; both drugs reduce TG by 20-50%, and increase HDL by 10-20%. Varying effects on LDL have been reported. One small head-to-head trial reported that fenofibrate resulted in greater reductions in TG and LDL than gemfibrozil; however, the gemfibrozil dose was lower than that recommended in the product labeling.

Two placebo-controlled trials with gemfibrozil have shown a benefit in reducing the risk of cardiovascular events in a primary prevention setting and the risk of nonfatal MI and CHD death in a secondary prevention setting. Mixed results were demonstrated with fenofibrate in a large outcomes trial in a primary/secondary prevention setting; fenofibrate did not result in a statistically significant benefit in reducing the composite of CHD death or nonfatal MI, but was associated with significant reductions in nonfatal MI and coronary revascularization.

b) Omega-3 fatty acids

i) Lipoprotein efficacy

Fish oil supplements: placebo-controlled trials – One meta-analysis of 36 crossover and 32 parallel studies of dietary and supplemental omega-3 fatty acids reported that a 3- to 4-gram daily dose resulted in a reduction of TG by

25-34%, and an increase in LDL by 4-11%, regardless of source or formulation.

Omacor: placebo-controlled trials – Ten prospective, randomized clinical trials have examined the effects of the marketed Omacor formulation on TG and LDL concentrations in patients with elevated TG levels. Overall, Omacor 4 grams daily resulted in a 20-45% reduction in TG levels when compared to placebo. The TG-lowering response appears to correlate with baseline TG levels (e.g. patients with higher baseline TG levels will generally have a greater TG-lowering response).

Increases in LDL ranging from 17 to 31% were reported in four of the ten studies. Increases in LDL also appeared to correlate with baseline TG levels. Concomitant use of a statin may blunt any increase in LDL associated with Omacor.

ii) Omacor vs. fish oil supplements – There are no head-to-head trials comparing the lipid effects of Omacor vs. nutritional omega-3 fatty acid supplements.

iii) Omacor vs. other lipid-lowering therapies – The TG-lowering effects of Omacor are slightly lower than those achieved with fibric acid derivatives or niacin. Omacor is associated with similar increases in HDL compared to fibric acid derivatives and niacin.

iv) Clinical outcomes

- *Fish oil supplements: systematic reviews/meta-analyses* – The effects of dietary or supplemental omega-3 fatty acids on cardiovascular disease outcomes have been evaluated in several meta-analyses and systematic reviews, with conflicting results reported. Some reports suggest a beneficial effect when omega-3 fatty acids are used for either primary or secondary cardiovascular disease prevention. In contrast, a 2004 Cochrane review of randomized controlled trials and cohort studies found no strong evidence that dietary or supplemental omega-3 fatty acids reduced total mortality, cardiovascular events, or cancer.
- *Fish oil supplements: placebo-controlled trial (GISSI-Prevenzione)* – In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto miocardico (GISSI)-Prevenzione Trial, an omega-3 fatty acid with a different ratio of EPA and DHA than Omacor was evaluated. Fish oil supplementation was associated with a 15% reduction in the risk of the composite endpoint of death, nonfatal MI, and stroke in 11,324 survivors of a recent MI. There was a 20% reduction in all-cause mortality, which was driven by a 45% reduction in sudden death. There was no difference in nonfatal MI between the groups. Limitations to the study include the open label study design, a dropout rate nearing 30% by study completion, use of a fish oil supplement different than Omacor, and high dietary intake of fish (which in itself has cardiovascular benefits).

- *Omacor: placebo-controlled trial* – One placebo-controlled, double-blinded trial evaluated the effect of Omacor on cardiovascular outcomes. In this study, 300 patients with acute MI were randomly assigned to receive Omacor 4 grams daily or corn oil placebo for a median time period of 1.5 years. There was no statistically significant difference in the rate of cardiac events (cardiac death, resuscitation, recurrent MI, and unstable angina) between groups (28% with Omacor vs. 24% with placebo, hazard ratio 1.19, 95% CI 0.76-1.86). The lack of difference was attributed to the small size and short duration of the trial, as well as the inclusion of Norwegian patients whose diets already contained a high content of fish.
- *Omacor vs. fish oil supplements* – There are no head-to-head trials of Omacor versus fish oil supplements.
- *Omacor vs. other lipid-lowering therapies* – Niacin and gemfibrozil both have clinical trial evidence supporting long-term benefits on cardiovascular outcomes.

v) *Efficacy conclusion:* Randomized clinical trials showed a reduction in TG levels of 20-45% with Omacor 4 grams once daily. However, Omacor has also been associated with increases in LDL, which may offset beneficial reductions in TG. Concomitant use of a statin may blunt increases in LDL.

The GISSI-Prevenzione trial is the largest trial showing a benefit of omega-3 fatty acids on cardiovascular outcomes, but it assessed a different omega-3 fatty acid product and not Omacor. Its validity may also be limited by its open-label design, high dropout rate, and high dietary fish intake. A small, short-duration placebo-controlled trial specifically assessing the cardio-vascular outcomes of Omacor did not demonstrate a reduction in cardiac events.

The TG-lowering effect of Omacor is slightly less than that achieved with either fibric acid derivatives or niacin. In the National Cholesterol Education Panel (NCEP) guidelines, fibric acid derivatives or niacin are listed as first-line treatments for patients with TG >500 mg/dL; both have clinical outcomes data supporting a benefit in reducing the risk of cardiovascular events.

c) *Bile Acid Sequestrants*

i) *Lipoprotein efficacy* – There are only a few clinical trials available for the BAS, and most were conducted in the 1970s and early 1980s. No trials have compared the older agents, cholestyramine and colestipol, with colesevelam.

- *Cholestyramine* – The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was a large placebo-controlled trial that compared cholestyramine 24 g QD to placebo in preventing coronary artery disease (CAD) in 3,806 men with primary hypercholesterolemia. Treatment with cholestyramine resulted in greater reductions in TC and

LDL than placebo (TC -17% with cholestyramine vs. -1% with placebo; LDL -26% with cholestyramine vs. -5% with placebo ($p<0.001$).

The National Heart, Lung, and Blood Institute (NHLBI) compared cholestyramine with placebo in 143 patients. Cholestyramine reduced LDL by 26% vs. 5% with placebo ($p<0.001$). There was no significant difference between cholestyramine and placebo in TG or HDL levels.

- *Colesevelam* – One double-blind study compared various doses of colesevelam to placebo for 24 weeks in 494 patients with primary hypercholesterolemia. LDL levels decreased by 18% at the highest dose; all colesevelam doses reduced LDL significantly versus placebo ($p<0.001$). There were small, non-clinically significant increases in HDL and TG.
- *Colestipol* – One large placebo-controlled trial with colestipol published in 1978 reported a 12% reduction in TC; LDL values were not reported.
- *Cholestyramine or colestipol vs. placebo* – In 1972, a study of 45 adults with hyperlipidemia examined the cholesterol lowering activity and safety of colestipol monotherapy or cholestyramine monotherapy versus placebo. After one year of therapy, colestipol and cholestyramine had a similar effect on TC (40% reduction).

ii) Combination therapy with a statin – The BAS are uncommonly used as monotherapy; they are more likely to be used as adjunctive therapy with a statin. Colestipol plus simvastatin (Zocor, generics) has produced LDL reductions of 45-50%. Colesevelam plus simvastatin has resulted in a 48% reduction in LDL.

iii) Clinical outcomes – The only BAS trial that evaluated clinical outcomes was the LRC-CPPT with cholestyramine. This trial reported a 19% reduction in the combined rate of CHD death plus nonfatal MI with cholestyramine vs. placebo (7% vs. 95, respectively; $p<0.05$).

iv) Efficacy conclusion – Treatment with a BAS reduces LDL by15-30%. Use of BAS as monotherapy has declined in popularity, since statins offer greater LDL reduction. Based on indirect comparison of placebo-controlled trials, cholestyramine, colestipol, and colesevelam have comparable efficacy in lowering LDL. There are no direct comparative trials. There is clinical evidence supporting the use of cholestyramine for reducing the risk of cardiovascular events; no such benefit has been documented with colestipol or colesevelam.

3) 3) Safety / Tolerability

a) Fibric Acid Derivatives

i) Myopathy with statin combination therapy

- *Background* – An increased risk of myositis and potentially fatal rhabdomyolysis has been reported with fibric acid derivatives, either as monotherapy or in combination with a statin (particularly cerivastatin); it

appears to be dose-related. This risk was first identified via spontaneous reports to the FDA Adverse Event Reporting System (AERS).

- *Gemfibrozil vs. fenofibrate* – Mechanistically, differences in glucuronidation pathways between gemfibrozil and fenofibrate are postulated to account for potential differences in the risk of developing myotoxicity. Gemfibrozil undergoes glucuronidation metabolism through the uridine diphosphate glucuronosyl transferase (UGT) 1A1 and 1A3 pathways, which results in competition with the statins. Fenofibrate is eliminated via UGT 1A9 and 2B7 pathways, which do not appear to interfere with statin glucuronidation.
- *FDA retrospective review* – A retrospective data analysis of the FDA AERS database found that half of the cases of statin-induced rhabdomyolysis identified were associated with concomitant medications affecting statin metabolism, and of these more than one third were associated with fibric acid derivatives, gemfibrozil in particular. Many of these reports involved cerivastatin, which has now been withdrawn from the market.

  Another study evaluating the FDA AERS database analyzed the reporting rate (not incidence rate) of myotoxicity between fenofibrate plus a statin vs. gemfibrozil plus a statin. Based on 606 adverse event reports compiled from 1998 to 2002, the reporting rate (rhabdomyolysis cases per million U.S. prescriptions) was 0.58 for fenofibrate and 8.6 with gemfibrozil. This study excluded cerivastatin, which has now been withdrawn from the market. Limitations include varying definitions of myotoxicity, lack of verification of data, and the use of spontaneous reporting rates, which are subject to reporting bias and do not establish a causal relationship.
- *Fenofibrate/statin combination trial* – In 2005, one randomized, double-blinded 18-week trial (n=600) evaluated safety of monotherapy with low-dose simvastatin (20 mg) versus combination therapy with a standard dose of fenofibrate plus simvastatin 20 mg. The incidence of myalgia in the combination group was 2.2% vs. 2.4% with simvastatin. There were no reports of rhabdomyolysis.
- *Clinical practice guidelines* – Professional organizations have not favored one fibric acid derivative over the other with respect to safety of use in combination with statins. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the NHLBI conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

ii) Minor adverse effects

- *Lab abnormalities* – Both gemfibrozil and fenofibrate have been associated with abnormal liver function tests when administered as monotherapy. Increases in serum creatinine ranging from 8 to 18% have

been reported with fenofibrate in patients with normal or impaired renal function. Product labeling advises monitoring of serum creatinine during therapy with either fenofibrate or gemfibrozil.

- *Gemfibrozil vs. fenofibrate: minor adverse effects* – Gastrointestinal (GI) complaints (e.g., nausea, vomiting, and diarrhea) are most common for both fenofibrate and gemfibrozil. Although they occur in fewer than 5% of patients taking fibric acid derivatives, they appear to occur more often with gemfibrozil than with fenofibrate, based on pooled data from product labeling. The head-to-head efficacy trial mentioned earlier (conducted in 21 patients) did not report adverse events.
- *Fenofibrate formulations: minor adverse effects* – There are no head-to-head trials assessing differences in adverse effects among the newer fenofibrate formulations. Differences in fenofibrate formulations are primarily related to decreases in particle size designed to address bioavailability issues, allowing the most recent products (Tricor, Antara, and Triglide) to offer once daily dosing and be taken without regard to meals. These differences do not appear to equate to differences in GI adverse effects, although comparative data are not available.

iii) Special populations – None of the fibric acid derivatives are FDA-approved for use in pediatric patients. All are rated Pregnancy Category C. Dosage adjustments for both gemfibrozil and fenofibrate are required in patients with mild renal impairment.

iv) Drug interactions –There appear to be no major clinical differences between the products with respect to drug interactions with products other than statins, which were discussed previously.

v) Safety conclusion – There are no head-to-head trials supporting a lower risk of myotoxicity with gemfibrozil than with fenofibrate, either alone or in combination with a statin, and professional organizations have not favored one fibric acid derivative over the other. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the NHLBI conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

GI complaints (e.g., nausea, vomiting, and diarrhea) are most common for both fenofibrate and gemfibrozil. Although they occur in fewer than 5% of patients taking fibric acid derivatives, they appear to occur more often with gemfibrozil than with fenofibrate, based on pooled data from product labeling. There are no comparative data. There are no clinically significant differences between gemfibrozil and fenofibrate with regard to use in special populations or drug interaction potential.

b) Omacor

i) Minor adverse events – Omacor appears to be safe and well tolerated, with GI disturbances reported most commonly. Patients frequently complain of fishy-smelling breath and taste perversion, which may limit compliance.

ii) *Special populations* – Safety of Omacor has not been evaluated in pediatric patients or pregnant patients. No dosage adjustments are required in renal or hepatic impairment.

iii) *Drug-drug interactions* – Patients receiving Omacor and anticoagulants require periodic monitoring, due to the potential risk of increased bleeding. Clinically significant drug interactions due to inhibition of CYP450 metabolism are not expected with Omacor.

c) *Bile Acid Sequestrants*

i) *Systemic adverse events* – The BAS are not absorbed, thus are associated with a low incidence of systemic effects. Non-GI effects (such as angina and tachycardia, or rash) are rare.

ii) *GI adverse events* – Constipation is the most common minor adverse effect with all the BAS, occurring with an incidence of greater than 10%. In the LRC-CPPT trial, the incidence of constipation with cholestyramine was 39% vs. 10% with placebo; however, GI distress from cholestyramine appeared to decrease with time. Constipation appears to occur less frequently with colesevelam than with other BAS, based on pooled data in product labeling. Rare reports of GI obstruction, including two deaths, have been reported in pediatric patients receiving cholestyramine.

Chronic use of BAS can cause bleeding due to hypoprothrombinemia secondary to malabsorption of vitamin K.

iii) *Drug-drug interactions* – Drug interactions with BAS are primarily due to effects on absorption of concomitant oral medications.

iii) *Special populations*

Pediatrics – Cholestyramine is the only BAS that is FDA-indicated to treat hypercholesterolemia in the pediatric population.

Pregnancy – Cholestyramine and colestipol have a Pregnancy Category C rating; colesevelam has a Category B rating. Because statins are rated Pregnancy Category X, NCEP guidelines state that BAS are recommended for women with elevated cholesterol who are considering pregnancy.

4) Other Factors

a) *Fibric Acid Derivatives* – Gemfibrozil is given twice daily before meals, while the newer formulations of fenofibrate ((Tricor, Triglide, Antara) may be given once daily without regard to meals.

b) *Omega-3 Fatty Acids* – Since Omacor has undergone the new drug approval process, the ratio and amount of DHA and EPA contained in each capsule and the amount of other ingredients is known. The FDA has more authority to oversee manufacturing of Omacor than fish oil supplements. Fish oil supplement manufacturers are not required to list ingredients other than omega-3 fatty acids (e.g., omega-6 fatty acids, cholesterol) in their label. The

Omacor formulation requires four capsules daily; higher capsule burdens are necessary with some fish oil supplements.

c) *Bile Acid Sequestrants* – Cholestyramine is only available in a powder form, which some patients find unpalatable. Cholestyramine and colestipol are available as powders or granules for oral suspension, with colestipol also available in tablet form. Both colestipol and colesevelam require large daily tablet burdens (up to sixteen tablets per day for colestipol and seven for colesevelam).

5) Place in Therapy

a) *Fibric Acid Derivatives* – Fibric acid derivatives have been used clinically since the 1970s and are effective at lowering TG levels and raising HDL. They are widely used as adjunctive treatment with statins, which primarily reduce LDL.

b) *Prescription Omega-3 Fatty Acids (Omacor)* – Omacor provides an alternative for patients with elevated TG who are not candidates for niacin or fibric acid derivatives. The American Heart Association (AHA) recommends niacin as first-line for elevated TG. The AHA recommends consumption of a variety of fish as primary prevention, with omega-3 fatty acids potentially considered for secondary prevention. NCEP guidelines recommend either fibric acid derivatives or niacin as first line for elevated TG, along with a high dietary intake of fatty fish or omega-3-containing vegetable oils.

c) *Bile Acid Sequestrants* – NCEP guidelines recommend BAS for LDL-lowering in patients with moderately elevated LDL; women who are considering pregnancy and have elevated LDL; and patients who need only modest reductions in their LDL to reach their target goal.

6) *Overall Clinical Effectiveness Conclusion* – The P&T Committee concluded that:

a) *Fibric Acid Derivatives*

i) Both gemfibrozil and fenofibrate reduce TG by 20-50% and raise high density lipoprotein (HDL) by 10-20%. There is insufficient evidence to conclude that gemfibrozil and fenofibrate differ in their ability to reduce TG and raise HDL.

ii) Two placebo-controlled trials with gemfibrozil have shown a benefit in reduction of cardiovascular events in a primary prevention setting and a reduction in nonfatal MI and CHD death in a secondary prevention setting. Mixed results were demonstrated with fenofibrate in a large outcomes trial in a primary/secondary prevention setting; fenofibrate did not result in a statistically significant benefit in reducing the composite of CHD death or nonfatal MI, but was associated with significant reductions in nonfatal MI ($p=0.01$) and coronary revascularization ($p=0.035$).

iii) Although GI adverse effects occurred in fewer than 5% of patients taking fibric acid derivatives, they appeared to occur more frequently in patients taking gemfibrozil than those taking fenofibrate, based on pooled data

from product labeling. Gemfibrozil must be taken twice daily prior to meals.

iv) Monotherapy with either fibric acid derivatives or statins has been associated with an increased risk of myalgia, myositis, and rhabdomyolysis. This risk appears to be increased with gemfibrozil/statin combination therapy, based on spontaneous adverse event reporting data from the FDA. These data showed a higher reporting rate of rhabdomyolysis with a statin plus gemfibrozil (8.6) compared to a statin plus fenofibrate (0.58), based on the number of spontaneous case reports per 1 million U.S. prescriptions from 1998 to 2002. This study excluded cerivastatin, which has now been withdrawn from the market. Limitations include varying definitions of myotoxicity, lack of verification of data, and the use of spontaneous reporting rates, which are subject to reporting bias and do not establish a causal relationship. It is unclear whether combination therapy with fenofibrate and a statin increases the risk of myotoxicity more than either agent given alone. One trial comparing statin monotherapy vs. combination therapy with fenofibrate plus a statin reported similar rates of myalgia.

v) Pharmacokinetic differences in glucuronidation pathways between gemfibrozil and fenofibrate are postulated to account for potential differences in the risk of developing myotoxicity when used in combination with a statin. However, there are no head-to-head trials supporting a lower risk of myotoxicity with gemfibrozil than with fenofibrate, either alone or in combination with a statin, and professional organizations have not favored one fibric acid derivative over the other. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the NHLBI conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

vi) Fenofibrate formulations include nanocrystallized fenofibrate (Tricor), micronized fenofibrate (Antara), insoluble drug delivery microparticle (IDD-P) fenofibrate (Triglide) and generic formulations of non-micronized and micronized fenofibrate (Lofibra). These newer formulations, regardless of dosage strength or particle size, are bioequivalent to 200 mg of the original fenofibrate formulation. Changes in particle size are designed to address bioavailability issues, allowing the most recent products (Tricor, Antara and Triglide) to offer once daily dosing and be taken without regard to meals. There is insufficient evidence to conclude that newer formulations offer improved efficacy, safety, or tolerability compared to each other or to older formulations.

b) Omega-3 Fatty Acids

i) Omacor is the only prescription omega-3 fatty acid product approved by the FDA. FDA oversight of the manufacturing process for Omacor offers

increased assurance of its omega-3 fatty acid content and purity, in contrast to some fish oil supplements.

ii) Overall, Omacor decreases TG by 20-45%. However, Omacor has also been associated with increases in LDL, which may offset beneficial reductions in TG.

iii) The TG-lowering effects of Omacor are slightly lower than those achieved with fibric acid derivatives or niacin. Omacor is associated with similar increases in HDL compared to fibric acid derivatives and niacin. Niacin and gemfibrozil both have clinical trial evidence supporting long-term benefits on cardiovascular outcomes.

iv) The omega-3 fatty acid formulation found in Omacor does not have outcomes studies that demonstrate beneficial cardiovascular effects (e.g., reductions in cardiovascular death, MI or stroke).

c) Bile Acid Sequestrants

i) The BAS agents reduce LDL by 15-30%. This subclass has largely been replaced by the statins, which decrease LDL by 18% to 55%. There is insufficient evidence to conclude that BAS differ in their ability to lower LDL. Cholestyramine is the only BAS to show beneficial effects on cardiovascular outcomes.

ii) Colesevelam has no major efficacy advantages compared to cholestyramine or colestipol, despite manufacturer claims of enhanced bile acid binding capacity. It has a more favorable pregnancy category rating than the older products (B vs. C) and may cause less constipation, which may be clinically relevant in patients with a previous history of GI obstruction.

iii) Issues with palatability of powder formulations and/or large daily tablet burdens are a concern with the class as a whole and may affect compliance.

iv) The BAS agents have a high degree of therapeutic interchangeability.

Overall Clinical Effectiveness Conclusion – Based on clinical issues alone, there are no compelling reasons to classify any of the LIP-2 agents as non-formulary under the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions above.

B. B. LIP-2s – 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 efficacy, safety, tolerability, 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).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the agents within the fibric acid derivative and BAS subclasses differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of hypertriglyceridemia and hyperlipidemia, respectively. As a result, cost minimization analyses (CMAs) were performed to compare the relative cost effectiveness of the agents within the fibric acid derivative and BAS subclasses. Since Omacor is the only prescription omega-3 fatty acid product, a cost effectiveness analysis (CEA) was conducted to compare it to other agents used in the treatment of hypertriglyceridemia.

Results from the fibric acid derivative CMA revealed: 1) gemfibrozil was the most cost-effective fibric acid derivative, and 2) IDD-P fenofibrate (Triglide) was by far the most cost effective fenofibrate. Among the bile acid sequestrants, the CMA showed that colesevelam was not cost-effective in the treatment of hyperlipidemia when compared to other available agents. The results for the prescription omega-3 fatty acids CEA showed that Omacor was not cost effective in the treatment of hypertriglyceridemia when compared to gemfibrozil, fenofibrate, and niacin. At this time, there is insufficient evidence to support a clinical benefit for omega-3 fatty acids in prevention of CHD. For this reason, the cost effectiveness of Omacor was not evaluated for this consequence or clinical outcome.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a budget impact analysis (BIA) of various UF scenarios for the LIP-2s was conducted. The goal of the BIA was to aid the Committee in determining which group of LIP-2s best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The DoD P&T Committee accepted the conclusions from the cost effectiveness analyses stated above. In addition, the Committee concluded that the UF scenario that maintained fenofibrate (Lofibra), IDD-P fenofibrate (Triglide), cholestyramine/aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil on the UF was the most cost effective UF scenario.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the relative CEA of the LIP-2 class.

C. LIP-2s – UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the LIP-2s, and other relevant factors, the P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) that: 1) fenofibrate (Lofibra, generics), IDD-P fenofibrate (Triglide), cholestyramine/ aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil be maintained as formulary on the UF; 2) micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and prescription omega-3 fatty acids (Omacor) be classified as non-formulary under the UF; and 3) the normal brand formulary cost-share of $9.00 for IDD-P fenofibrate (Triglide) be lowered to the generic formulary cost-share of $3.00.

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate." The objective is to maximize use of IDD-P fenofibrate (Triglide) in the retail network and mail order, given its significantly lower cost relative to other fenofibrate products. Lowering the cost-share for brand name IDD-P fenofibrate (Triglide) will provide a greater incentive for beneficiaries to use the most cost effective fenofibrate formulation in the purchased care arena

D. LIP-2s – MN Criteria

Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and omega-3 fatty acids (Omacor):

1) The use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Formulary alternatives have resulted in therapeutic failure.

The P&T Committee noted that some circumstances under which criterion #2 might be considered to apply may be 1) Omacor for patients who cannot take statins or fibric acid derivatives due to a history of myopathy and who cannot tolerate niacin, or 2) colesevelam for patients with a history of GI obstruction or pregnant patients who require treatment with a bile acid sequestrant.

COMMITTEE ACTION: The P&T Committee voted (13 for, 1 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. LIP-2s – UF Implementation Period

Given the relatively low number of beneficiaries are affected (approximately 83,612 patients (65%) of approximately 127,901 beneficiaries at all three points of service), the P&T Committee recommended an effective date of 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 micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, or prescription omega-3 fatty acids (Omacor) 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) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary LIP-2 agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day

implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. LIP-2s – BCF Review and Recommendation

Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that gemfibrozil and IDD-P fenofibrate (Triglide) be designated as the BCF selections in this class.

7. DRUG CLASS REVIEW – 5-ALPHA REDUCTASE INHIBITORS (5-ARIs)

The P&T Committee evaluated the relative clinical effectiveness of the 5-alpha reductase inhibitor agents (5-ARIs) available in the U.S. The 5-ARI drug class includes finasteride (Proscar, generics) and dutasteride (Avodart). These two agents have been marketed for a number of years; finasteride is available generically. The class review did not include the lower dosage (1 mg) strength of finasteride, which is marketed for alopecia (hair loss) under the brand name Propecia, since this indication is not covered by TRICARE.

The 5-ARI drug class accounted for $31.2 million in the MHS expenditures for the period October 2005 to September 2006 and is ranked #50 in terms of total expenditures during that time period. More than 281,000 prescriptions for 5-ARIs were filled in the MHS during a one-year period (January 2006 to December 2006). Of these, 59% were for finasteride and 41% were for dutasteride.

Pharmacologically, the 5-ARIs reduce prostate volume by inhibiting the conversion of testosterone to dihydrotestosterone (DHT). Finasteride selectively inhibits type I 5-alpha receptors, while dutasteride inhibits both type I and type II receptors; the clinical significance of this difference is unknown. 5-ARIs are used for the treatment of benign prostatic hyperplasia (BPH) in men with an enlarged prostate. Their effect on lower urinary tract symptoms (LUTS) associated with BPH (e.g., urinary frequency, urgency, nocturia, decreased / intermittent force of stream, and the sensation of incomplete bladder emptying) is related to relief of urethral obstruction and may take several months of treatment to become clinically evident. BPH to the point of prostatic obstruction can cause acute urinary retention (AUR), which is considered a medical emergency.

Standard treatments for BPH include watchful waiting (in men with mild symptomatic BPH); alpha blockers (which rapidly relieve symptoms by relaxing prostate and bladder smooth muscle but do not affect prostate volume); 5-ARIs (reduce prostate volume); combination alpha blocker/5-ARI treatment (in men with moderate-to-severe symptomatic BPH); and surgery (in men with severe symptomatic BPH).

A. 5-ARIs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the 5-ARI agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes 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(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) FDA-approved indications

   Both finasteride and dutasteride are indicated for the treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, reduce the risk of AUR, and reduce the risk of the need for BPH-related surgery. Finasteride is approved for combination therapy with the alpha blocker doxazosin to reduce the risk of symptomatic progression of BPH; labeling for dutasteride does not include an indication for combination therapy. Both are dosed once daily without regard to meals.

2) Efficacy Measures

   The primary outcome measures used to assess efficacy of the 5-ARIs are changes in symptom scores (AUA-SI or IPSS), urinary flow rate (Qmax), reductions in total prostate volume (TPV), and decreased risk of AUR or BPH-related surgery. In trials, a decrease in symptom score of three or more points is generally considered clinically significant; although men rate themselves as slightly improved with a decrease of one to two points. A change in the urinary flow rate of 2 to 3 mL/sec is considered clinically significant.

3) Efficacy

   a) *Long term placebo-controlled trials* – The most extensive data supporting long term efficacy and safety of the 5-ARIs are from two large randomized, double-blind, placebo-controlled trials. The four-year Proscar Long-Term Efficacy and Safety Study (PLESS) [McConnell et al, 1998] showed a significant reduction in symptom scores, Qmax, TPV, risk of AUR, and risk of BPH-related surgery with finasteride, compared to placebo. Data for dutasteride come from pooled analyses of three identical parallel-group trials (ARIA 3001, 3002, 3003) [Roehrborn et al, 2002]. All three trials had a two-year double-blinded phase comparing dutasteride to placebo, followed by a two-year open-label extension phase during which all patients were treated with dutasteride. At the end of the two-year double-blind phase, dutasteride significantly reduced symptom scores, Qmax, TPV, risk of AUR, and risk of BPH-related surgery with finasteride, compared to placebo.

      Reductions in the risk of AUR and BPH-related surgery appeared similar. The calculated risk reduction after two years with finasteride (PLESS) was a 57% reduction in AUR (95% CI 40-69%) and a 58% reduction in BPH-related surgery 58% (95% CI 41-65%), compared with placebo. For dutasteride, the risk reduction after two years (ARIA pooled data) was 57% for AUR (95% CI 38-71%) and 48% for BPH-related surgery (95% CI 26-63%), compared with placebo.

   b) *Systematic reviews and meta-analysis* – Two systematic reviews [Clifford et al, 2000; Edwards et al, 2002] and one meta-analysis [AUA Guideline, 2003] concluded that finasteride offers consistent improvement in terms of symptom

relief, urinary flow rate, and decreased risk of AUR and the need for prostatic surgery, compared to placebo. No systematic reviews or meta-analyses are available for dutasteride.

Head-to-head trials – The only fully published head-to-head trial [Clark et al, 2004] compared effects of finasteride and dutasteride on DHT, testosterone, and leutinizing hormone (LH) levels. This 24-week, Phase II, double-blind, placebo-controlled, dose-ranging trial randomized 399 men with BPH to dutasteride (0.01, 0.05, 0.5, 2.5, or 5.0 mg), 5 mg finasteride, or placebo. The mean percent decrease in DHT with dutasteride was more profound and less variable than with finasteride [dutasteride 0.5 mg (the labeled dose) 94.7 ± 3.3% vs. finasteride 5 mg 70.8 ± 18.3%]. Mean testosterone levels increased but remained in the normal range for all treatment groups. Whether or not differences between finasteride and dutasteride with respect to DHT suppression result in a clinically significant difference in patient outcomes has yet to be determined. Limitations of this trial include its short duration relative to the typical onset of benefits from 5-ARIs and its small sample size, especially given that only one of the dutasteride arms was at the labeled dose (0.5mg).

Unpublished summary data from a second head-to-head trial, the Enlarged Prostate International Comparator Study (EPICS), were furnished by the manufacturer of dutasteride [data on file, GlaxoSmithKline]. EPICS compared dutasteride 0.5 mg and finasteride 5 mg in men with BPH. Following a 4-week placebo run-in period, 1630 men were randomized to dutasteride (n=813) or finasteride (n=817) for twelve months. After one year similar improvements from baseline were seen with dutasteride vs. finasteride, respectively, with respect to changes in symptom scores (-5.8 vs.- 5.5), reductions in TPV (-26.3% vs. -26.7%) and Qmax (2.0 vs. 1.7 mL/sec). No statistically significant differences in outcome measures between treatment groups were reported.

c) *Combination therapy trials* – Three short-term combination trials (finasteride plus an alpha blocker) demonstrated no additional benefit compared to alpha blockers alone. However, the large, long-term Medical Therapy of Prostatic Symptoms (MTOPS) trial demonstrated improvements in LUTS and a greater reduction in overall disease progression (including reduced risk of AUR and need for BPH-related surgery) with combination therapy (finasteride plus doxazosin) versus monotherapy with either agent. The AUA meta-analysis of finasteride trials reported improved AUA-SI scores and Qmax with combination therapy and supported its use in men with LUTS and demonstrable prostate enlargement. There are no published long-term combination trials with dutasteride; therefore, there is insufficient evidence to compare finasteride to dutasteride when used in combination with an alpha blocker.

d) *Prostate cancer* – There is limited evidence concerning the potential use of 5-ARIs for prostate cancer prevention. The only large, long-term trial [Thompson et al, 2003] reported a 24.8% reduction in the prevalence of

prostate cancer in patients receiving finasteride vs. placebo; however, a higher percentage of high-grade prostate cancer tumors was reported with finasteride, compared to placebo. It is not known whether or not dutasteride produces the same effect.

e) *Efficacy conclusion* – There is insufficient evidence to conclude that there are significant differences in efficacy between finasteride and dutasteride. Indirect comparisons from long-term efficacy trials suggest similar decreases in total prostate volume, increases in urinary flow rate, improvement in symptoms, and similar reductions in the risk of AUR and BPH-related surgery. Summary results from an unpublished head-to-head trial (the Enlarged Prostate International Comparator Study – EPICS) showed similar improvements in symptom scores, TPV, and Qmax; no statistically significant differences in outcome measures were reported. There is insufficient evidence to compare the two agents for use in combination with alpha blockers. More data are available with finasteride than with dutasteride, including a long-term trial with finasteride and doxazosin (the Medical Therapy of Prostatic Symptoms trial – MTOPS); there are no published long-term combination trials with dutasteride. The clinical significance of more profound suppression of DHT with dutasteride than with finasteride is unknown. The overall effect of 5-ARIs on prostate cancer prevention is unclear.

4) Safety and Tolerability

a) *Serious adverse events* – There have been no notable reports of serious adverse events with either agent.

b) *Overall adverse events* – The most common adverse effects are related to sexual dysfunction. Similar incidences of sexual adverse events and gynecomastia have been reported with finasteride and dutasteride. In general, clinical trials report rates of decreased libido of 2 to10%, erectile dysfunction 3 to16%, ejaculatory disorders 0 to 8%, and gynecomastia 1 to 2%. The incidence of sexual dysfunction is generally higher during the first six to twelve months of treatment and diminishes with chronic dosing.

c) *Withdrawals due to adverse events during clinical trials* – With the exception of gynecomastia, adverse effects are generally not severe enough to discontinue use of 5-ARIs. There do not appear to be major differences between the two agents with respect to withdrawal rates due to adverse events. Reported withdrawal rates in clinical trials of finasteride and dutasteride were low overall, similar in the first year of therapy, and decreased further for both agents during continued treatment.

d) *Drug interactions* – No major comparative disadvantage was noted for either agent based on its potential for drug-drug interactions. Both are metabolized via the cytochrome P450 (CYP) 3A4 enzyme system and should be used cautiously in patients taking potent CYP 3A4 inhibitors.

e) *Special populations* – There are no major differences between finasteride and dutasteride with regard to use in special populations; both are pregnancy category X, contraindicated in children and women, and carry warnings regarding exposure to 5-ARIs of women who are pregnant or may become pregnant, due to the potential risk of transdermal absorption and fetal exposure (feminization of male fetuses is an expected consequence of the inhibition of the conversion of testosterone to DHT by 5-ARIs). Men taking a 5-ARI should defer blood donation for six months from discontinuation of therapy to avoid possible administration of the drug to a pregnant female transfusion recipient. Neither finasteride nor dutasteride requires dosing adjustments or has special dosing requirements, although caution is advised in hepatic dysfunction.

f) *Other factors* – 5-ARIs as a class are associated with a decrease in prostate specific antigen (PSA) concentrations of about 50% after six months of treatment. Neither drug appears to interfere with detection of prostate cancer when PSA values used for prostate cancer screening are appropriately adjusted (they should be doubled in men who have received 5-ARI therapy for at least six months).

g) *Safety and tolerability conclusion* – There appear to be few differences in the incidence of adverse effects with finasteride or dutasteride, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated; with the most common adverse effects related to sexual dysfunction and diminishing with chronic dosing. Reported withdrawal rates due to adverse effects are low overall in clinical trials of finasteride and dutasteride, similar during the first year of therapy, and decrease further with both agents during continued treatment. The two agents appear similar with regard to potential drug interactions and use in special populations (both are contraindicated in women and children and carry special warnings against exposure of women who are or may become pregnant). Neither agent appears to interfere with the prostate cancer detection.

5) Therapeutic Interchangeability

Finasteride and dutasteride appear similar in terms of efficacy, safety, and tolerability, and are used in the same patient population. Neither drug offers a unique benefit, nor is it likely that a patient who did not have an adequate response with one 5-ARI would have a better response with the other. Either finasteride or dutasteride could be expected to meet the needs of the majority of DoD BPH patients.

6) 5-ARIs – Overall Clinical Effectiveness Conclusion

The P&T Committee concluded that:

a) There is insufficient evidence to conclude that there are significant differences in efficacy between finasteride and dutasteride. Indirect comparisons from long-term efficacy trials suggest similar decreases in total prostate volume,

increases in urinary flow rate, improvement in symptoms, and similar reductions in the risk of AUR and BPH-related surgery.

b) The only fully published head-to-head trial suggests that dutasteride therapy reduces serum DHT levels by 95%, compared to 71% with finasteride. The clinical significance of this finding has yet to be determined. This 24-week trial contributes no useful comparative data concerning long-term efficacy. A large but as yet unpublished head-to-head trial (EPICS) reported no differences in efficacy outcomes with finasteride vs. dutasteride after one year of treatment.

c) There is insufficient evidence to compare the two agents when used in combination with alpha blockers. More data are available with finasteride than with dutasteride, including a long-term trial with finasteride and doxazosin (MTOPS); there are no published long-term combination trials with dutasteride.

d) The overall effect of 5-ARIs on prostate cancer prevention is unclear.

e) There appear to be few differences in the incidence of adverse effects with finasteride or dutasteride, based on placebo-controlled trials and limited comparative data. Both agents are well tolerated. The most common adverse effects are related to sexual dysfunction; they diminish with chronic dosing.

f) Reported withdrawal rates due to adverse effects are low in clinical trials of finasteride and dutasteride, similar during the first year of therapy, and decrease further with both agents during continued treatment.

g) There are no major differences between finasteride and dutasteride with regard to use in special populations or drug interactions.

h) Neither agent appears to interfere with prostate cancer detection.

i) Finasteride and dutasteride appear to have a high degree of therapeutic interchangeability; either could be expected to meet the needs of the majority of DoD BPH patients.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. 5-ARIs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the 5-ARIs in relation to efficacy, safety, tolerability, 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).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the 5-ARI medications differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of BPH. As a result, several CMAs were performed to compare the relative cost effectiveness of the 5-ARIs by condition set. The CMAs compared the weighted average cost per day of treatment

for each drug product across all three points of service. In addition, a CEA was conducted evaluating the cost per BPH surgery avoided for each of the 5-ARIs.

Results from the CMAs showed that finasteride was the most cost effective agent with a lower cost per day of treatment than dutasteride across all conditions sets evaluated. In addition, finasteride was the preferred choice in the CEA with a lower expected cost per BPH surgery averted than dutasteride.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the Committee in determining which group of 5-ARIs best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The P&T Committee accepted the conclusions from the cost effectiveness analyses stated above. In addition, the Committee concluded that the UF scenario that placed finasteride as the sole 5-ARI on the UF was the most cost effective scenario.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, and 2 absent) to accept the 5-ARI relative CEA as presented by the PEC.

C. 5-ARI – UF Recommendations

COMMITTEE ACTION: In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the 5-ARIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that finasteride be maintained as formulary on the UF and that dutasteride be classified as non-formulary under the UF.

D. 5-ARI – MN Criteria

Based on the clinical evaluation for dutasteride, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for dutasteride:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. 5-ARI – UF Implementation Period

Because of the relatively few number of beneficiaries affected (approximately 20,917 patients (41%) of approximately 51,017 beneficiaries at all three points of service), the P&T Committee recommended an effective date of 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 dutasteride 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) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary 5-ARI agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. 5-ARIs – BCF Review and Recommendations

Currently there are no 5-ARI agents on the BCF. The P&T Committee had previously determined at the November 2006 meeting that at least one 5-ARI would be placed on the BCF. Finasteride is widely used at MTFs, has clinical data supporting efficacy for decrease in total prostate volume, increase in urinary flow rate, and improvement in symptoms, reductions in risk of acute urinary retention and BPH-related surgery. Finasteride is clinically similar to dutasteride with respect to safety and tolerability, and is the most cost effective 5-ARI. The P&T Committee agreed that finasteride should be placed on the BCF.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend adding finasteride as the BCF selection in this class.

8. DRUG CLASS REVIEW – PROTON PUMP INHIBITORS (PPIs)

The P&T Committee evaluated the relative clinical effectiveness of the PPIs. The PPI drug class includes the following agents: esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec and generics), omeprazole/ sodium bicarbonate (Zegerid), omeprazole magnesium (Prilosec OTC), pantoprazole (Protonix), and rabeprazole (Aciphex). Omeprazole magnesium (Prilosec OTC) was added to the UF for purposes of the OTC Demonstration Project as a result of the February 2007 P&T Committee meeting. The PPI class was previously reviewed by the P&T Committee in February 2005.

As of March 07, about 350,000 MHS prescriptions for PPIs are filled per month. This drug class is now #1 in terms of MHS expenditures: more than $485 million over the 12 months from April 06 to March 07, compared to about $350 million in FY 2005. MTF pharmacies dispense 47% of all PPI tablets, compared to 36% dispensed by retail network pharmacies and 17% dispensed by the TMOP. Across the MHS, rabeprazole is the most commonly prescribed PPI, due mainly to its favorable formulary status and high utilization at MTFs. The next four most-prescribed PPIs – lansoprazole, esomeprazole, pantoprazole, and omeprazole – have similar utilization patterns. Of the PPIs, only prescription omeprazole is generically available.

Pharmacologically, PPIs suppress the final step in gastric acid production. They have become the standard of care for treatment of acid-related disorders, particularly treatment of erosive or ulcerative disease.

Standard practice in the initial management of dyspepsia or gastroesophageal reflux disease (GERD) indicates that if certain "alarm features" (i.e., signs of potential underlying cancer such as melena, persistent vomiting, dysphagia, hematemesis, anemia, or involuntary weight loss) are not present, patients should be treated with an empiric trial of 4 to 8 weeks of PPI therapy. In populations where the prevalence of *H. pylori* is greater than 10%, *H. pylori* testing should occur prior to further evaluation, with subsequent treatment if positive. Patients with inadequate symptom relief after 8 weeks should receive endoscopy and further management based on endoscopy results. GERD is often a relapsing-remitting disease which requires long-term medical maintenance therapy; in many cases PPIs will be continued for an extended period of time.

A. PPIs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the PPIs currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes 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(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) FDA-Approved Indications and Other Uses

All of the PPIs are FDA-approved for the treatment of erosive esophagitis (EE) and maintenance of healed EE. All PPIs except pantoprazole have at least one indication for ulcer treatment (e.g., duodenal or gastric ulcers and/or ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs) or caused by *H. pylori*). All PPIs except pantoprazole and omeprazole/sodium bicarbonate have an FDA indication as part of a multi-drug regimen for the eradication of *H. pylori.* All PPIs except omeprazole/sodium bicarbonate have an indication for the treatment of hypersecretory conditions such as Zollinger-Ellison.

In practice, most of the agents have published data showing effectiveness for use in any of the acid related disorders, and are commonly prescribed to treat all acid related conditions, regardless of FDA indication. Omeprazole, lansoprazole, and esomeprazole are indicated for use in children.

PPIs are also being studied and used outside the area of acid-related disorders (e.g., for surgical procedure prophylaxis, posterior laryngitis, and chronic cough). More data are needed to support broader use of PPIs for these conditions.

2) Efficacy Measures

Comparative efficacy was evaluated on a disease state basis based on FDA indicated uses of the PPIs. The emphasis was on objective clinical endpoints (ulcer healing, esophagitis healing, maintenance of healing / prevention of disease, and symptomatic resolution) rather than surrogate endpoints (such as pH

measurements, supplemental antacid use and serum drug levels), given the uncertain relationship of surrogate endpoints to clinical outcomes.

3) Clinical Evidence

The review focused primarily on randomized, double-blinded trials where one PPI was compared to another (head-to-head or direct comparison trials), or to another active comparator such as histamine-2 receptor antagonists (e.g., ranitidine, cimetidine, etc). Three good quality systematic reviews summarized the available data, supplemented by more recently published trials. The systematic reviews included PPI reviews from the Oregon Health and Science University's Drug Effectiveness Review Project (DERP; July 2006) and the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS; Aug 2005), and the Agency for Healthcare Research and Quality (AHRQ) 2005 Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease guideline.

It should be noted that no published outcomes evidence is available for either omeprazole magnesium (Prilosec OTC) or the immediate release/sodium bicarbonate (Zegerid) formulations of omeprazole. FDA approval of these formulations relied on the original omeprazole data.

4) Efficacy

a) EE healing

Evidence from head-to-head trials suggests the majority of patients obtain complete healing of erosive disease within eight weeks of treatment on any PPI, with most patients achieving symptom relief within four weeks of initiating treatment.

Of the 25 head-to-head trials published in the clinical literature, only six showed a statistically significant difference in healing rates among the PPIs. One of these predictably found omeprazole 20 mg to be more efficacious than lansoprazole 15 mg, but similar to lansoprazole 30 mg, which is the dose typically used for EE healing.

Two trials comparing esomeprazole and lansoprazole reported differences favoring esomeprazole, with one trial reporting statistically significant differences in healing and symptom resolution at four weeks that disappeared by 8 weeks and the other reporting a small but statistically significant difference in healing and symptom resolution at four weeks and healing at eight weeks. Another head-to-head trial of esomeprazole and lansoprazole showed no significant difference in healing or symptom resolution at the same time points.

Two trials comparing esomeprazole and omeprazole reported differences favoring esomeprazole; both trials compared esomeprazole 40 mg to omeprazole 20 mg, which are not equivalent doses. Two adequately powered later trials, one comparing esomeprazole 40 mg to omeprazole 20 mg and one comparing esomeprazole 20 mg to omeprazole 20 mg, failed to show

statistically significant differences in healing rates at four and eight weeks or symptom resolution at 4 weeks.

One trial comparing esomeprazole to pantoprazole reported differences favoring esomeprazole; this trial appears to have some internal validity issues. Another trial comparing esomeprazole 40 mg and pantoprazole 40 mg failed to find any statistically significant differences in healing or symptom relief.

Conclusion – Although some trials appear to demonstrate superior efficacy for healing of EE with esomeprazole, actual differences are small and inconsistent among trials. Evidence for clinical efficacy is similar enough to consider all agents equally effective in healing of EE.

b) *Maintenance of healing in erosive esophagitis*

The evidence includes six clinical trials comparing various PPIs, along with a placebo-controlled rabeprazole trial and a comparison of pantoprazole and ranitidine. There are substantial methodological differences among trials (e.g., methods of evaluating healing, duration, study populations, and comparators used), as well as internal validity issues and small trial sizes that make it impossible to draw conclusions regarding the superiority of one agent over another.

Conclusion – There is sufficient evidence to support the use of PPIs for maintenance of initial healing and symptomatic relief of EE for as long as five years. However, the evidence is insufficient to conclude that one PPI is superior to others for maintenance of EE healing.

c) *Ulcer healing and maintenance of healing*

Fifteen head-to-head trials compared efficacy of various PPIs to omeprazole for initial healing and/or maintenance of healing in duodenal, gastric, and NSAID-induced ulcers. No statistically significant differences were found for any comparators versus omeprazole for primary endpoints of ulcer healing and maintenance of healing or for measures of symptom resolution and improvement.

Conclusion – There appear to be no comparative differences among PPIs for healing, maintenance of healing, or symptom improvement in peptic ulcer disease (PUD) and/or NSAID-induced ulcers.

d) *Endoscopy negative reflux disease (ENRD)*

ENRD is an incompletely understood variant of GERD. It is estimated that as many as half of patients diagnosed with GERD may fall into this category; however, there are few clinical trials specifically focusing on ENRD. Patients with ENRD are generally considered more difficult to treat than patients with positive findings on endoscopy.

Six trials show efficacy of various healing or maintenance doses of PPIs for initial resolution of heartburn (the primary outcome in all of the trials). Three other trials compare on-demand use of a PPI to placebo or an active

comparator (e.g., a histamine-2 blocker) as continuation therapy after initial resolution of symptoms.

Conclusion – Based on available clinical trials, PPIs appear to be similarly efficacious as short-term treatment for ENRD; there are insufficient data to draw conclusions regarding efficacy for long-term or on-demand treatment.

e) H. pylori eradication with multi-drug regimens

There are at least 39 head-to-head trials comparing all of the PPIs in various multi-drug combination regimens with antibiotics. Substantial differences among studies in doses of PPIs and antibiotics, duration of treatment, methods of assessing *H. pylori* eradication, and patient populations make comparisons across studies difficult. A good quality meta-analysis (2003) using omeprazole as the reference for comparison found no difference in eradication rates among PPIs; earlier systematic reviews (1998, 1999) came to similar conclusions.

Conclusion – H. pylori eradication rates appear similar among PPIs when differing doses of antibiotics and treatment duration are taken into account.

f) Efficacy in Pediatric Patients

Omeprazole, lansoprazole and esomeprazole have indications for treatment of symptomatic GERD in pediatric patients, while omeprazole and lansoprazole have indications for treatment and maintenance of healing of EE. Comparisons of PPIs across trials is difficult; most trials in pediatric patients were small, some were open-label or non-controlled, and surrogate endpoints used to assess symptom resolution varied widely. There was no evidence to support greater efficacy for any one PPI compared to others.

Conclusion – There are insufficient data to suggest superiority of one PPI over others for treatment of pediatric patients. Pantoprazole and rabeprazole do not have an FDA-approved pediatric indication.

5) Safety/Tolerability

a) *Serious adverse events* – A long-standing potential safety concern with PPIs is prolonged hypergastrinemia, which can lead to hyperplasia of both normal and neoplastic enterochromaffin-like cells in the GI tract, potentially leading to cancer. However, the precise role of achlorhydria-induced increases in gastrin expression in gastrointestinal carcinogenesis is unknown. Risk of atrophic gastritis and gastric bacterial overgrowth is increased with long-term PPI use, although the clinical significance is unclear.

PPIs have been associated with *C. difficile* infection, especially in patients taking concomitant antibiotics; caution is particularly indicated with *H. pylori* eradication regimens.

Acute interstitial nephritis has been rarely reported with PPIs. In addition, epidemiological data have suggested an association between PPIs and increased risk of fracture; potential study limitations are numerous, and no definitive evidence is available.

b) *Overall adverse events and withdrawal due to adverse events* – In general, adverse effects are similar to placebo, with an overall incidence rate of less than 5%. Most commonly reported are headache, diarrhea, abdominal pain, and nausea. Head-to-head trials have shown no differences in short-term tolerability; withdrawal rates due to adverse events are very low. There are no clear differences among PPIs with respect to adverse effects or withdrawal rates due to adverse events during clinical trials.

c) Drug interactions – PPIs have the potential for causing drug interactions based on several mechanisms, including CYP450 inhibition, effects on the P-glycoprotein membrane transport system in columnar cells of the small intestine, and changes in gastric pH, which can affect absorption of other medications. Omeprazole and esomeprazole may have the most potential for CYP450 drug interactions. Increased effects of warfarin have been reported most frequently with omeprazole, lansoprazole, or pantoprazole, although this is a potential interaction for all PPIs. Most drug interactions are minor in nature.

d) *Special populations* – Dosage adjustments for all PPIs, except pantoprazole, should be considered in patients with severe hepatic disease. None of the PPIs require adjustment in patients with chronic renal insufficiency, elderly patients, or based on gender or race. Omeprazole is classified as Pregnancy Category C; other PPIs are Pregnancy Category B. PPIs are excreted in breast milk and are not recommended for use during breastfeeding.

Zegerid contains 300-460 mg of sodium per tablet due to its sodium bicarbonate component; caution is advised for patients who should avoid consumption of large amounts of sodium.

e) *Other factors* – Lansoprazole, esomeprazole and omeprazole/sodium bicarbonate have dosage forms that can be used in pediatric patients or patients with swallowing difficulties. All three are available as packets for oral suspension; lansoprazole is also available as an orally disintegrating tablet. Omeprazole capsules contain enteric-coated granules commonly used to prepare a bicarbonate-based extemporaneous suspension.

Pantoprazole was the only PPI available in intravenous (IV) form for several years; however, both esomeprazole and lansoprazole have recently developed IV formulations. (It should be noted that due to their route of administration and lack of outpatient use, the IV formulations are not eligible for inclusion on the UF and not included in this review.)

f) *Safety and tolerability conclusion* – The class as a whole is well-tolerated, with an adverse effect profile similar to placebo; most drug interactions are minor in nature. There are no clear differences among PPIs with respect to adverse effects or withdrawal rates due to adverse events during clinical trials. In general, agents appear very similar with respect to safety and tolerability. Minor differences include the lack of a requirement to adjust the dose of pantoprazole in patients with severe hepatic disease (unlike other PPIs); a less favorable pregnancy category rating for omeprazole than the more recently

introduced PPIs (C vs. B); and the availability of liquid dosage forms for esomeprazole, lansoprazole, and omeprazole/sodium bicarbonate.

6) PPIs – Overall Clinical Effectiveness Conclusion:

The P&T Committee concluded that:

a) Based on head-to-head and other controlled trials, PPIs have similar efficacy in a wide range of acid related disorders and are highly therapeutically interchangeable.

b) Although some trials appear to demonstrate superior efficacy for healing of EE with esomeprazole, actual differences are small and inconsistent among trials. Evidence for clinical efficacy is similar enough to consider all agents equally effective in healing of EE.

c) There is sufficient evidence to support the use of PPIs for maintenance of initial healing and symptomatic relief of EE for as long as five years. However, the evidence is insufficient to conclude that one PPI is superior to the others for maintenance of EE healing.

d) There appear to be no comparative differences among PPIs for healing, maintenance of healing, or symptom improvement in PUD and/or NSAID-induced ulcers.

e) Based on available clinical trials, PPIs appear to be similarly efficacious in the short-term treatment of ENRD; there are insufficient data to draw conclusions regarding efficacy for long-term or on-demand treatment.

f) *H. pylori* eradication rates appear similar among PPIs when differing doses of antibiotics and treatment duration are taken into account.

g) There are insufficient data to suggest superiority of one PPI over the others for treatment of pediatric patients; omeprazole, lansoprazole, and esomeprazole have FDA indications for use in pediatric patients.

h) The class as a whole is well-tolerated, with an adverse effect profile similar to placebo; most drug interactions are minor in nature. In general, PPIs appear very similar with respect to safety and tolerability.

i) Minor differences include the lack of a requirement to adjust the dose of pantoprazole (Protonix) in patients with severe hepatic disease (unlike other PPIs); a less favorable pregnancy category rating for omeprazole than the more recently introduced PPIs (C vs. B); and the availability of liquid dosage forms for esomeprazole, lansoprazole, and omeprazole/sodium bicarbonate.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. PPIs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the PPIs in relation to efficacy, safety, tolerability, 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).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the PPI medications differed in regard to efficacy, safety, tolerability, or clinical outcomes data in the treatment of EE healing and maintenance of healing, ulcer healing and maintenance of healing, *H. pylori* eradication, and ENRD. As a result, several CMAs were performed to compare the relative cost effectiveness of the PPIs by condition set (the seven condition sets are listed below). The CMAs compared the weighted average cost per day of treatment for each potential UF scenario across all three points of service.

1) C7301: Two or fewer PPIs are selected for the UF and one PPI is selected for the BCF. (≤2 UF, 1 BCF)
2) C7302: Three or four PPIs are selected for the UF and one PPI is selected for the BCF. (3-4 UF, 1 BCF)
3) C7303: Three or four PPIs are selected for the UF and two PPIs are selected for the BCF. (3-4 UF, 2 BCF)
4) C7304: Five or more PPIs are selected for the UF and one PPI is selected for the BCF. (≥5 UF, 1 BCF)
5) C7305: Five or more PPIs are selected for the UF and two PPIs are selected for the BCF. (≥5 UF, 2 BCF)
6) C7306: Two PPIs (generic omeprazole and one other PPI) are selected for the UF and generic omeprazole is the only PPI selected for the BCF. In addition, a PA process requires all new PPI users to complete an adequate trial of generic omeprazole before any other PPI is provided to a new user through an MTF pharmacy, the TMOP, or a TRICARE retail network pharmacy.
7) C7307: Two PPIs (generic omeprazole and one other PPI) are selected for the UF. Generic omeprazole will be selected to the BCF and the other PPI may be selected for the BCF. In addition, a PA process requires all new PPI users to complete an adequate trial of generic omeprazole or the second UF PPI before any third tier PPI is provided to a new user through an MTF pharmacy, the TMOP, or a TRICARE retail network pharmacy.

Results from the PPI CMAs showed three important findings: 1) as expected, the more restrictive the UF scenario, the lower the cost per day of treatment; 2) for the three condition sets that evaluated UF scenarios with two or fewer UF agents (C7301, C7306, and C7307), omeprazole and esomeprazole were the most cost effective agents; and 3) for the two condition sets that evaluated UF scenarios with three to four UF agents (C7302 and C7303), omeprazole, esomeprazole, pantoprazole, and rabeprazole were the most cost effective agents.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the Committee in

determining which group of PPIs best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The DoD P&T Committee accepted the conclusions from the cost effectiveness analyses stated above. In addition, the Committee concluded that the UF scenario (condition set C7307) that maintained omeprazole and esomeprazole as the only two agents on the UF in conjunction with a step therapy PA was the most cost effective scenario.

COMMITTEE ACTION: The DoD P&T Committee voted (14 for, 0 opposed, 0 abstention, and 3 absent) to accept the PPI relative CEA as presented by the PEC.

C. PPIs – UF Recommendations

COMMITTEE ACTION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that: 1) omeprazole and esomeprazole be maintained as formulary on the UF with a PA requiring a trial of either agent for new patients; 2) that rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate be classified as non-formulary under the UF with a PA requiring a trial of either omeprazole or esomeprazole for new patients; and 3) that the normal brand formulary cost-share of $9.00 for esomeprazole be lowered to the generic formulary cost-share of $3.00.

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate." Lowering the cost-share for brand name esomeprazole will provide a greater incentive for beneficiaries to use esomeprazole rather than the less cost effective branded products – rabeprazole, lansoprazole, pantoprazole, or omeprazole/sodium bicarbonate – in the purchased care arena.

D. PPIs – PA Criteria

The P&T Committee agreed that the following PA criteria should apply to PPIs other than omeprazole or esomeprazole. Coverage would be approved if a patient met any of the following criteria:

3) Automated PA criteria:
    a) The patient has received a prescription for any PPI agent at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.
4) PA criteria if automated criteria are not met:
    a) The patient has tried omeprazole or esomeprazole and had an inadequate response or was unable to tolerate treatment due to adverse effects.
    b) Treatment with omeprazole or esomeprazole is contraindicated.

The P&T Committee noted that in order for a patient to receive a non-formulary PPI agent at the formulary cost-share, both the PA and MN criteria must be met. If the PA criteria are met without an approved MN determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved PA for rabeprazole, lansoprazole, pantoprazole, or omeprazole/sodium bicarbonate would NOT automatically receive it at the formulary cost-share.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend the PA criteria outlined above.

E. PPIs – MN Criteria

Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.
3) Use of formulary alternatives has resulted in therapeutic failure.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

F. PPIs – UF Implementation Period

Even though a large number of beneficiaries are affected (approximately 453,525 patients [64%] of approximately 702,841 beneficiaries at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The P&T Committee believed the considerable cost avoidance associated with this recommendation warranted a more aggressive implementation period. Furthermore, the P&T Committee was anxious to extend the $3.00 cost-share for esomeprazole to beneficiaries as soon as possible. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have rabeprazole, lansoprazole, pantoprazole, or omeprazole/sodium bicarbonate 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) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary PPI agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

G. PPIs – BCF Review and Recommendations

Based on the relative clinical effectiveness and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend designating generic omeprazole (Prilosec 40 mg specifically omitted) and esomeprazole as the BCF selections in this class.

9. DRUG CLASS REVIEW – ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

The P&T Committee evaluated the relative clinical effectiveness of the seven angiotensin receptor blockers (ARBs) marketed in the U.S. The ARB drug class is comprised of losartan (Cozaar), irbesartan (Avapro), valsartan (Diovan), candesartan (Atacand), telmisartan (Micardis), eprosartan (Teveten), olmesartan (Benicar) and their respective combinations with hydrochlorothiazide (HCTZ).

Utilization of the ARBs has been steadily increasing in the MHS. The ARB drug class accounted for $137 million in MHS expenditures in FY 2006, and is ranked #10 in terms of total expenditures during that time period. Approximately 140,000 30-day equivalent ARB prescriptions are dispensed monthly in both retail network pharmacies and MTFs; approximately 80,000 30-day equivalent ARB prescriptions are dispensed monthly in the TMOP. The most frequently dispensed ARBs in the MHS are valsartan at 50,000 prescriptions per month and valsartan at 40,000 prescriptions per month. However, the angiotensin converting enzyme (ACE) inhibitor lisinopril is still by far the most frequently prescribed ACE inhibitor or ARB in the MHS, with over 150,000 prescriptions dispensed monthly.

A. ARB Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the ARBs marketed in the U.S. by considering information regarding their safety, effectiveness, and clinical outcomes. 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 ARB drug class was previously evaluated for UF status in February 2005. The P&T Committee focused on efficacy differences with respect to labeled indications, particularly in those areas where a benefit in clinical outcomes (e.g., death, hospitalization for heart failure, decreased need for dialysis or renal transplantation) was demonstrated. The primary areas evaluated were efficacy for hypertension, chronic heart failure (HF), and type 2 diabetic nephropathy.

Evidence of the ARBs for use in indications other than hypertension is difficult to interpret, due to the lack of head to head trials between the ARBs that assess clinical outcomes. There are no head-to-head trials assessing efficacy of the ARBs compared to ACE inhibitors for reducing cardiovascular outcomes in HF or type 2 diabetic nephropathy.

1) Efficacy

a) Efficacy Measures

The P&T Committee considered evidence of benefit in improving clinical outcomes of greater importance than effects on physiologic endpoints when evaluating relative clinical effectiveness differences among ARBs. Clinical outcomes include all-cause mortality, cardiovascular mortality, hospitalization for HF, stroke, development of end stage renal disease (ESRD), need for dialysis, and need for renal transplant. Examples of physiologic endpoints include reduction in blood pressure (BP), changes in pulmonary capillary wedge pressure, changes in urinary protein excretion rate, reduced rate of decline in glomerular filtration rate (GFR), changes in urinary albumin to creatinine ratio, and changes in urinary albumin excretion rate.

b) Hypertension

All seven ARBs are approved by the FDA for treating hypertension. One meta-analysis evaluating the ARBs (with the exception of olmesartan) examined data from over 51 clinical trials enrolling over 12,000 patients with hypertension. The meta-analysis reported that treatment with any ARB reduced systolic blood pressure by 7.5-10 mm Hg and diastolic blood pressure (DBP) by 4.5 to 6.5 mm Hg, compared to placebo (placebo-corrected values). Pooled clinical trial data from seven studies with olmesartan enrolling over 2,600 patients show similar BP reductions to the other six ARBs.

All of the ARBs combinations with HCTZ are approved solely for treatment of hypertension. Joint National Commission (JNC) guidelines for treating hypertension state that many patients will require more than one drug to reach blood pressure goals. Addition of HCTZ to an ARB increases efficacy. Treatment with an ARB as monotherapy results in a 53-63% response rate, based on a goal DBP < 90 mm Hg. The response rate increases to 56-70% with the addition of HCTZ to the ARB.

c) Hypertension and Clinical Outcomes

The ARBs have been evaluated in four large clinical trials to assess efficacy for reducing the risk of cardiovascular events in patients with hypertension. Based on the results of the LIFE trial, losartan is labeled to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy (LVH), however the benefit does not apply to Africa Americans. The benefits of losartan were likely due to greater reductions in BP compared to that achieved with the comparator drug, atenolol (Tenormin, generics). JNC guidelines mention that several antihypertensive drugs classes, including ACE inhibitors and diuretics, are associated with regression of LVH. Reducing BP is well-proven as an effective mechanism to reduce stroke risk, regardless of the antihypertensive agent administered.

Candesartan was found to reduce non-fatal stroke in the SCOPE trial in elderly patients when compared to placebo. When valsartan was compared to amlodipine (Norvasc) in the VALUE trial, there were no differences noted in

cardiovascular mortality or all-cause mortality between the two drugs, however, there were fewer MIs, fatal strokes, and nonfatal strokes with amlodipine. The beneficial results with amlodipine were attributed to a greater percentage of patients achieving target BP goals vs. valsartan (64% versus 58%). In the Jikei Heart Study, valsartan was found to reduce cardiovascular events and strokes, compared to placebo, in a Japanese population.

Candesartan and valsartan are not currently labeled to reduce cardiovascular outcomes in hypertensive patients. For all four trials (LIFE, SCOPE, VALUE, Jikei Heart Study), differences in blood pressure reduction largely account for reported differences in cardiovascular outcomes of ARBs versus other antihypertensives.

e) Chronic Heart Failure

There are no head to head trials comparing the ARBs for use in chronic heart HF. Two large, randomized, placebo-controlled trials, one each with valsartan and candesartan, demonstrated a reduction in the risk of hospitalization due to chronic HF, a clinically relevant outcome.

Based on the results of the Val-HeFT trial, the FDA approved valsartan for use in patients with heart failure. In the Val-HeFT trial, valsartan treatment resulted in a significant 4.4% absolute risk reduction in HF hospitalizations, vs. placebo. A significant reduction in the primary composite endpoint (all-cause mortality/HF hospitalization) was also seen. The previous limitation in the package insert that valsartan should be restricted for use only in HF patients intolerant of ACE inhibitors has now been removed.

The CHARM trials with candesartan support its use in chronic HF, and it is FDA-approved for this indication. A 4.3% absolute risk reduction in HF hospitalization occurred with candesartan treatment, compared to placebo. A significant reduction in the composite primary endpoint (cardiovascular mortality/HF hospitalization) was also shown.

For the other ARBs, losartan was not superior to captopril in reducing death and HF hospitalization in the ELITE II trial. Two pilot studies are available with irbesartan and telmisartan that show reduction in pulmonary capillary wedge pressure. No trials assessing use of eprosartan or olmesartan in HF have been published.

The P&T Committee agreed that there was no evidence that either valsartan or candesartan were preferable relative to the other for the treatment of chronic HF. Since none of the other ARBs have an indication for HF or evidence showing a reduction in clinically relevant outcomes related to chronic HF, the P&T Committee agreed that valsartan and candesartan were preferable to the other five ARBs for the treatment of HF.

f) Type 2 Diabetic Nephropathy

Patients with type 2 diabetes frequently progress from microalbuminuria to overt proteinuria, with decreasing GFR and eventual development of ESRD.

However, the most common cause of death in diabetic patients is due to cardiovascular complications.

i) Microalbuminuria

Head-to-head trials – Two abstracts noted no difference between telmisartan vs. losartan, and telmisartan vs. valsartan in reducing the rate of decline of renal function, as measured by change in urinary protein excretion ratio. However, neither study has been published in a peer-reviewed journal.

Placebo- or active-controlled trials – Benefits on physiologic outcomes in patients with microalbuminuria have been shown with candesartan, irbesartan, telmisartan and valsartan in small studies with placebo or active comparators (usually an ACE inhibitor or calcium channel blocker). There is no published data evaluating efficacy of eprosartan or olmesartan in either microalbuminuria or nephropathy.

ii) Nephropathy

Two ARBs have shown efficacy in clinical outcomes for patients with overt nephropathy and type 2 diabetes mellitus. Both irbesartan and losartan are labeled for use in patients with type 2 diabetic nephropathy, based on the results of the IDNT and RENAAL trials, respectively.

Treatment with losartan resulted in a significant 16% relative reduction (3.6% absolute risk reduction) in the primary composite endpoint (risk of doubling of serum creatinine, death, and ESRD, defined as the need for dialysis or renal transplant), compared to placebo. In the IDNT trial, a significant 20% relative reduction (6.4% absolute risk reduction) was seen with irbesartan compared to placebo when the same composite endpoint was evaluated.

The P&T Committee agreed that there was no evidence that either irbesartan or losartan were preferable relative to the other in patients with type 2 diabetic nephropathy. Since none of the other ARBs has an indication for HF or evidence showing a reduction in clinically relevant outcomes related to type 2 diabetic nephropathy, the P&T Committee agreed that irbesartan and losartan were preferable to the other five ARBs for reducing the risk of doubling of serum creatinine, death, and ESRD in type 2 diabetic nephropathy.

g) Post MI

Valsartan has an additional indication for use in clinically stable patients with left ventricular systolic dysfunction (LVSD) following an MI, to reduce the risk of MI. FDA approval was based on the VALIANT trial, where valsartan was compared with the ACE inhibitor captopril (Capoten, generics). There was no significant difference between valsartan and captopril in all-cause mortality or cardiovascular mortality post-MI.

Overall, ACE inhibitors have a larger body of evidence supporting a mortality benefit in post-MI patients with LVSD than does valsartan. The aldosterone antagonists spironolactone and eplerenone (Inspra) are also labeled for use or have shown efficacy in the post-MI setting.

2) Safety / Tolerability

The ACE inhibitors and ARBs have similar safety concerns regarding hyperkalemia, elevations of serum creatinine, angioedema, and pregnancy category labeling. The ARBs have an incidence of cough similar to placebo.

These medications are generally well-tolerated, with adverse event rates for all the ARBs similar to placebo in controlled trials. The likelihood of potentially serious adverse events, including hyperkalemia, elevations of serum creatinine, and angioedema, does not appear to differ among agents. Drug interaction profiles are similar. All ARBs are rated pregnancy category C during the first trimester, and pregnancy category D during the second and third trimesters, based on the occurrence of fetal abnormalities with ACE inhibitors. The P&T Committee agreed that there is no evidence that any one ARB is preferable to the others with respect to safety or tolerability.

3) Other Factors

The P&T Committee agreed that although there were no clinically significant differences in minor factors between the ARBs, including twice daily dosing and availability in bulk bottles.

4) DoD Utilization

A data analysis of ARB prescriptions using the Pharmacy Data Transaction Service (PDTS) was conducted to determine DOD ARB utilization by FDA approved indication. FDA-approved indication was based on presence of other background medications in the pharmacy profile, (e.g., evidence of digoxin, a loop diuretic or aldosterone antagonist for HF; and use of insulin, oral diabetic medication or blood glucose test strips for diabetic nephropathy). A two-day cross section of 11,317 patients receiving an ARB or ARB/HCTZ combination on 30-31 Mar 07 found 59% of MHS patients were using the ARB for hypertension, 28% for diabetes, 21% for HF, and 8% for both HF and diabetes.

5) Therapeutic Interchangeability

For hypertension, there is a high degree of therapeutic interchangeability for all seven ARBs. Candesartan and valsartan have a high degree of therapeutic interchangeability for chronic HF. For type 2 diabetic nephropathy, irbesartan and losartan have a high degree of therapeutic interchangeability.

6) Clinical Coverage

To meet the needs of the majority of patients in DoD, ideally the UF would include availability of one ARB with evidence for treating HF, and one ARB with evidence for treating type 2 diabetic nephropathy. A third ARB is not necessarily required, as all the ARBs are effective for hypertension, regardless of whether they have additional labeled indications.

7) ARB Overall Clinical Effectiveness Conclusion

The DoD P&T Committee concluded that:

a) There is no evidence that any one ARB is more efficacious than the others for lowering blood pressure.

b) Although losartan is labeled to reduce the risk of stroke in patients with LVH, JNC guidelines support use of other antihypertensive drugs (e.g., ACE inhibitors, diuretics) in this setting. Differences in blood pressure reduction largely account for differences in cardiovascular outcomes seen in trials comparing ARBs to other antihypertensives.

c) There is no evidence to support clinically significant differences in efficacy between candesartan and valsartan in reducing HF hospitalizations in patients with chronic HF.

d) There is no evidence to support clinically significant differences in efficacy between irbesartan and losartan in improving clinical outcomes (e.g., reducing the risk of doubling of serum creatinine, death, or development of ESRD) in patients with type 2 diabetic nephropathy.

e) Valsartan is the only ARB labeled to reduce death and development of heart failure in post-MI patients with LVSD. However, ACE inhibitors have a larger body of evidence supporting a mortality benefit in post-MI patients with LVSD than valsartan. The aldosterone antagonists spironolactone (Aldactone, generics) and eplerenone are also labeled for use or have shown efficacy in the post-MI setting.

f) There is no evidence that the ARBs differ significantly with regard to safety and tolerability profiles.

g) Based on clinical issues alone, there are no compelling reasons to classify any of the ARBs as nonformulary under the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 against, 0 abstained, 2 absent) to accept the ARB clinical effectiveness conclusion stated above.

B. ARBs – Relative Cost Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the ARBs in relation to efficacy, safety, tolerability, 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).

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the ARB medications differed in regards to efficacy, safety, or tolerability in the treatment of hypertension. However, several products did have additional clinical outcomes data and FDA approved indications for the treatment of chronic HF (candesartan and valsartan) and type 2 diabetic nephropathy (losartan and irbesartan). The clinical review determined that a UF scenario with an agent from these two additional subgroups would be clinically advantageous. As a result, several CMAs were performed to determine the relative cost effectiveness of the agents by

condition set (3 or fewer agents on the UF, 4 – 5 agents on the UF, and 6 or more agents on the UF) and by indication (hypertension, chronic HF, and type 2 diabetic nephropathy). The CMAs compared the weighted average cost per day of treatment for each drug product across all three points of service.

Results from the ARB CMA showed several important findings: (1) a UF scenario with three or fewer agents on the UF was the most cost effective condition set; (2) telmisartan was the most cost effective agent for the management of hypertension; (3) among agents for the management of chronic HF, candesartan was more cost effective than valsartan when three or fewer agents were included on the UF; and (4) losartan and irbesartan had similar cost effectiveness profiles for the treatment of type 2 diabetic nephropathy.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the Committee in determining which group of ARBs best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS.

Cost Effectiveness Conclusion – The Committee accepted the conclusions stated above and determined from the BIA that the UF scenario that included candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ was the most cost effective UF scenario.

COMMITTEE ACTION: The DoD P&T Committee voted (15 for, 0 opposed, 0 abstention, and 2 absent) to accept the ARB relative CEA as presented by the PEC.

C. ARBs – UF Recommendations

COMMITTEE ACTION: In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ARBs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ be maintained as formulary on the UF and that eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ be classified as non-formulary under the UF.

D. ARBs – MN Criteria

Based on the clinical evaluation for eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ:

1) Formulary alternatives are contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.

3) Use of formulary alternatives has resulted in therapeutic failure.

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

The P&T Committee specifically noted that some circumstances under which criterion #4 might be considered to apply may be for 1) post-MI patients with previous angioedema or other intolerance to ACE inhibitors, who are stabilized on valsartan or valsartan/HCTZ, or 2) chronic HF patients stabilized on a non-formulary ARB or ARB/HCTZ combination for whom changes in therapy might result in destabilization.

COMMITTEE ACTION: The P&T Committee voted (13 for, 1 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. ARBs – UF Implementation Period

Because of the large number of beneficiaries affected (approximately 228,000 patients (59%) of approximately 387,000 beneficiaries at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan, and valsartan/HCTZ 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) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary ARB agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. ARBs – BCF Review and Recommendation

COMMITTEE ACTION: Based on the results of the clinical and economic evaluations, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that telmisartan and telmisartan/HCTZ remain on the BCF.

G. Therapeutic Class Reclassification

The Committee agreed that the ARB class should be reclassified and consolidated with other drug classes that affect the renin-angiotensin system. These include ACE inhibitors, ACE/CCB combinations, ARBs, ARB/CCB combinations, and any newly approved antihypertensives affecting the renin-angiotensin system. The new class will be called the Renin-Angiotensin Antihypertensives (RAAs).

10. QUANTITY LIMITS

A. **Mometasone nasal spray (Nasonex)** – The current QL for mometasone nasal spray is 1 inhaler (17 gm = 120 sprays) per 30 days or 3 inhalers (51 gm) per 90 days. Nasonex, which was previously indicated only for allergic rhinitis at a maximum dose of 2 sprays in each nostril QD (4 sprays per day), received an indication in late 2004 for the treatment of nasal polyps at a maximum dose of 2 sprays in each nostril twice daily (8 sprays per day). TMOP personnel recently reported an increased number of QL override requests for Nasonex, based on dosing consistent with the nasal polyp indication. Accordingly, the P&T Committee recommended an increase in the QL to accommodate the higher maximum dose for nasal polyps.

COMMITTEE ACTION: The Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that the QL for mometasone nasal spray (Nasonex) be increased to 34 gm (2 inhalers) per 30 days (TRRx), 102 gm (6 inhalers) per 90 days (TMOP), based on daily maximum dosing recommended in product labeling.

B. **Ipratropium nasal spray 0.03% and 0.06% (Atrovent Nasal Spray)** – The current QL for Atrovent nasal spray is a collective limit (including both strengths) of 30 mL per 30 days or 90 mL per 90 days. The 0.03% strength, supplied in 30 mL bottles containing 345 sprays per bottle, is indicated for perennial rhinitis in divided doses of up to 12 sprays per day. Taking into account initial priming (7 sprays), 30 mL would equal 28 days supply, assuming consistent use at the maximum recommended dose. The 0.06% strength, supplied in 15 mL bottles containing 165 sprays per bottle, has two indications: 1) rhinorrhea associated with the common cold at divided doses of up to 16 sprays per day; and 2) rhinorrhea associated with seasonal allergic rhinitis at divided doses of up to 16 sprays per day. Based on the indication for seasonal allergic rhinitis and taking into account initial priming, 30 mL would equal 20 days supply, assuming consistent use at the maximum recommended dose.

The P&T Committee also reviewed data concerning QL rejections for Atrovent 0.03% and 0.06%, indicating that approximately 7% of prescriptions for either strength (about 300 prescriptions per month at retail network pharmacies and the TMOP) are initially rejected by the PDTS based on QLs. This is consistent with recent reports from TMOP of an increased number of QL override requests for Atrovent nasal spray.

Based on these data and given that seasonal allergic rhinitis can last considerably longer than 3 weeks, the P&T Committee agreed that the QL for the higher 0.06% strength should be increased. The P&T Committee also agreed that the QL for the lower 0.03% strength should be increased, but requested follow-up monitoring to determine if the change in QLs unduly affected utilization patterns, since the majority of patients should need no more than 1 inhaler per 30 days.

COMMITTEE ACTION: The Committee voted (13 for, 0 opposed, 2 abstained, and 2 absent) to recommend that 1) the QL for ipratropium nasal spray (Atrovent) be changed from a collective limit to a QL by strength; 2) the QL for the 0.03% strength be increased to 2 inhalers (60 mL) per 30 days (TRRx), 6 inhalers (180 mL) per 90 days (TMOP); and 3) the QL for the 0.06% strength be increased to 3 inhalers (45

mL) per 30 days (TRRx), 9 inhalers (135 mL) per 90 days (TMOP), based on daily maximum dosing recommended in product labeling.

11. RE-EVALUATION OF NON-FORMULARY AGENTS

Amlodipine (Norvasc) was designated non-formulary at the August 2005 P&T Committee meeting. In early 2007, the FDA approved Mylan Pharmaceutical's first-time generic for Norvasc (amlodipine, Pfizer). The price of amlodipine remains high enough that the Committee felt that even the generic was not cost effective relative to other drugs in the calcium channel blocker class. However, as part of its re-evaluation of the non-formulary UF status of amlodipine, the P&T Committee recognized that there will be situations in the future in which it would be helpful if a procedure were in place that allowed reclassification of such a drug from non-formulary to generic in a more expeditious manner than can be accomplished through the normal quarterly P&T Committee cycle. Such a procedure would be advantageous for both the MHS and its beneficiaries. The P&T Committee proposed the following process to more expeditiously reclassify non-formulary agents:

1) For each drug class in which such a reclassification is a possibility, the P&T Committee will recommend criteria under which non-formulary agents will be reclassified as generic agents under the UF. These criteria will be reviewed and adopted as a recommendation of the committee. The recommendation will be subject to comment by the BAP), and final decision by the Director, TMA (see recommended criteria below).
2) When the pre-established criteria for reclassification are met, the Chairperson of the P&T Committee will call for an electronic vote by the members of the P&T Committee on the matter.
3) Upon a majority vote affirming that the non-formulary drug should be reclassified as generic, that agent will be changed from non-formulary status to formulary status as a generic.
4) Committee members will be briefed on any reclassification of a non-formulary agent at the next meeting of the P&T Committee. This information will be recorded as an information-only item in the meeting minutes. The item will be included in information provided for the BAP's next meeting; however, since the BAP will have already made any comments on the subject, the item will normally not be subject to further BAP comment.

The DoD P&T Committee recommended the following criteria for the re-evaluation of non-formulary agents for UF status. These criteria would apply only to drug classes in which UF status was NOT awarded based on condition sets that specified the number of similar agents on the UF (i.e., agents in the same class or subclass). All three criteria must be met for the reclassification of a non-formulary agent.

1) The P&T Committee had concluded previously that the non-formulary agent had similar relative clinical effectiveness (i.e., similar efficacy, safety, and tolerability) compared to similar agents on the UF, and that the drug had not been excluded from the UF based on clinical issues alone.

2) The non-formulary agent becomes generically available and:

   a) The generic product is "A-rated" as therapeutically equivalent to the brand name product according to the FDA's classification system

   b) The generic market supply is stable and sufficient to meet DoD MHS supply demands.

3) The non-formulary agent is cost effective relative to similar agents on the UF. A non-formulary agent becomes cost-effective when:

   a) The non-formulary agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the UF class to which they were compared.

   b) The non-formulary agent's total weighted average cost based on an alternate measure used during the previous review is less than or equal to that for the UF class to which they were compared. F or example, antibiotics may be compared on the cost per course of therapy used to treat a particular condition.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 against, 3 absent) that the process and criteria described above should be adopted.

12. CLASS OVERVIEWS

Class overviews for the newer antihistamines, targeted immunomodulatory biologics, leukotriene modifiers, beta/alpha-beta blockers, and alpha blockers for BPH were presented to the P&T Committee. Preliminary information for the technical review for the blood glucose test strips was also presented.

The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed during the August 2007 or November 2007 meetings; no action is necessary.

13. ADJOURNMENT

The second day of the meeting adjourned at 1700 hours on 16 May 2007. The next meeting will be August 14-15, 2007.

Patricia Buss

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

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

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	Pending approval	Pending approval
May 07	Antilipidemic Agents II	▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	▪ gemfibrozil ▪ fenofibrate IDD-P (Triglide)	Pending approval	Pending approval
May 07 re-review (Feb 05 original)	ARBs	▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	Pending approval	Pending approval
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	Pending approval	Pending approval
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	NA

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 06	ADHD Agents	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07 (90 days)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)
May 06 (updated for new drugs Nov 06)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg drospironone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			Pending approval	Pending approval
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
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 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
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 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated for new drugs Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
		Recommended Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			Pending approval	Pending approval
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-
Feb 05	ARBs	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

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 = Uniform Formulary

ER = extended release; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle

ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs = thiazolidinediones

*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. May 2007 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Lapatinib tablets **(Tykerb,** Glaxo) tyrosine kinase inhibitor	Mar 07 ▪ In combination with capecitabine for treatment of patients with advanced or metastatic breast cancer whose tumors over express HER2, and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.	No UF recommendation at this meeting. Consideration of UF status deferred until oral cancer drugs are reviewed; UF review not anticipated in the next 12 months. Quantity limits recommended: ▪ TMOP o Days supply limit 45 days o 250 mg: 225 tabs per 45 days ▪ Retail Network o Days supply limit 30 days o 250 mg: 150 tabs per 30 days
Vorinostat capsules **(Zolinza;** Merck) histone deactylase inhibitor	Oct 06 ▪ Treatment of cutaneous manifestations in patients with cutaneous T cell lymphoma (CTCL) who have progressive, persistent, or recurrent disease on or following two systemic therapies.	No UF recommendation at this meeting. Consideration of UF status deferred until oral cancer drugs are reviewed; UF review not anticipated in the next 12 months. Quantity limits recommended: ▪ TMOP o Days supply limit 45 days o 100 mg: 180 caps per 45 days ▪ Retail Network o Days supply limit 30 days o 100 mg: 120 caps per 30 days
Arformoterol inhalation solution **(Brovana;** Sepracor) inhaled long-acting beta agonist	Oct 06 (launched Apr 07) ▪ Long term twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. For use by nebulization only.	No UF recommendation at this meeting. Consideration of UF status deferred until inhaled long-acting beta agonists are reviewed; UF review anticipated in the next 12 months. Quantity limits recommended: ▪ TMOP o 180 unit dose 15 mcg/2 mL vials per 90 days ▪ Retail Network o 60 unit dose 15 mcg/2 mL vials per 30 days

Appendix C – Table 3. Table of Abbreviations

5-ARI	5-alpha reductase inhibitor
ACE	angiotensin converting enzyme
AERS	adverse event reporting system
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ARB	angiotensin receptor blocker
AUA	American Urological Association
AUA-SI	American Urological Association symptom index
AUR	acute urinary retention
BAP	Beneficiary Advisory Panel
BAS	bile acid sequestrant
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BPA	blanket purchase agreement
BP	blood pressure
BPH	benign prostatic hyperplasia
CAD	coronary artery disease
CCB	calcium channel blocker
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CHD	coronary heart disease
CMA	cost minimization analysis
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CPAP	continuous positive airway pressure
CYP	cytochrome (P450)
DERP	Drug Effectiveness Review Project (state of Oregon)
DHA	docosahexaenoic acid
DHT	dihydrotestosterone
DoD	Department of Defense
DBP	diastolic blood pressure
EE	erosive esophagitis
ENRD	endoscopy-negative reflux disease
EPA	eicosapentaenoic acid
EPICS	Enlarged Prostate International Comparator Study
ESRD	end stage renal disease
ER	extended release
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes trial
FY	fiscal year
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto miocardico (GISSI)-Prevenzione
GFT	glomerular filtration rate
HCTZ	hydrochlorothiazide
HDL	high density lipoprotein
HF	heart failure
HHS	Helsinki Heart Study
IDD-P	Insoluble drug delivery microparticle
IPSS	International Prostate Symptom Score
IV	intravenous

Appendix C – Table 3. Table of Abbreviations (continued)

JNC	Joint National Council
LDL	low density lipoprotein
LH	leutinizing hormone
LIP-2	Antilipidemics II
LRC-CPPT	Lipid Research Clinics – Coronary Primary Prevention Trial
LUTS	lower urinary tract symptoms
LVH	left ventricular hypertrophy
LVSD	left ventricular systolic dysfunction
MHS	Military Health System
MI	myocardial infarction
MN	medical necessity
MTF	military treatment facility
MTOPS	Medical Therapy of Prostatic Symptoms
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Lung, and Blood Institute
NSAIDs	non-steroidal anti-inflammatory drugs
OTC	over-the-counter
PA	prior authorization
PPI	proton pump inhibitor
P&T	Pharmacy and Therapeutics
PDTS	Pharmacy Data Transaction Service
PEC	Pharmacoeconomic Center
PSA	prostate specific antigen
PUD	peptic ulcer disease
QD	once daily
Qmax	urinary flow rate
RAAs	renin-angiotensin antihypertensives
TC	total cholesterol
TG	triglyceride
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TPV	total prostate volume
TRRx	TRICARE Retail Network
UF	Uniform Formulary
UGT	uridine diphosphate glucuronosyl transferase
VA-HIT	Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial
VARR	voluntary agreements for TRICARE retail pharmacy rebates

17 July 2007

Executive Summary

UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL COMMENTS
June 2007

The Uniform Formulary Beneficiary Advisory Panel commented on the recommendations from the DoD Pharmacy & Therapeutics Committee May 2007 meeting.

1. **Antilipidemic II (LIP-2) Drug Class:** The P&T Committee recommended that: 1) fenofibrate, IDD-P fenofibrate, cholestyramine/aspartame, cholestyramine/sucrose, colestipol, and gemfibrozil be maintained as formulary on the UF; 2) micronized fenofibrate (Antara), nanocrystallized fenofibrate, colesevelam, and Omacor be classified as non-formulary under the UF; and 3) the normal brand formulary cost-share of $9.00 for IDD-P fenofibrate (Triglide) be lowered to the generic formulary cost-share of $3.00.

The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

Summary of Panel Vote/Comments:

- The Panel voted 8 Concur, 1 Non-Concur regarding the recommendations for formulary and non-formulary agents.
- The one non-concurrence was based on the absence of Omacor from the Uniform Formulary recommendation. Omacor is a different mechanism of action and is the only one of its kind in the class.
- The Panel voted 0 Concur, 9 Non-Concur regarding the recommended implementation period of 90-days.
- The Panel had several concerns regarding the lack of a communications plan with beneficiaries. Additionally, the Panel thought that 90-days was too short of a period to transition patients to the formulary medication.

Director, TMA:

☑ These comments were taken under consideration prior to my final decision.

2. **5-Alpha Reductase Inhibitors (5-ARIs):** The P&T Committee recommended that: 1) finasteride be classified as formulary on the UF, and 2) that dutasteride be classified as non-formulary.

The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

Summary of Panel Vote/Comments:

- The Panel voted 8 Concur, 1 Non-Concur regarding the recommendations for formulary and non-formulary agents.
- The Panel member non-corcurring stated his vote was based on the fact that there are only two drugs in this class. He believes that it would be prudent to have a choice between them.
- The Panel voted 4 Concur; 5 Non-Concur regarding the recommended implementation period of 90 days.

***Director, TMA*:**

These comments were taken under consideration prior to my final decision.

3. **Proton Pump Inhibitors (PPIs)**: The P&T Committee recommended that: 1) omeprazole and esomeprazole be maintained as formulary on the UF with a PA requiring a trial of either agent for new patients; 2) that rabeprazole, lansoprazole, pantoprazole, and omeprazole/sodium bicarbonate be classified as non-formulary under the UF with a PA requiring a trial of either omeprazole or esomeprazole for new patients; and 3) that the normal brand formulary cost-share of $9.00 for esomeprazole be lowered to the generic formulary cost-share of $3.00.

The P&T Committee recommended that the following PA criteria should apply to PPIs other than omeprazole or esomeprazole. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:
    a) The patient has received a prescription for any PPI agent at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.
    2) PA criteria if automated criteria are not met:
        a) The patient has tried omeprazole or esomeprazole and had an inadequate response or was unable to tolerate treatment due to adverse effects.
        b) Treatment with omeprazole or esomeprazole is contraindicated.

The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

Summary of Panel Vote/Comments:

- The Panel voted 5 Concur; 4 Non-concur regarding the recommendations for formulary and non-formulary agents and the prior authorization criteria for the Proton Pump Inhibitor class
- The panel did not formulate any specific comments for the class recommendations; however, their discussions revealed an overall concern for the dramatic change of formulary agents in the class and the number of beneficiaries affected by the change.
- The Panel vote 0 Concur; 9 Non-Concur regarding the recommended implementation period of 90 days. The Panel commented that a period of 120 days should be allowed for implementation. In addition, the Panel requests additional information about the decision process used for recommending third tier and PA determinations.

Director, TMA:

These comments were taken under consideration prior to my final decision.

4. **Angiotensin Receptor Blockers (ARBs)**: The P&T Committee, based upon its collective professional judgment, recommended that candesartan, candesartan/HCTZ, losartan, losartan/HCTZ, telmisartan, and telmisartan/HCTZ be maintained as formulary on the UF and that eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, olmesartan, olmesartan/HCTZ, valsartan and valsartan/HCTZ be classified as non-formulary.

The P&T Committee recommended an effective date of the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

Summary of Panel Vote/Comments:

- The Panel voted 2 Concur; 7 Non-Concur regarding the recommendations for formulary and non-formulary agents.
- The Panel commented that the significance of the proposed cost saving has not been articulated well enough for the Panel to understand why the most commonly used agent is being taken off formulary.
- Additionally, this recommendation will result is a huge burden to switch patients over and titrate them. Additionally, there are concerns about quality and the appropriateness of indications.
- The Panel voted 8 Concur; 1 Non-Concur regarding the recommended implementation period of 120 days
- One Panel member commented that he hoped the money saved would be used to improve the notification process, noting that the Panel is clearly not comfortable with the

formulary recommendations. He believes a lot of patients who are doing fine now [on their medication] are being moved to a different medication just based on cost.

***Director, TMA*:**

☑ These comments were taken under consideration prior to my final decision.