DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

August 2006

1. CONVENING

2. ATTENDANCE

3. REVIEW MINUTES OF LAST MEETING

4. ITEMS FOR INFORMATION

5. REVIEW OF RECENTLY APPROVED AGENTS

The P&T Committee was briefed on five new drugs that were approved by the Food and Drug Administration. None of the medications fall into drug classes already reviewed by the P&T Committee, therefore Uniform Formulary (UF) consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits, dasatinib (Sprycel), which is an oral multi-kinase inhibitor approved for treatment of patients with chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia. The Committee agreed that quantity limits were needed for dasatinib, based on the risk of discontinuation of therapy, the probability that dosage adjustments requiring changes in tablet strength will be needed, potential for drug interactions, and variable patient response to therapy and drug-related adverse effects. Other oral chemotherapy drugs also have quantity limits.

COMMITTEE ACTION: The DoD Pharmacy and Therapeutics (P&T) Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend quantity limits for dasatinib in the TRICARE Mail Order Pharmacy (TMOP) Program of 90 tablets for the 70 mg strength, 180 tablets for the 50 mg strength, and 180 tablets for the 20 mg strength per 45 days, with a days supply limit of 45 days (not collective across strengths). In the TRICARE Retail Pharmacy Network (TRRx), the recommended quantity limits were 60 tablets for the 70 mg strength, 120 tablets for the 50 mg strength, and 120 tablets for the 20 mg strength per 30 days, with a days supply limit of 30 days (not collective across strengths). (See page 14 of the P&T Committee minutes.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

6. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR EXENATIDE (BYETTA)

The Committee agreed that a PA was needed for exenatide subcutaneous injection due to the potential for inappropriate use.

COMMITTEE ACTION: Based on exenatide's potential use for indications not covered by TRICARE (i.e., weight loss) and/or not supported by clinical evidence, the P&T Committee recommended (14 for, 1 against, 0 abstained, 2 absent) that PA be required for exenatide. The criteria recommended by the P&T Committee incorporate modifications to the Pharmacy Data Transaction Service (PDTS) that will allow automation of some PA criteria, reducing paperwork burden and cost. These modifications are scheduled for completion by December 2006. (See pages 14-16 of the P&T Committee minutes for rationale and summary of PA criteria.)

Director, TMA, Decision: BW ☑Approved ☐ Disapproved

Approved, but modified as follows:

COMMITTEE ACTION: The Committee recommended (14 for, 1 against, 0 abstained, 2 absent) that the PA for exenatide should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible based on availability of the automated PA capability in PDTS. The implementation period will begin immediately following the approval by the Director, TRICARE Management Activity (TMA). (See pages 14-16 of the P&T Committee minutes.)

Director, TMA, Decision: BW ☑Approved ☐ Disapproved

Approved, but modified as follows:

7. THIAZOLIDINEDIONE (TZD) DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost-effectiveness of the TZD drugs marketed in the United States. The drugs in this class include the parent compounds rosiglitazone (Avandia) and pioglitazone (Actos); their respective combinations with metformin, rosiglitazone/metformin (Avandamet) and pioglitazone/metformin (Actoplus Met); and one combination of a TZD with a sulfonylurea, rosiglitazone/ glimepiride (Avandaryl). The TZDs accounted for approximately $110 million dollars in Fiscal Year (FY) 2005 and are ranked 12th in Military Health System (MHS) drug class expenditures.

The Committee voted (16 for, 0 opposed, 1 abstained, 0 absent) that:

1) Neither rosiglitazone nor pioglitazone appears less effective in reducing elevated hemoglobin A1c or fasting plasma glucose values.

2) There is insufficient evidence to determine if there are significant differences between the two parent compounds in the prevention of microvascular or macrovascular complications of diabetes.

3) Neither rosiglitazone nor pioglitazone appears less likely to cause hepatotoxicity, congestive heart failure, weight gain, edema, decreased blood pressure, hypoglycemia, or reduced hemoglobin and hematocrit.

4) Safety and tolerability differences appear to be limited to the potential for more drug interactions with pioglitazone.

5) Rosiglitazone appears to have a less favorable effect on lipid parameters than pioglitazone, however the clinical significance of this is unknown.

6) There are only minor differences between the two TZDs based on dosing frequency and receptor binding – provider opinion was split between preferring pioglitazone and no preference.

7) Neither rosiglitazone nor pioglitazone – or their respective combination products – appears sufficiently less clinically effective than the other to warrant classification as non-formulary under the UF based on clinical issues alone.

Based on the results of the cost-effectiveness analysis (CEA) and other clinical and cost considerations, the Committee concluded (16 for, 0 opposed, 1 abstained, 0 absent) that the UF scenario that maintained rosiglitazone, pioglitazone, rosiglitazone/metformin, pioglitazone/metformin, and rosiglitazone/glimepiride on the UF formulary 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 TZD drugs, and other relevant factors, the P&T Committee voted (13 for, 1 opposed, 2 abstained, 1 absent) to recommend that rosiglitazone, pioglitazone, rosiglitazone/metformin, pioglitazone/metformin, and rosiglitazone/glimepiride be maintained as formulary on the UF and that no agents from this class be classified as non-formulary under the UF. (See paragraphs 7A and 7B on pages 16-23 of the P&T Committee minutes.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. ***COMMITTEE ACTION: BASIC CORE FORMULARY (BCF) RECOMMENDATION*** – Based on the relative clinical and cost-effectiveness analysis, the P & T Committee voted (13 for, 1 opposed, 3 abstained, 0 absent) to recommend retaining rosiglitazone and rosiglitazone/metformin as the BCF selections in this class. The Committee did not recommend addition of rosiglitazone/glimepiride to the BCF. (See paragraph 7E on page 23 of the P&T Committee minutes for rationale.

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

8. HISTAMINE-2 (H2) ANTAGONISTS AND OTHER GASTROINTESTINAL (GI) PROTECTANT AGENTS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the H2 antagonists and other GI protectant agents. The drug class comprises: the four H2 antagonists, ranitidine (Zantac, generics), cimetidine (Tagamet, generics), famotidine (Pepcid, generics), and nizatidine (Axid, generics); the prostaglandin analog misoprostol (Cytotec, generics); and the mucosal protectant sucralfate (Carafate, generics). These six drugs have been marketed for several years, and all are available in generic formulations. This drug class accounted for $10.9 million in FY 2005, and is ranked 75th in MHS drug class expenditures.

The Committee voted (16 for, 0 opposed, 1 abstained, 0 absent) that:

1) The four H2 antagonists ranitidine, cimetidine, famotidine, and nizatidine are widely considered interchangeable for treatment of gastroesophageal reflux disease, peptic ulcer disease, and *H. pylori* infections, despite differences in potency, duration of action, and onset of action.
2) Compared to the other three H2 antagonists, cimetidine has evidence for use in non-gastrointestinal conditions.
3) Ranitidine is the most widely used H2 antagonist across the MHS, is dosed once or twice daily, has a low potential for drug interactions, and is available in an oral syrup for pediatric patients.
4) Famotidine and nizatidine have similar dosing intervals, drug interaction profiles and formulations as ranitidine, but are less frequently prescribed in the MHS.
5) Cimetidine is more difficult to use clinically compared to the other three H2 antagonists due to its need for multiple daily dosing (BID-QID) and drug interaction profile.
6) Misoprostol serves a unique niche for use in high risk patients for non-steroidal anti-inflammatory drug (NSAID)-induced ulcers, despite its adverse effect profile and warnings in women of child bearing age.
7) Sucralfate has a unique mechanism of action (physical barrier formation) and offers an alternative to proton pump inhibitors and H2 antagonists for stress ulcer prophylaxis.

Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) that: (1) ranitidine was the most cost effective H2 antagonist; (2) two other H2 antagonists, famotidine and cimetidine, were shown to have similar relative cost-effectiveness compared to ranitidine; (3) nizatidine was found to be slightly more costly compared to the other generic H2 antagonists, due to recent

availability of the generic version; and (4) misoprostol and sucralfate are available in generic versions and have an established niche in therapy for select patients.

A. ***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 voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend that the H2 antagonists ranitidine, cimetidine, famotidine and nizatidine; the prostaglandin analog misoprostol; and the mucosal protective agent sucralfate should be maintained as formulary on the UF, and that no agents from this class be classified as non-formulary under the UF. (See paragraphs 8A and 8B on pages 23-27 of the P&T Committee minutes).

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. ***COMMITTEE ACTION: BCF RECOMMENDATION*** – Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend retaining ranitidine as the BCF selection in this class, excluding the effervescent tablet and gel-filled capsule formulations. (See paragraph 8E on page 27 of the P&T Committee minutes for rationale.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

9. ANTILIPIDEMIC I (LIP-I) AGENTS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the agents in the LIP-1 drug class. This class is currently ranked number one in the MHS with drug class expenditures exceeding $595 million annually. The individual drugs included in the LIP-1 class are listed below:

- *Statins*: atorvastatin (Lipitor), fluvastatin (Lescol), fluvastatin extended release (Lescol XL), lovastatin (Mevacor, generics), lovastatin extended release (Altoprev), pravastatin (Pravachol, generics), rosuvastatin (Crestor), and simvastatin (Zocor, generics)
- *Statin combination products*: atorvastatin/amlodipine (Caduet), lovastatin/niacin extended release (Advicor), and ezetimibe/simvastatin (Vytorin)
- *Add-on therapies:* niacin immediate release (Niacor), niacin extended release (Niaspan), and ezetimibe (Zetia)

The Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) that the following conclusions apply:

1) Across equipotent doses, the statins achieve similar % low density lipoprotein (LDL) lowering, with rosuvastatin 40 mg and ezetimibe/simvastatin 10/80 mg as the only statins capable of achieving LDL lowering >55%.

2) Across equipotent doses, the statins achieve similar % high density lipoprotein (HDL) raising ability, but all statins show a plateau and drop-off of HDL raising effect at increasing doses.

3) There are no head-to-head trials comparing equivalent doses of statins that evaluate clinical outcomes for reducing mortality or other clinical outcomes (e.g., myocardial infarction, stroke, need for revascularization).

4) In low to moderate doses, the effects of atorvastatin, pravastatin and simvastatin appear similar for long-term cardiovascular protection, based on one meta-analysis [Zhou 2006].

5) In trials assessing the primary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin 10 mg, lovastatin 20 to 40 mg, pravastatin 40 mg, and simvastatin 40 mg.

6) In trials assessing the secondary prevention of CHD, beneficial effects on clinical outcomes have been noted with atorvastatin 10 to 80 mg, lovastatin 40 to 80 mg, pravastatin 40 mg, simvastatin 20-40 mg, and fluvastatin 40 mg (administered BID).

7) In one trial assessing acute coronary syndrome patients, beneficial effects on clinical outcomes were noted with atorvastatin 80 mg when it was compared to pravastatin 40 mg [PROVE-IT 2004].

8) There are no published trials assessing the benefits of rosuvastatin on clinical outcomes.

9) There is no evidence that increases in liver function tests or minor adverse events (gastrointestinal disturbances, headaches, rash, itching) are less likely to occur with one statin vs. another, and these adverse effects are dose-related.

10) Concerns of proteinuria and myotoxicity remain with rosuvastatin; the overall incidence of rhabdomyolysis occurs rarely with statins.

11) Fluvastatin, pravastatin, and rosuvastatin have the most favorable drug-drug interaction profiles.

12) There is insufficient evidence to determine whether one statin is less tolerable than another.

13) In terms of other factors, the statins can be initiated at maximum doses, with the exception of rosuvastatin 40 mg.

14) There is insufficient evidence to determine the clinical applicability of differences between the statins in terms of pleiotropic effects or effects on markers of atherosclerotic progression (intravascular ultrasound or carotid intima media thickness).

15) Ezetimibe offers an additional 15-20% LDL lowering by a mechanism distinct from that of the statins, but has not yet been evaluated for clinical outcomes.

16) Ezetimibe/simvastatin provides added efficacy in terms of LDL lowering and has a safety and efficacy profile reflecting that of its two individual components.

17) Niacin extended release is required in the MHS as its primary benefit is to raise HDL by 25%.

18) Lovastatin/niacin extended release, atorvastatin/amlodipine, lovastatin extended release, and fluvastatin extended release do not offer additional clinical benefits over the other LIP- I agents and have low utilization in the MHS (<5,000 Rxs/month dispensed).

19) A survey of MTF providers, including cardiologists, was overwhelmingly in support of simvastatin for treating the 80-85% of MHS patients requiring LDL lowering ≤45%, and also supported use of ezetimibe.

20) Based on clinical issues alone, none of the LIP-1 agents are sufficiently less effective than the others agents within the class to be classified as non-formulary.

Based on the results of the CEA and other clinical and cost considerations, the P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) that (1) simvastatin could meet the vast majority of the needs of patients requiring low to moderate % LDL lowering agents (≤ 45%); (2) ezetimibe/simvastatin was the most cost-effective intensive % LDL lowering agent; (3) some low to moderate % LDL lowering agents were considered to be clinically necessary (pravastatin, ezetimibe, and niacin); (4) of the remaining low to moderate % LDL lowering agents, nothing would be gained clinically or economically by making them non-formulary, especially considering their low market share; (5) atorvastatin/amlodipine was considerably more costly compared to the combination of atorvastatin and a UF dihydropyridine calcium channel blocker, regardless of point of service; and (6) the UF scenario that included the intensive % LDL lowering agents atorvastatin and ezetimibe/simvastatin 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 relative cost effectiveness determinations of the LIP-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 1 opposed, 1 abstained, and 0 absent) to recommend that atorvastatin, fluvastatin immediate and extended release, pravastatin, simvastatin, lovastatin immediate and extended release, lovastatin/niacin, ezetimibe/simvastatin, niacin extended & immediate release, and ezetimibe be maintained as formulary on the UF, and that rosuvastatin and the combination product atorvastatin/amlodipine be classified as non-formulary under the UF. (See paragraphs 9A and 9B on pages 28-38 of the P&T Committee minutes.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Our efforts to sustain the TRICARE benefit, and the TRICARE Rx benefit, require that MTF prescribers continue using simvastatin when that drug is clinically appropriate. I strongly encourage MTF commanders, doctors and pharmacists to maximize the use of simvastatin.

B. COMMITTEE ACTION: MEDICAL NECESSITY CRITERIA – Based on the clinical evaluation of rosuvastatin and atorvastatin/amlodipine, and the conditions for establishing medical necessity for a non-formulary medication provided in the UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) medical necessity criteria for the LIP-1 agents. (See paragraph 9C on pages 38-39 of the P&T Committee minutes for criteria

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (15 for, 0 opposed, 2 abstained, 0 absent) to recommend an effective date no sooner than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. (See paragraph 9D on page 39 of the P&T Committee minutes for rationale.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BCF RECOMMENDATION – Based on the relative clinical effectiveness and cost-effectiveness analysis, the P&T Committee voted (15 for, 1 opposed, 1 abstained, 0 absent) to recommend simvastatin, pravastatin, ezetimibe/ simvastatin, and niacin extended release as the BCF selections in this drug class. (See paragraph 9E on page 40 of the P&T Committee minutes.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

10. CLASS OVERVIEWS. ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY MEDICATIONS; SEDATIVE HYPNOTICS I (NON-BENZO-DIAZEPINE SEDATIVE HYPNOTICS); SEDATIVE HYPNOTICS II

Portions of the clinical reviews for each class were presented to the Committee. The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review, and for developing the appropriate cost effectiveness models. Both the clinical and economic

analyses of these three classes will be completed during the November 2006 meeting; no action necessary.

Appendix A – Table 1. Implementation Status of UF Decisions

Appendix B – Table 2. Newly Approved Drugs

Appendix C – Table 3. Abbreviations

Appendix D – Figure 1. Estimated Percent of Population Expected to Reach ATP-III LDL Goals with Increasing LDL Reduction

Appendix E – Table 4. Expected Mean LDL Reductions, by Statin and Dose

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

William Winkenwerder, Jr., M.D.
Date: 23 October, 2006

Department of Defense
Pharmacy and Therapeutics Committee Minutes
16 August 2006

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 15 August 2006 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
CAPT Mark Richerson, MSC, USN	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
LtCol Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
LtCol Brian Crownover, MC	Air Force, Physician at Large
LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer (Pharmacy Consultant)
LCDR Michelle Perrello, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatric Physician
Not Appointed	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer (Pharmacy Consultant)
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
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
LT Thomas Jenkins, MSC, USN	TMOP/TRRx COR
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

COL Isiah Harper, MSC	Army, Pharmacy Officer

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Mr. Lynn T. Burleson	Assistant General Counsel, TMA
Mr. John Felicio *for* Ms Martha Taft	Health Plan Operations, TMA
Major Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

None	

E. Others Present

CAPT Don Nichols, MC, USN	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Mr. Dan Remund	DoD Pharmacoeconomic Center
Ms. Shana Trice	DoD Pharmacoeconomic Center
Mr. David Bretzke	DoD Pharmacoeconomic Center
Ms Angela Allerman	DoD Pharmacoeconomic Center
Mr. Eugene Moore	DoD Pharmacoeconomic Center
Ms. Julie Liss	DoD Pharmacoeconomic Center
Ms. Elizabeth Hearin	DoD Pharmacoeconomic Center
Mr. Dave Flowers	DoD Pharmacoeconomic Center
Mr. David Meade	DoD Pharmacoeconomic Center
Ms. Harsha Mistry	DoD Pharmacoeconomic Center
LCDR Joe Lawrence, MSC, USN	DoD Pharmacoeconomic Center
LTC Bret Kelly, MSC, USA	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
Mr. Charles R. Brown	TMA/CMB
Mr. Vincent Calabrese	Department of Veterans Affairs

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – May 2006 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. May Minutes Approval – Dr. William Winkenwerder, Jr., M.D., approved the minutes of the May 2006 DoD P&T Committee meeting on July 26, 2006.

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 and CAPT Richerson briefed the members of the DoD P&T Committee regarding the June 29, 2006 BAP meeting. The Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. **Administrative Action: Quantity Limits for Tramadol Extended Release (Ultram ER)** – Quantity limits apply to all tramadol-containing products, including new formulations, based on DoD P&T Committee recommendations made at the February 2005 meeting and subsequently approved by the Director, TMA, on 18 April 2005. The major potential concern with tramadol is safety (risk of seizure at higher than recommended doses); the potential for overuse or diversion may also exist. The Committee concurred with the specific quantity limits established for a new extended release formulation of tramadol (Ultram ER): 30 tablets per 30 days or 90 tablets per 90 days for all strengths, with quantity limits for the 200- and 300-mg tablets applied collectively. These limits were based on available strengths, dosing, titration, and maximum dose recommendations in product labeling (100-, 200-, and 300-mg extended release tablets initiated at 100 mg once daily and titrated up as necessary by 100-mg increments every five days to a maximum of 300 mg per day). The quantity limit is not collective with the immediate release formulations (tramadol 50 mg tablets and tramadol/acetaminophen 37.5/325 mg tablets) because of differences in strengths, Food and Drug Administration (FDA)-approved indications, and dosing recommendations. The Committee noted that Express Scripts, Inc. (ESI), the contractor for the TRICARE Mail Order Pharmacy (TMOP), and TRICARE Retail Pharmacy Network (TRRx) programs, has established procedures to deal with circumstances that may require temporary overrides of quantity limits (e.g., increases in dose).

C. **Administrative Action: Removal of Carbinoxamine/Pseudoephedrine Drops from the Basic Core Formulary (BCF)** – Like a number of older products, carbinoxamine combination products have been widely used, but were never approved by the FDA as safe and effective. On 8 June 2006, the FDA announced enforcement actions to stop manufacture of unapproved carbinoxamine-containing products due to safety concerns in children $\leq$ 2 years of age, and as part of ongoing FDA efforts to bring all unapproved products in line with provisions of the Food, Drug, and Cosmetic Act. Manufacturers of unapproved products containing carbinoxamine have been directed to cease manufacture over the next 30 to 90 days. One FDA-approved carbinoxamine 4 mg tablet and one 4 mg/5 mL oral solution will remain on the market, but no combination products. The Committee concurred with an administrative action removing carbinoxamine 1 mg / pseudoephedrine 15 mg per mL oral drops from the BCF. They did not feel that addition of another antihistamine/ decongestant combination to the BCF was warranted at the present time, pending future UF review of these medications.

D. **UF Change Request Process** – The P&T Committee discussed the process by which MTF healthcare providers could request that the DoD P&T Committee consider potential changes to the BCF, Extended Core Formulary (ECF), or UF, including changes to

medical necessity criteria for non-formulary medications, prior authorization criteria, or quantity limits. The P&T Committee agreed on three general process goals:

1) Requests should contain adequate supporting evidence, including a fair, balanced, and thorough discussion of the relevant clinical literature, and present a rational argument supporting suggested changes.

2) The process should address potential conflicts of interest and discourage pharmaceutical industry representatives from putting pressure on providers to submit requests.

3) The process should require review and concurrence by the local military treatment facility (MTF) P&T Committee.

A request form and supporting materials are currently under development.

E. Fentanyl Patch (Duragesic, generics) – The P&T Committee discussed various issues related to the use of fentanyl patches, including safety warnings from the DoD Patient Safety Center, the FDA, and the Institute of Safe Medication Practices; and the July 2006 Air Force policy on the use of fentanyl patches. Fentanyl, a strong opioid narcotic, can cause severe respiratory depression in patients who are not tolerant to opioids. Other safety issues include failing to remove old patches, unsafe disposal of old patches, application of heat to the patch site (e.g., heating pads, water beds), concurrent use of potent CYP3A4 inhibitors, conditions that affect respiratory function or affect metabolism of fentanyl, abuse, and diversion.

Product labeling for fentanyl patches was strengthened in July 2005 following reports of serious adverse events and fatalities. Fentanyl patches are indicated for management of *persistent*, moderate to severe chronic pain requiring continuous, around-the-clock administration for an extended period of time, that cannot be managed by other means, and ONLY in patients who are already receiving opioids, have demonstrated opioid tolerance, and require a total daily dose at least equivalent to fentanyl 25 mcg/hr. They should not be used for management of acute pain or short periods of opioid analgesia; postop pain, including outpatient/day surgeries; mild pain; or intermittent pain.

F. Implementation Status of UF Decisions – The PEC briefed the members of the Committee on the progress of implementation for drug classes reviewed for UF status since August 2005. The Committee made the following observations:

1) Utilization in all UF classes continues to remain stable, suggesting continued access to drugs within the reviewed classes.

2) Collective utilization of UF agents across all reviewed drug classes and points of service (MTF, TMOP, and TRRx) continues to increase as a percentage of prescriptions dispensed, while utilization of non-formulary agents has decreased. Based on the UF decisions that have been fully implemented since the first UF DoD P&T meeting in February 2005, there has been a 26% reduction in the use of non-formulary agents, including those classes where implementation has only just begun (July 2006).

3) Success in terms of generating increased market share for UF agents (while decreasing market share for non-formulary agents) varies by class and by point of service.

4) Market shares by point of service continue to reflect the degree of utilization management applied to each point of service. The more highly managed points of service (i.e., MTFs) are generating higher market shares of UF agents than the unmanaged points of service (i.e., TMOP and TRRx).

5) For drug classes fully implemented, MTFs have reduced the use of non-formulary drugs by 84% as projected, but the change in the use of non-formulary medications at mail (+1%) and retail (-14%) is significantly less.

6) It appears that more beneficiaries are electing to receive non-formulary medications through TMOP.

5. REVIEW OF RECENTLY-APPROVED AGENTS

The P&T Committee was briefed on five new drugs that were approved by the FDA. None of the medications fall into drug classes already reviewed by the P&T Committee; therefore, UF consideration was deferred until the corresponding drug class reviews are completed.

The P&T Committee reviewed one new drug for quantity limits. Dasatinib (Sprycel) is an oral multi-kinase inhibitor approved for treatment of patients with chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia, with resistance or intolerance to prior therapy including imatinib (Gleevec). Dasatinib is available in 20-, 50- and 70-mg tablets which should not be crushed or cut. It is administered at a target dosage of 70 mg twice daily, but dosing can vary from 20 mg once daily to 100 mg twice daily, based on potential drug interactions, patient response, or drug-related adverse effects. Quantity limits were recommended for dasatinib due to the risk of discontinuation of therapy and the probability that dosage adjustments requiring changes in tablet strength will be needed, based on potential drug interactions, patient response to therapy, or drug-related adverse effects. Quantity limits also apply to other oral chemotherapy drugs, including imatinib, erlotinib (Tarceva), sorafenib (Nexavar), and sunitinib (Sutent), based on previous DoD P&T Committee recommendations and subsequent approval by the Director, TMA.

COMMITTEE ACTION – The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend quantity limits for dasatinib in TMOP of 90 tablets for the 70 mg strength, 180 tablets for the 50 mg strength, and 180 tablets for the 20 mg strength per 45 days, with a days supply limit of 45 days. In TRRx, the recommended quantity limits were 60 tablets for the 70 mg strength, 120 tablets for the 50 mg strength, and 120 tablets for the 20 mg strength per 30 days, with a days supply limit of 30 days.

6. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR EXENATIDE (BYETTA)

Exenatide is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus (DM) who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, but have not achieved adequate glycemic control. Pharmacologically, exenatide is an incretin mimetic agent that stimulates insulin production in the pancreatic islet cells when glucose levels are elevated, slows gastric emptying, and helps produce a feeling of satiety. Exenatide also reduces the secretion of glucagon, thus lowering elevated post-prandial blood glucose levels. It is given twice daily by subcutaneous injection, prior to the morning and evening meals. Exenatide should not be used as a

substitute for insulin in patients who need insulin, has not been studied in patients also using insulin, and is not indicated for use in patients with type 1 DM.

In clinical trials, exenatide decreased glycosylated hemoglobin A1c (HbA1c) by 0.7 to 1.1% (insulin typically decreases HbA1c by 1-2%). Also noted during clinical trials were reduced sulfonylurea requirements and reductions in weight (1.9 to 4.5 kg). From a safety standpoint, use of exenatide with a sulfonylurea may increase the risk of hypoglycemia, and the sulfonylurea dose may need to be reduced. Concurrent use of exenatide and metformin is relatively unlikely to cause hypoglycemia. Because it slows gastric emptying, exenatide may alter the rate and extent of absorption of oral drugs; drugs dependent on threshold concentrations for efficacy (e.g., antibiotics, contraceptives) should be taken at least one hour prior to exenatide. Exenatide is not recommended in patients with severe gastrointestinal (GI) disease, including gastroparesis, or in patients with severe/end stage renal disease. It is associated with GI adverse effects, including nausea, vomiting, and diarrhea; patients receiving exenatide in clinical trials also complained of significantly more jitteriness, dizziness, and headache than those receiving placebo.

Exenatide has achieved some notoriety as a weight loss medication (even in non-diabetic patients), an off-label use that is both not supported by clinical evidence and not covered by TRICARE. In addition, it appears likely that exenatide may be used in some patients with metabolic syndrome or "pre-diabetes," another off-label use not supported by clinical evidence. Based on results of a utilization study performed by the PEC, about 90% of Military Health System (MHS) patients who received a first prescription for exenatide from June 2005 to May 2006 had also filled a prescription for an oral antidiabetic drugs, blood glucose test strips, or both during the 180 days prior to starting exenatide (8,681 out of a total of 9,634 patients). In other words, about 10% of MHS patients starting exenatide appear unlikely to be diabetic, based on absence of prescription fills for either diabetic medications or blood glucose testing supplies during the six months prior to starting exenatide. While there may be alternative explanations for some of these cases, it appears that some of these patients are receiving exenatide as a weight-loss medication and/or in a setting of "pre-diabetes." Many health plans have PA requirements for exenatide, primarily based on its FDA indication.

The cost of exenatide ranges from $1250 to $2500 per year, depending on dose and pharmacy point of service. Exenatide prescription fills are increasing rapidly at retail network pharmacies, where most exenatide fills are dispensed; relatively few fills and a slower rate of increase are seen at TMOP or MTFs.

Based on the following considerations, the P&T Committee agreed that a PA should be required for exenatide:

- In the MHS, up to 10% of exenatide usage appears likely to be used for indications not covered by TRICARE and/or not supported by clinical evidence. The use of exenatide for weight loss may increase based on continued coverage in the lay press increasing familiarity with the medication. Overall, utilization of exenatide is increasing.
- Modifications to the Pharmacy Data Transaction Service (PDTS) scheduled for completion by December 2006 will add the capability of "looking back" at a given patient's profile for the presence or absence of prescription fills for specific medications within a defined time period. This will allow automation of some PA criteria, reducing

paperwork burden and cost (PA fees), and limiting the scope of the PA to those patients most likely to fail to meet the established criteria.

COMMITTEE ACTION – Based on its potential use for indications not covered by TRICARE and/or not supported by clinical evidence, the P&T Committee recommended that a PA be required for exenatide (14 for, 1 against, 0 abstained, 2 absent). The Committee recommended that the PA should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible based on availability of the automated PA capability in PDTS. The implementation period will begin immediately following the approval by the Director, TMA.

The Committee agreed that the following PA criteria should apply (14 for, 1 against, 0 abstained, 2 absent). Patients meeting the automated PA criteria would not be required to have their providers submit any additional information and in all likelihood would not even be aware of the existence of the PA. PA approvals would be valid indefinitely.

1) Automated PA criteria:
   - Patient has received any oral antidiabetic agent in the last 120 days
2) PA criteria if automated criteria are not met:
   - Coverage is approved if the patients meets both of the following criteria:
     - Diagnosis of type 2 DM
     - Patient has not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea

7. THIAZOLIDINEDIONE DRUG CLASS REVIEW

The drugs in the thiazolidinedione (TZD) class include the parent compounds rosiglitazone (Avandia) and pioglitazone (Actos); their respective combinations with metformin, rosiglitazone/metformin (Avandamet) and pioglitazone/metformin (Actoplus Met); and one combination of a TZD with a sulfonylurea, rosiglitazone/glimepiride (Avandaryl). The TZDs accounted for approximately $110 million dollars in Fiscal Year (FY) 2005 and are ranked 12th in MHS drug class expenditures.

A. TZD Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the TZD products currently marketed in the United States. 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) Efficacy for Glycemic Control

Rosiglitazone and pioglitazone and their fixed-dose combinations with metformin or

glimepiride are FDA-approved for treating patients with type 2 DM. The primary efficacy measures evaluated included HbA1c and fasting plasma glucose (FPG).

- *Monotherapy* – TZDs may be given as monotherapy, but are usually administered with other antidiabetic drugs, including metformin, sulfonylureas, or insulin. Placebo-controlled trials show that rosiglitazone monotherapy reduces HbA1c by 0.6% to 1.5% and FPG by 33 mg/dL to 55 mg/dL, while pioglitazone monotherapy reduces HbA1c by 0.7% to 1.2% and FPG by 36 mg/dL to 56 mg/dL.
  - *Head-to-Head Monotherapy Trials* – The only rigorously designed head-to-head clinical trial comparing rosiglitazone and pioglitazone monotherapy included 802 patients. The trial showed similar reductions in HbA1c after 24 weeks of therapy (0.6% with rosiglitazone vs. 0.7% with pioglitazone, p=0.129) and FPG (36 mg/dL with rosiglitazone vs. 33 mg/dL with pioglitazone, p=0.233). [Goldberg 2005]
  - *Meta-Analyses* – A meta-analysis of 23 placebo-controlled TZD monotherapy trials concluded that, when relatively equivalent doses of the TZD were compared, similar mean changes from baseline in HbA1c were reported: -0.90% (95% Confidence Interval [CI] -1.42% to -0.38%) with rosiglitazone 4 mg once daily (QD); -0.99% (95% CI -1.32% to -0.66%) with pioglitazone 30 mg QD. Similar point estimates and overlapping confidence intervals were reported for rosiglitazone 8 mg QD and pioglitazone 45 mg QD for reductions in both HbA1c and FPG. [Chiquette 2004]
- *Combination Therapy* – When a TZD is added on to another antidiabetic drug, greater reductions in HbA1c and FPG are seen than if the TZD is administered as monotherapy.
  - *Head-to-Head Combination Therapy Trials* – There is one head-to-head trial comparing the TZDs used in combination with the sulfonylurea glimepiride, which enrolled 91 patients. Similar changes in glycemic parameters from baseline were reported in both treatment groups. HbA1c decreased by 1.3% with rosiglitazone plus glimepiride vs. 1.4% with pioglitazone plus glimepiride; FPG decreased by 31 mg/dL in both groups. [Derosa 2004]
  - *Meta-analyses* – A meta-analysis of 15 clinical trials evaluating metformin, sulfonylurea or insulin plus a TZD compared to metformin, sulfonylurea, or insulin plus placebo concluded that when relatively equivalent doses of the TZDs were compared, similar mean changes from baseline in HbA1c were reported: [-1.05 (95% CI-1.2 to -0.9) with rosiglitazone 4 mg QD plus other antidiabetic drugs vs. -1.16 (95% CI -1.4 to -0.0) with pioglitazone 30 mg QD plus other antidiabetic drugs]. Similar reductions in HbA1c and FPG, with overlapping confidence intervals, were reported for rosiglitazone 8 mg QD plus other antidiabetic drugs vs. pioglitazone 45 mg QD plus other antidiabetic drugs. [Chiquette 2004]
- *Monotherapy and Combination Therapy* – A systematic review evaluating placebo-controlled trials with the TZDs used as either monotherapy or added on to other antidiabetic drugs reported an adjusted indirect comparison between

rosiglitazone and pioglitazone. Overall, there was no significant difference between the two drugs (adjusted mean difference, pioglitazone minus rosiglitazone, of -0.12% (95% CI -0.50 to 0.26)). [State of Oregon 2006]

Conclusion: Efficacy for Glycemic Control – The available evidence suggests that neither rosiglitazone nor pioglitazone is superior to the other in reducing HbA1c or FPG.

2) *Effectiveness for Prevention of Microvascular and Macrovascular Events*

For clinical outcomes, endpoints evaluated included microvascular (e.g., nephropathy, retinopathy, neuropathy) and macrovascular (e.g., cardiovascular disease, cerebral vascular disease, peripheral vascular disease) complications of type 2 DM, when available.

- *Microvascular Complications* – There are no clinical trials with either rosiglitazone or pioglitazone that evaluate the effects of long-term TZD therapy on prevention of microvascular complications. However, both TZDs reduce HbA1c, and reductions in HbA1c are correlated with a reduced risk of microvascular events, as previously shown in the United Kingdom Prospective Diabetes Study.
- *Macrovascular Complications* – Coronary heart disease is the major cause of mortality in diabetic patients, thus clinical trials evaluating cardiovascular outcomes are of importance when comparing the TZDs. There is one published trial, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE), that evaluated the effects of pioglitazone on clinical outcomes in over 5,000 patients. After three years, there was no significant difference with pioglitazone added to other antidiabetic medications compared to placebo plus other antidiabetic medications in the primary composite outcome, which included both disease and procedure-related endpoints (i.e., myocardial infarction (MI), stroke, need for coronary artery bypass grafting, percutaneous coronary intervention or leg amputation). Overall, 21% of patient reached the primary endpoint with pioglitazone vs. 23% with placebo; p=0.095). However, a significant difference in favor of pioglitazone was reported in a secondary composite endpoint that only included disease-related endpoints (all-cause death, non-fatal MI and stroke); 11.6% with pioglitazone vs. 13.6% with placebo, p=0.027. The design of this trial has been debated, and the clinical applicability of these results is limited. There are no completed trials with rosiglitazone evaluating clinical outcomes, although two trials (ADOPT and RECORD) are underway.

Conclusion: Effectiveness for Prevention of Microvascular and Macrovascular Events – Due to the absence of published trials with rosiglitazone and design limitations of the one published trial with pioglitazone PROACTIVE, there is insufficient evidence to determine whether one TZD is superior to the other in preventing the clinical complications of diabetes.

3) *Safety and Tolerability*

- *Hypoglycemia* – One meta-analysis compared the differences in the incidence of hypoglycemia between rosiglitazone and pioglitazone. The pooled risk

differences were compared with each drug vs. placebo, and the results were similar for each TZD; rosiglitazone risk difference vs. placebo 3% (95% CI 0% to 5%) and pioglitazone risk difference vs. placebo 2% (95% CI -1% to 4). [State of Oregon 2006]

- *Edema* – Mild to moderate edema has been reported with the TZDs and appears to be dose-related. One meta-analysis reported the pooled risk difference for the incidence of edema with the TZDs in placebo-controlled trials. The pooled risk difference compared to placebo was similar between the two TZDs: rosiglitazone 4% (95% CI 2% to 5%), pioglitazone 4% (95% CI 2% to 7%). [State of Oregon 2006]
- *Heart Failure* – Both rosiglitazone and pioglitazone have been linked to development of heart failure; neither are recommended for use in patients with New York Heart Association Class III or IV heart failure Product labeling for both rosiglitazone and pioglitazone are similar regarding warnings for fluid retention, which may lead to or worsen heart failure. The highest risk occurs when a TZD is used in combination with insulin. A retrospective review using a large health plan database found no difference between the two TZDs in the development of heart failure in a cohort of over 28,000 patients: rosiglitazone 2.39% vs. pioglitazone 1.63%; p=0.091. [Delea 2003]
- *Weight Gain* – Both TZDs cause statistically significant increases in body weight from baseline. The effect on body weight appears similar between TZDs, as evidenced by the results from head-to-head clinical trials – mean weight gain of 1.6 kg with rosiglitazone vs. 2.0 kg with pioglitazone – and published meta-analyses showing similar weight gain (about 3 kg with each TZD, with overlapping confidence intervals).
- *Hepatotoxicity* – Clinical trials for both TZDs report an incidence <1% for elevations in ALT three times the upper limit of normal. Both TZDs carry similar labeling regarding monitoring of liver enzymes.
- *Blood Pressure* – An association between TZD use and small but statistically significant reductions in blood pressure has been reported. There is insufficient information at this time to determine whether the blood pressure effects are different between rosiglitazone and pioglitazone.
- *Hematologic Effects* – Reductions in hemoglobin and hematocrit have been reported with both TZDs. This may be due to an increase in plasma volume rather than a decrease in red cell mass. The clinical significance of these hematologic effects is unknown.
- *Macular Edema* – An association between TZD use and macular edema has been reported in the literature. GlaxoSmithKline issued a "Dear Doctor Letter" on January 5, 2006 regarding the association of rosiglitazone with new onset and worsening macular edema. Takeda, the manufacturer of pioglitazone, disputes the occurrence of this adverse effect and has not issued a similar warning.
- *Drug-Drug Interactions* – The potential for drug-drug interactions may be greater with pioglitazone than rosiglitazone, due to metabolism of the former by CYP3A4

enzymes. However, the clinical significance of the drug-drug interactions with pioglitazone may be counterbalanced by the availability of multiple metabolic pathways. Of note, use of pioglitazone with oral contraceptives containing ethinyl estradiol and norethindrone has resulted in reduced plasma concentrations of both hormones by 30%, which could result in decreased contraceptive efficacy. The clinical significance of this interaction is unknown, and no dosage adjustments are required in the package labeling for pioglitazone.

- *Withdrawal Due to Adverse Effects* – Drug discontinuations due to adverse effects were similar for rosiglitazone and pioglitazone in one head-to-head monotherapy trial: 2.7% for both TZDs [Goldberg 2005]. A systematic review reported withdrawal rates due to adverse effects of 4.9% with rosiglitazone vs. 4.8% with pioglitazone. [State of Oregon 2006]

Conclusion: Safety and Tolerability – The risk of heart failure, hypoglycemia, weight gain and edema do not appear to differ between rosiglitazone and pioglitazone. Hepatotoxicity has not been a concern with either TZD. There is insufficient evidence to determine whether the TZDs differ in respect to macular edema, changes in blood pressure, hemoglobin or hematocrit; only small changes from baseline in these parameters have been noted. The potential for drug-drug interactions may be greater with pioglitazone than rosiglitazone, but this does not appear to have translated into a clinically significant difference between the two TZDs. The tolerability profiles of both TZDs appear similar, based on drug withdrawals due to adverse effects during clinical trials.

4) *Effects on Lipid Parameters*

The TZDs exhibit other actions that can have unintended consequences in type 2 DM patients. Treatment with rosiglitazone and pioglitazone can affect serum lipid parameters, including total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG). Diabetes is a coronary heart disease (CHD) risk equivalent, and most type 2 DM patients require treatment with lipid lowering therapy. CHD is the number one cause of death in type 2 DM patients.

- Two head-to-head trials (one as monotherapy, the other as add-on therapy with other diabetic medications) reported that rosiglitazone adversely affected the lipid panel, as reflected by increases in TC (by 15-16%), LDL (by 17-23%), and TG (by 15-18%). In contrast, pioglitazone showed a favorable effect on the lipid profile, as reflected by to increases in HDL (by 15%), and decreases in TG (by 12 to 22%). However, these two head-to-head trials differed in the reported results for the effect of pioglitazone on TC and LDL. Goldberg et al (2005) showed an increase in TC (6%) and LDL (16%), while Derosa et al (2003) showed a reduction in TC (by 6%) and LDL (by 12%).
- Two meta-analyses [Chiqeutte 2004 and Canada 2002] concluded that rosiglitazone therapy resulted in increases in TC (10-21%), LDL (7-15%), and HDL (2-3%), but did not affect TGs. Pioglitazone increased HDL (2-5%) and reduced LDL (0.4 to 0.5%). Reductions in TG were more pronounced with pioglitazone, but a statistically significant difference was noted only for

pioglitazone in the Canadian analysis. Both TZDs were associated with modest increases in HDL (by 2-5%); the marked difference between rosiglitazone and pioglitazone seen in the two head-to-head trials is not as noticeable in the two meta-analyses.

Conclusion: Effects on Lipid Parameters – Results from two head-to-head clinical trials and two meta-analyses that assessed the lipid effects with TZDs vary, but are mostly consistent with the results of the head-to-head monotherapy trial. [Goldberg 2005] Pioglitazone appears to have a more favorable effect on lipid parameters than rosiglitazone. The clinical significance of this difference has yet to be determined.

5) *Other Factors*

- Rosiglitazone is dosed either once or twice daily, while pioglitazone is dosed once daily.
- Rosiglitazone binds primarily to peroxisome proliferator-activated receptors (PPARs) gamma receptors, while pioglitazone binds to both PPAR gamma and alpha receptors; differences in receptor binding are theorized to account for differences in the effects on lipid parameters.
- There are no differences in the product labeling for the two TZDs for FDA-approved indications, contraindications, and use in special populations.
- Neither rosiglitazone nor pioglitazone are indicated for use in the pediatric population, in pregnancy, or while breast feeding.
- A survey of MTF providers revealed a split opinion as to whether the TZDs were therapeutically interchangeable, with half of the respondents favoring pioglitazone due to once-daily dosing and lack of detrimental effect on lipids, and the other half voicing no preference.

Conclusion: Other factors – There are only minor differences in terms of other factors for the TZDs. MTF provider opinion is split between preferring pioglitazone and no preference between the two.

Overall Clinical Effectiveness Conclusion – The Committee concluded that:

1) Neither rosiglitazone nor pioglitazone appears less effective in reducing elevated hemoglobin A1c or fasting plasma glucose values.
2) There is insufficient evidence to determine if there are significant differences between the two parent compounds in the prevention of microvascular or macrovascular complications of diabetes.
3) Neither rosiglitazone nor pioglitazone appears less likely to cause hepatotoxicity, congestive heart failure, weight gain, edema, decreased blood pressure, hypoglycemia, or reduced hemoglobin and hematocrit.
4) Safety and tolerability differences appear to be limited to a possibly greater potential for drug interactions with pioglitazone.
5) Rosiglitazone appears to have a less favorable effect on lipid parameters than pioglitazone, however the clinical significance of this is unknown.

6) There are only minor differences between the two TZDs based on dosing frequency and receptor binding; provider opinion was split between preferring pioglitazone and no preference.

7) Neither rosiglitazone nor pioglitazone – or their respective combination products – appears sufficiently less clinically effective than the other to warrant classification as non-formulary under the UF based on clinical issues alone.

COMMITTEE ACTION – The P&T Committee voted (16 for, 0 opposed, 1 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

B. TZD Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the TZDs 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).

Given the evidence-based relative clinical effectiveness evaluation conclusion that there was insufficient evidence to suggest that the TZDs differed in regards to efficacy, safety, tolerability, or clinical outcomes in the treatment of type 2 DM, two cost-minimization analyses (CMAs) were performed to determine the relative cost-effectiveness of the agents within the TZD class.

1) The first CMA evaluated the agents based on their total weighted average cost per day of treatment, which was derived from their submitted prices for UF condition sets (1 of 1 TZD agent on the UF or 1 of 2 TZD agents on the UF) and their utilization history. The results of this analysis revealed that pioglitazone was more cost-effective compared to rosiglitazone for a 1 of 1 position on the UF, whereas rosiglitazone was more cost-effective compared to pioglitazone for a 1 of 2 position on the UF.

2) The second CMA evaluated the agents under various UF scenarios which placed one or more agents on the UF. In this analysis, all viable UF scenarios were considered. The various UF scenarios were evaluated on their projected post-decision total weighted average cost per day of treatment. The results of this analysis showed that the UF scenario that included both agents on the UF to be the most cost-effective.

To account for other factors and costs associated with a UF decision (market share migration, switch costs, non-formulary cost shares, and medical necessity processing fees), a budget impact analysis was performed. The goal of the budget impact analysis (BIA) was to assist the Committee in determining which group of TZDs best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS.

Cost Effectiveness Conclusion – Based on the BIA results and other clinical and cost considerations, the Committee agreed that the UF scenario that included both of the TZD agents and their associated combination products on the UF best achieved this goal when compared to other more restrictive alternative UF scenarios, and thus was determined to be more cost-effective relative to other UF scenarios. The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 1 abstention, 0 absent) to accept the TZD cost analysis presented by the PEC. The P&T Committee concluded that the UF scenario that maintained rosiglitazone, pioglitazone, rosiglitazone/metformin,

pioglitazone/metformin, and rosiglitazone/glimepiride on the UF was the most cost effective UF scenario considered.

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the TZD agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 1 abstention, 1 absent) to recommend that rosiglitazone, pioglitazone, rosiglitazone/metformin, pioglitazone/metformin, and rosiglitazone/glimepiride be maintained as formulary on the UF and that no agents from this class be classified as non-formulary under the UF.

C. TZD Medical Necessity Criteria – Since no agents were recommended for non-formulary status under the UF, establishment of medical necessity criteria is not applicable.

D. TZD UF Implementation Period – Since no agents were recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

E. TZD Basic Core Formulary (BCF) Review and Recommendations – The P&T Committee had previously determined that no more than one parent TZD, with or without its associated combinations, should be added to the BCF based on the clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that rosiglitazone and rosiglitazone/metformin be maintained on the BCF. The Committee did not recommend addition of rosiglitazone/glimepiride to the BCF.

COMMITTEE ACTION – The P&T Committee voted (13 for, 1 opposed, 3 abstention, 0 absent) to recommend retaining rosiglitazone and rosiglitazone/metformin as the BCF selections in this class. The Committee did not recommend addition of rosiglitazone/glimepiride to the BCF.

8. HISTAMINE-2 (H2) ANTAGONISTS AND OTHER GASTROINTESTINAL (GI) PROTECTANTS

This drug class is comprised of the four H2 receptor antagonists (H2 antagonists), ranitidine (Zantac, generics), cimetidine (Tagamet, generics), famotidine (Pepcid, generics), and nizatidine (Axid, generics); the prostaglandin analog misoprostol (Cytotec, generics); and the mucosal protectant sucralfate (Carafate, generics). These six drugs have been marketed for several years, and all are available in generic formulations. This drug class accounted for $10.9 million dollars in FY 2005, and is ranked approximately 75th in MHS drug class expenditures. More than 440,000 prescriptions for these medications are filled annually in the MHS, based on prescription data from July 2005 to June 2006.

A. H2 Antagonists & Other GI Protectants Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the H2 antagonists and other GI protectant agents. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR, 199.21 (e)(1).

1) Efficacy

- *H2 Antagonists and GI Indications* – All four of the H2 antagonists have been

shown in numerous clinical trials to reduce gastric acid pH, particularly after a meal. They are all effective when used before meals to reduce reflux symptoms associated with food or exercise. Although largely replaced by proton pump inhibitors (PPIs) in clinical practice, H2 antagonists may still play a role in the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease, and *H. pylori* infections. A 1997 drug class review conducted by the Department of Veterans Affairs, as well as the 1999 American College of Gastroenterology guidelines for the treatment of GERD, concluded that, although there are differences in the potency, duration of action and onset of action, H2 antagonists may be used interchangeably at equivalent doses. A search of the literature since 1999 yields little additional clinical literature concerning the H2 antagonists and does not change this conclusion.

- *H2 Antagonists and Non-GI Indications* – Cimetidine is distinct from the other H2 antagonists in that it has evidence to support use in non-GI conditions based both on its histamine-blocking characteristics and its apparent immunomodulating effects. Non-GI uses for cimetidine are numerous, and include treatment of chronic idiopathic urticaria, adjunctive treatment of cancer or herpes virus infections, and intermittent porphyria.
- *Sucralfate* – Sucralfate does not affect gastric acid pH, but is thought to act by forming a non-absorbable physical barrier over mucosal ulcerations. At least ten clinical trials addressing the treatment of both gastric and duodenal ulcers (all conducted in the 1980s) reported similar healing rates with sucralfate compared to cimetidine or ranitidine. Overall, sucralfate appears to be as effective and safe as the H2 antagonists for treating duodenal and gastric peptic ulcers, but it is only approved for treating duodenal ulcers. One landmark clinical trial comparing intravenous (IV) ranitidine with nasogastric sucralfate reported benefits for use in stress ulcer prophylaxis in the intensive care setting, where it may offer an advantage over IV use of the H2 antagonists, due to a reduced potential for development of aspiration pneumonia. Sucralfate should be reserved for mild cases of esophagitis only. As with the H2 antagonists, the popularity of sucralfate has diminished due to availability of PPIs.
- *Misoprostol* – Misoprostol is a synthetic prostaglandin analog that inhibits gastric acid secretion by directly stimulating parietal cells. It also appears to function as a mucosal protective agent. The drug is effective as an adjunctive medication to reduce GI events associated with non-steroidal anti-inflammatory drug (NSAID) use, and has been shown to significantly reduce the risk of NSAID-associated serious GI complications and symptomatic ulcers by about 40-60%. Non-GI (off-label) uses of misoprostol are primarily gynecological in nature. A review of MHS utilization patterns, based on quantities dispensed and the age and gender of patients receiving misoprostol, confirms that the overwhelming majority of misoprostol usage in DoD is for treatment of GI conditions.

2) *Safety and Tolerability*

- *H2 Antagonists* – There are no major differences between the four H2 antagonists with respect to safety and tolerability, with the exception of a greater potential for

drug interactions with cimetidine. Cimetidine inhibits cytochrome P450 enzymes, and is associated with several clinically significant drug interactions when administered concomitantly with other drugs metabolized via the CYP450 pathway, including theophylline, phenytoin, quinidine, nifedipine, amitriptyline, and warfarin. Labeling for all four H2 antagonists contains warnings concerning an association of H2 antagonist use with necrotizing enterocolitis in the fetus or neonate. All four are associated with minor complaints of nausea, vomiting, diarrhea or constipation.

- *Sucralfate* – The major safety concern with sucralfate is the risk of seizures due to aluminum absorption in patients with impaired renal function. There are reports of bezoar development in patients with gastroparesis. Constipation develops in about 3% of patients receiving sucralfate, and complaints of metallic taste and diarrhea are frequent. The aluminum component of sucralfate may interact with antacids.
- *Misoprostol* – A Cochrane review addressing adverse events found that significantly more patients receiving misoprostol vs. placebo withdrew from therapy due to adverse effects, primarily diarrhea, abdominal pain, and nausea [Rostom 2004]. Diarrhea occurs in 13% to 40% of patients. It is dose-related, occurs early in treatment, usually resolves with continued treatment, and can be minimized with administration with meals and at bedtime and avoidance of magnesium-containing antacids. Abdominal pain is reported in 7% to 20% of patients. Misoprostol is rated pregnancy category X, and is contraindicated in women of child-bearing age unless the benefits exceed the risks.

3) *Other Factors*

- *Dosing* – The four H2 antagonists exhibit minor differences in potency, duration of action, onset of action, and frequency of dosing. Cimetidine requires twice daily to four times daily dosing, while the remaining three H2 antagonists can be dosed once to twice daily.
- *Available formulations* – All four H2 antagonists are available in tablet and liquid dosage formulations. The available dosage formulations for sucralfate include a tablet and oral suspension, while misoprostol is only available in a tablet. Ranitidine is also available in a gel-filled capsule, granule, and effervescent tablet.
- *Utilization* – Of the six drugs included in the class, the H2 antagonists account for over 90% of the prescriptions written in the MHS for this drug class. Ranitidine is the most widely prescribed H2 antagonist in the MHS, accounting for 67% of all H2 antagonist prescriptions, followed by famotidine (22%), cimetidine (8%) and nizatidine (3%).
- *Pediatrics* – Ranitidine and famotidine are indicated for use in children as young as two years of age; nizatidine is indicated in children older than 11 years, and cimetidine is indicated for use in children older than 15 years of age.
- *Pregnancy* – The four H2 antagonists and sucralfate are rated as pregnancy category B. Misoprostol is rated as pregnancy category X.

Overall Clinical Effectiveness Conclusion - The Committee concluded that:

1) The four H2 antagonists ranitidine, cimetidine, famotidine, and nizatidine are widely considered interchangeable for treatment of GERD, peptic ulcer disease and *H. pylori* infections, despite differences in potency, duration of action, and onset of action.
2) Compared to the other three H2 antagonists, cimetidine has evidence for use in non-gastrointestinal conditions.
3) Ranitidine is the most widely used H2 antagonist across the MHS, is dosed once or twice daily, has a low potential for drug interactions, and is available in an oral syrup for pediatric patients.
4) Famotidine and nizatidine have similar dosing intervals, drug interaction profiles and formulations as ranitidine, but are less frequently prescribed in the MHS.
5) Cimetidine is more difficult to use clinically compared to the other three H2 antagonists due to its need for multiple daily dosing (BID-QID) and drug interaction profile.
6) Misoprostol serves a unique niche for use in high risk patients for NSAID-induced ulcers, despite its adverse effect profile and warnings in women of child bearing age.
7) Sucralfate has a unique mechanism of action (physical barrier formation) and offers an alternative to PPIs and H2 antagonists for stress ulcer prophylaxis.

COMMITTEE ACTION – The P&T Committee voted (16 for, 0 opposed, 0 abstained, 0 absent) to accept the clinical effectiveness conclusions stated above.

B. H2 Antagonists & Other GI Protectants Relative Cost Effectiveness

In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 CFR 199.21(e)(2).

A simple cost analysis was employed to assess the relative cost-effectiveness of the agents within the H2 antagonist/GI protective therapeutic class. The agents within this class were evaluated on their weighted average cost per unit. The results of the cost analysis showed ranitidine to be the most cost effective H2 antagonist. A sole source joint DoD/VA contract is currently in place for ranitidine. The other generic H2 antagonists were shown to have similar relative cost-effectiveness compared to ranitidine, with the exception of nizatidine. Not surprisingly, nizatidine was found to be slightly more costly compared to the other generic H2 antagonists, since a generic version has only recently become available. In regards to misoprostol and sucralfate, both of these agents are available in generic versions and have a niche place in therapy for select patients.

Conclusion – The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 1 abstention, 0 absent) to accept the H2 antagonists and other

GI protectants cost analysis presented by the PEC. The P&T Committee concluded that the H2 antagonists ranitidine, cimetidine, famotidine and nizatidine; the prostaglandin analog misoprostol; and the mucosal protective agent sucralfate should be maintained on the UF.

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the H2 antagonists and other GI protectants, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend that the H2 antagonists ranitidine, cimetidine, famotidine and nizatidine; the prostaglandin analog misoprostol; and the mucosal protective agent sucralfate should be maintained on the UF and that no agents from this class be classified as non-formulary under the UF.

C. H2 Antagonists & Other GI Protectants Medical Necessity Criteria – Since no agents were recommended for non-formulary status under the UF, establishment of medical necessity criteria is not applicable.

D. H2 Antagonists & Other GI Protectants UF Implementation Period – Since no agents were recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

E. H2 Antagonists & Other GI Protectants BCF Review and Recommendations – The P&T Committee had previously determined that one or more agents in this class should be considered for addition to the BCF. Currently, ranitidine (Zantac, generics) is on the BCF, with the effervescent tablet and gel-filled capsule formulations specifically excluded. The committee agreed that ranitidine should remain on the BCF. Since the gel-filled capsule and effervescent tablet dosage formulations were shown to be 19 to 64 times more costly per unit than generic ranitidine without offering any substantial increase in clinical effectiveness, the P&T Committee agreed that the gel-filled capsule and effervescent tablet formulations should continue to be excluded from the BCF.

COMMITTEE ACTION – The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to recommend retaining ranitidine as the BCF selection in this class, excluding the effervescent tablet and gel-filled capsule formulations.

9. ANTILIPIDEMIC AGENTS 1 DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the Antilipidemic Agents I (LIP-1) agents. This class is currently ranked number one in the MHS with drug class expenditures exceeding $595 million annually. On average, during a twelve month period from July 2005 and ending June 2006, there were approximately 975,000 unique utilizers per quarter. Individual drugs in the LIP-1 class are listed below:

- *Statins*. atorvastatin (Lipitor), fluvastatin (Lescol), fluvastatin extended release (Lescol XL), lovastatin (Mevacor, generics), lovastatin extended release(Altoprev), pravastatin (Pravachol, generics), rosuvastatin (Crestor, generics), and simvastatin (Zocor, generics)
- *Statin combination products*. atorvastatin/amlodipine (Caduet), lovastatin/niacin extended release (Advicor), and ezetimibe/simvastatin (Vytorin)

- *Add-on therapies:* niacin immediate release (Niacor), niacin extended release (Niaspan), and ezetimibe (Zetia)

A. LIP-1 Relative Clinical Effectiveness Review:

Information regarding the safety, effectiveness, and clinical outcomes of the LIP-1 agents was considered. The Committee's review focused primarily on the agents' ability to lower LDL concentrations, to raise HDL concentrations, and to reduce clinical outcomes including all-cause mortality, cardiovascular mortality, myocardial infarction (MI), stroke, and need for revascularization. Differences in the agents' effect on triglyceride concentrations, and benefits in treating non-cardiovascular conditions were not assessed in detail. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1).

1) Efficacy for %LDL lowering and %HDL raising

Endpoints: The differences between the statins in terms of %LDL lowering and %HDL raising were assessed. Elevated LDL concentrations and low HDL concentrations are both strong independent risk factors of CHD.

%LDL Lowering:

- The primary action of the statins is to reduce elevated LDL concentrations, which is the main target of cholesterol-lowering therapy recommended by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines. LDL reduction occurs in a dose-dependant fashion with the statins. However, increasing a statin dose provides only an additional 5 to 6% LDL lowering.
- Data obtained from the individual statin product labeling and clinical trials was used to compare differences in the agents' ability to lower LDL. The statins were divided into two groups: the low to moderate group can achieve ≤45% LDL lowering, and the intensive group can achieve >45% LDL lowering. (See Appendix E)
- The following statins are considered low to moderate %LDL lowering statins: all doses of fluvastatin, fluvastatin extended release, pravastatin, lovastatin, lovastatin extended release, atorvastatin 10 and 20 mg (as well as corresponding Caduet doses which include atorvastatin 10 or 20 mg), simvastatin 10, 20, and 40 mg, ezetimibe/simvastatin 10/10 mg, and rosuvastatin 5 mg.
- The following statins are considered intensive %LDL lowering statins: atorvastatin 40 and 80mg (as well as corresponding Caduet doses which include atorvastatin 40 and 80 mg), rosuvastatin 10, 20, and 40 mg, simvastatin 80 mg, and ezetimibe/simvastatin 10/20, 10/40, and 10/80 mg.
- When equipotent doses are used, the statins achieve similar %LDL lowering (e.g., atorvastatin 20 mg, simvastatin 40 mg and ezetimibe/simvastatin 10/10 mg all attain 41 to 45% LDL lowering). Rosuvastatin 40 mg and ezetimibe/simvastatin 10/80 mg are the only statins capable of attaining >55% LDL lowering.
- Based on a previous model constructed by the PEC that evaluated National Health and Nutrition Examination Survey data, 80 to 85% of the DoD population

requiring a statin is expected to attain their LDL goal on simvastatin doses ≤40mg. Simvastatin is the highest utilized statin in the DoD. (See Figure 1).

%HDL Raising:

- The primary clinical use of the statins is to reduce elevated LDL concentrations; however beneficial effects on HDL are also seen.
- Evidence from published trials and product labeling support the conclusion that HDL generally rises in a dose-dependent fashion, however all statins show a plateau and drop-off of HDL raising effect as the highest doses are approached. For example, atorvastatin 20 mg, simvastatin 40 mg and ezetimibe/simvastatin 10/10 mg can achieve an 8 to 9% increase in HDL concentrations, but at doses of atorvastatin 80 mg and ezetimibe/simvastatin 10/40 mg, only achieve a 5-6% increase in HDL.
- The Committee commented that other drugs that primarily target HDL are available (e.g., niacin, fibrates, bile acid resins), and that providers should choose a drug other than a statin if the primary goal is to raise HDL concentrations. Currently the most potent option for raising HDL is niacin.

2) *Efficacy for clinical outcomes:*

Endpoints: The main clinical endpoints used to evaluate differences in statin efficacy include all-cause mortality, cardiovascular mortality, MI, stroke, and need for revascularization. Numerous clinical trials have shown the benefits of statin therapy on reducing cardiovascular events. However, differences in clinical outcomes between the statins are difficult to compare, due to widely varying patient populations evaluated, vaguely defined endpoints, and comparison of non-equipotent statin doses.

Meta-analyses:

- There are no head-to-head trials comparing equivalent doses of statins that evaluate differences in mortality or other clinical outcomes. One meta-analysis (Zhou 2006) evaluated the differences between low to moderate doses of atorvastatin, simvastatin, and pravastatin in reducing mortality or cardiovascular events. Eight clinical trials (comprising both primary and secondary prevention trials) met the criteria for inclusion in the analysis. An adjusted indirect comparison was calculated.
- For all comparisons between the three statins (e.g., atorvastatin vs. pravastatin, atorvastatin vs. simvastatin, and simvastatin vs. pravastatin), there was no significant difference between the drugs in all-cause mortality, major coronary events (fatal CHD and nonfatal MI), cardiovascular death (coronary and cerebrovascular death), and major cardiovascular events (stroke); ($p>0.05$ for all comparisons).

Efficacy for primary prevention of CHD: Primary prevention trials consist of patients without clinically evident CHD. Beneficial effects on clinical outcomes for primary prevention of CHD have been noted with atorvastatin 10 mg (ASCOT-LLA and CARDS trials), lovastatin 20 to 40 mg (AFCAPS, TexCAPS trials), pravastatin 40 mg (WOSCOPS), and simvastatin 40 mg (HPS).

Efficacy for secondary prevention of CHD: Secondary prevention trials include patients with pre-existing cardiovascular disease, such as prior MI, or prior revascularization procedures. In trials assessing the secondary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin 10 to 80 mg (GREACE, TNT), lovastatin 40 to 80 mg (CABG), pravastatin 40 mg (LIPID, CARE), simvastatin 20 to 40 mg (4S), and fluvastatin 40 mg (administered bid) (LIPS).

- TNT: In the Treat to Target (TNT) trial, low dose atorvastatin 10 mg was compared to intensive dose atorvastatin 80 mg for 5 years in 10,000 patients with stable CHD. Intensive dose atorvastatin 80 mg was associated with significantly fewer patients reaching the primary composite outcome (which included non-fatal MI) vs. atorvastatin 10 mg (28.1% vs. 33.5%, p<0.001). There was no benefit of intensive dose atorvastatin when mortality was assessed as a single endpoint. The main conclusion was that reducing LDL to <100 mg/dL yielded incremental clinical benefits.
- IDEAL: In the Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) trial, intensive dose atorvastatin 80 mg was compared to low to moderate dose simvastatin 20 to 40 mg. In contrast to TNT, intensive dose atorvastatin did not show a benefit in the primary composite endpoint (CHD death, hospitalized non-fatal MI, resuscitated cardiac arrest); (9.3% of atorvastatin patients reached the primary endpoint, vs. 10.4% of simvastatin patients; p=0.07).

Efficacy for ACS: A subgroup of secondary prevention trials focuses on ACS patients who can experience unstable angina and myocardial ischemia due to severe atherosclerotic plaque progression.

- PROVE-IT:
  - In the Pravastatin or Atorvastatin Evaluation and Intensive Therapy (PROVE-IT) trial, moderate dose pravastatin 40 mg was compared to intensive dose atorvastatin 80 mg for two years in over 4,000 recently hospitalized (< 10 days) patients with ACS. Significantly fewer patients receiving intensive dose atorvastatin 80 mg reached the primary composite endpoint (all cause death, MI, unstable angina requiring hospitalization, stroke) than moderate dose pravastatin 40 mg (22.4% vs. 26.3%, p=0.005).
  - The PROVE-IT trial provides evidence for immediate use of intensive dose statin in ACS patients. Additionally, a goal LDL <70 mg/dL should be considered in this population, as the ending mean atorvastatin LDL was 62 mg/dL vs. 95 mg/dL with pravastatin 40 mg.
  - It is unknown whether the beneficial results seen in the PROVE-IT trial would be duplicated if an intensive dose statin other than atorvastatin were evaluated, as no such studies have been published.
- PACT: In the Pravastatin in Acute Treatment (PACT) trial, pravastatin 20 to 40 mg did not show a reduction in coronary events vs. placebo, however statin administration was delayed for 24 hours and the trial duration was only 4 weeks.

- A to Z: In the Aggrastat to Zocor (A to Z) trial, no statistically significant reduction in coronary events was shown after 2 years in 4,000 ACS patients receiving early initiation (after one month) intensive dose simvastatin 40 to 80 mg vs. delayed initiation (after four months) of low dose simvastatin 20 mg. The long delay in statin administration, and not the individual statin evaluated, likely contributed to the negative results.

Rosuvastatin and ezetimibe/simvastatin: There are no published trials assessing the benefits of rosuvastatin on clinical outcomes; one large trial (JUPITER) is in progress. While there are no clinical trials specifically assessing the ezetimibe/ simvastatin formulation, there is evidence for clinical benefits of the simvastatin component from the Scandinavian Simvastatin Survival Study (4S) and Heart Protection Study (HPS) trials. There is no evidence to suggest that addition of ezetimibe to simvastatin would negate the clinical benefits of the simvastatin component.

3) *Safety and Tolerability*

Minor Adverse Events: The statins show similar common adverse event profiles. Data from the package insert suggests that the there is no evidence that minor adverse events (GI disturbances, headaches, rash, itching) are less likely to occur with one statin vs. another. These adverse effects appear dose-related.

Serious Adverse Events: The P&T Committee specifically focused on three main areas, elevated liver transaminases, proteinuria, and myotoxicity.

- Elevations in liver transaminases
  - Transient elevations of aspartate aminotransferase and alanine amino-transferase (AST/ALT) to greater than three times the upper limit of normal (ULN) can occur with all the statins. The incidence of elevations in transaminases with all the statins ranges from 0.3 to 3%, according to data from statin package inserts.
  - Increases in liver transaminases are more likely to occur with intensive dose statins vs. low to moderate dose statins. No evidence suggests that one statin is less likely than another to cause increased liver transaminases. There is no data to date that suggest elevations in ALT or AST are predictive of liver injury or long term hepatotoxicity.
- Proteinuria:
  - A retrospective analysis conducted by the FDA using preclinical NDA submissions reported that rosuvastatin 40 mg was associated with a 4 to 5% incidence of proteinuria. This was higher than the incidence reported with rosuvastatin doses $\leq$20 mg (1 to 4%), atorvastatin 10 to 80 mg (0.4% to 2%), simvastatin 20 to 80 mg (0.6% to 4%), or pravastatin 20 to 40 mg (0 to 1%). Limitations to this analysis include the use of spot urine dipstick testing rather than 24-hour urine collections, and the inclusion of data from both open label and placebo-controlled trials.

- Currently there are no requirements for monitoring of renal function with any of the statins. Due to the insufficient and poor quality evidence available at this time, it cannot be determined whether the incidence of proteinuria differs between the statins.

- Myotoxicity:
  - Varying definitions of the terms myotoxicity, myopathy, myalgia, myositis, and rhabdomyolysis make interpretation of the literature difficult. Rhabdomyolysis (symptoms of muscle pain accompanied by increased creatine kinase >10 times ULN, increased serum creatine and brown colored urine) occurs rarely with all the statins. Muscle symptoms with the statins appear to be dose related, and the intensive dose statins should be used with caution in patients at increased risk of myotoxicity.
  - One meta-analysis [CTTC 2004] reported an overall low incidence of rhabdomyolysis with simvastatin, pravastatin, lovastatin and fluvastatin that did not differ from placebo (0.023% with the statins vs. 0.015% with placebo).
  - Rosuvastatin was associated with an incidence rate of rhabdomyolysis two times higher than that of the other marketed statins after the first six months of therapy (hazard ratio 1.98; [95% CI 0.18 to 21.90] in one retrospective cohort study of health claims. [McAfee 2006]. This result was not statistically significant. The analysis excluded cerivastatin (Baycol), as it was removed from the market in 2001 due to a high risk of rhabdomyolysis.
  - Spontaneous adverse event reporting data from the FDA uses a reporting rate (number of spontaneous case reports for rhabdomyolysis per 1 million US prescriptions) instead of an incidence rate to determine differences in myotoxicity between the statins.
    - Cerivastatin had the highest reporting rate of rhabdomyolysis (72.88 per 1 million US prescriptions) based on data from the years 1988 to 2000 were analyzed, while it was still marketed.
    - Data from 2002 to 2004 show that the reporting rate of rhabdomyolysis is higher with rosuvastatin at 13.54 reports per 1 million prescriptions, compared to simvastatin (8.71), fluvastatin (3.44), lovastatin (2.76), atorvastatin (1.67) and pravastatin (1.63).
    - Limitations to the FDA reporting system include the lack of a control group, reliance on spontaneous reports which may not reflect the true incidence of an adverse event, and the low overall occurrence of rhabdomyolysis. FDA reporting rates are more useful to signal a trigger of concern, rather than to quantify relative risks between different drugs in a class.
    - Despite the differences between rosuvastatin and the other marketed statins in terms of reporting rates and incidence rates of myotoxicity, definitive conclusions cannot be drawn. However, concerns remain with rosuvastatin, particularly at intensive doses.

Drug interactions: Fluvastatin, pravastatin, and rosuvastatin have the most favorable drug-drug interaction profiles as they are not appreciably metabolized via the CYP3A4 system. Atorvastatin, lovastatin, and simvastatin do undergo CYP3A4 metabolism, which results in concerns of drug-drug interactions with amiodarone, diltiazem, "azoles", and other 3A4 metabolized drugs.

Special populations: Fluvastatin, pravastatin, and rosuvastatin are preferred in patients with renal or hepatic insufficiency, in HIV/AIDS patients, or in recipients of solid organ transplants, as they are not metabolized via the CYP3A4 system. These patient groups represent about 2 to 3% of the 9 million DoD beneficiaries.

Pediatrics: Pravastatin is approved by the FDA for use in children as young as 8 years old. Atorvastatin, simvastatin, and lovastatin are approved for use in children as young as 10 years with heterozygous familial hypercholesterolemia, a rare condition.

Pregnancy: All the statins are rated Pregnancy Category X, due to the risk of fetal malformations.

Tolerability: There is insufficient evidence to determine whether one statin is less tolerable than another due to a lack of meta-analyses or retrospective claims data evaluating this outcome and the varying results reported in head-to-head trials.

4) *Other Factors:*

Dosing titration and initiation: The statins can be initiated at maximum doses, with the exception of rosuvastatin 40 mg. Rosuvastatin 40 mg should only be initiated in patients failing to reach target LDL goals with rosuvastatin 20 mg.

Pleiotropic effects: The majority of the observational data suggesting pleiotropic benefit (e.g., beneficial effects other than LDL lowering) with the statins rests with atorvastatin. None of the pleiotropic markers (e.g., C-reactive protein,) have been shown consistently in randomized trials to cause CHD. There is insufficient evidence to determine the clinical applicability of differences between the statins in terms of pleiotropic effects.

Markers of atherosclerotic progression: Rosuvastatin 40 mg was shown to cause plaque regression in the ASTEROID trial, and atorvastatin 80 mg was shown to slow the progression of plaque formation in the REVERSAL trial; both trials used intravascular ultrasound. Benefits on carotid intima media thickness have been shown with all the statins, except for rosuvastatin for which there is no published study.

5) *Efficacy and safety of ezetimibe:*

- Ezetimibe lowers LDL by a mechanism distinct from that of the statins, as it inhibits absorption of dietary cholesterol.
- Use of ezetimibe as monotherapy attains 15 to 19% LDL lowering and provides a treatment option for patients who are at risk for statin adverse events. Use of ezetimibe in combination with low to moderate statin doses provides greater LDL lowering (12 to 20% LDL lowering) vs. increasing the statin dose alone (5 to 6% LDL lowering).

- The combination of ezetimibe with a statin can be used to reach target LDL goals when statin monotherapy has failed, or to avoid the potential risks with using intensive statin doses as monotherapy.
- The proven benefits of cardiovascular outcomes seen with the statins have yet to be duplicated with ezetimibe, as there are no published trials.
- The most common adverse events with ezetimibe are abdominal pain, diarrhea and headache. The risk of elevations in liver transaminases is slightly increased when ezetimibe is combined with a statin (1.3 to 2%) vs. using statin monotherapy (0.4%). To date, there are only rare case reports of myotoxicity and rhabdomyolysis.
- Current MHS utilization and provider opinion support the need for ezetimibe in the MHS.

6) *Efficacy and safety of ezetimibe/simvastatin:*
   - The combination of simvastatin with ezetimibe provides additional efficacy for LDL lowering.
   - Doses of ezetimibe/simvastatin greater than 10/20 mg provide 45% to more than 55% LDL lowering, allowing a treatment option in those 15 to 20% of DoD patients unable to meet goal LDL with simvastatin alone.
   - The efficacy profile of ezetimibe/simvastatin reflects that of the individual components.
   - To date, no clinically important increases in safety issues, such as risk of liver transaminase elevation or myotoxicity have been reported.
7) *Efficacy and safety of niacin*
   - Niacin is FDA-approved to raise HDL (along with fibrates). Niacin can raise HDL by 25%, and can be used as monotherapy or in combination with other drugs.
   - Clinical outcomes including reduced stroke, MI, and all-cause mortality have been reported with niacin.
   - The formulation of niacin extended release is associated with a reduced risk of GI adverse events and hepatotoxicity compared to niacin immediate release or over the counter forms of long-acting niacin (Slo-Niacin).
   - The risk of myotoxicity and drug-drug interactions is reduced when niacin is used in combination with a statin, vs. using the combination of fibrates with a statin.
   - The benefits of niacin extended release are limited to those patients who can tolerate the associated adverse effects (flushing and GI disturbances).
8) *Clinical issues with lovastatin/niacin extended release, atorvastatin/amlodipine, lovastatin extended release, and fluvastatin extended release*
   - Lovastatin/niacin extended release is difficult to initiate and titrate, since it is available in a fixed dose formulation.

- Atorvastatin/amlodipine contains a statin in combination with the dihydropyridine calcium channel blocker amlodipine. Amlodipine (Norvasc) was designated non-formulary under the UF in August 05. No outcomes trials have specifically assessed the benefits of the fixed dose Caduet formulation, and there is no evidence to suggest improved adherence or additional LDL lowering with the combination.
- Lovastatin extended release does not offer additional LDL lowering or safety benefits over lovastatin. Unlike lovastatin, lovastatin extended release is available in a 60 mg tablet, but does not attain a >45% LDL lowering.
- Fluvastatin extended release has proven benefits from one trial assessing revascularization (LIPS) and is a non-CYP3A4 metabolized statin. However, it does not offer additional benefits over fluvastatin immediate release and does not attain a >45% LDL lowering.
- Overall, these drugs do not offer additional clinical benefits over the other antilipidemic agents and have low utilization in the MHS (<5,000 Rxs/month dispensed).

9) A survey of MTF providers, including cardiologists, was overwhelmingly in support of simvastatin for treating the 80-85% of MHS patients requiring LDL lowering <45%, and also supported use of ezetimibe. Providers were also concerned with the safety profile of rosuvastatin.

Overall Clinical Effectiveness Conclusion – The Committee concluded that:

1) Across equipotent doses, the statins achieve similar %LDL lowering, with rosuvastatin\40 mg and ezetimibe/simvastatin 10/80 mg as the only statins capable of attaining LDL lowering >55%.
2) Across equipotent doses, the statins achieve similar %HDL raising ability, but all statins show a plateau and drop-off of HDL raising effect at increasing doses.
3) There are no head-to-head trials comparing equivalent doses of statins that evaluate clinical outcomes for reducing mortality or other clinical outcomes (e.g., myocardial infarction, stroke, need for revascularization).
4) In low to moderate doses, the effects of atorvastatin, pravastatin and simvastatin appear similar for long-term cardiovascular protection, based on one meta-analysis (Zhou 2006).
5) In trials assessing the primary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin 10 mg, lovastatin 20 to 40 mg, pravastatin 40 mg, and simvastatin 40 mg.
6) In trials assessing the secondary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin 10 to 80 mg, lovastatin 40 to 80 mg, pravastatin 40 mg, simvastatin 20-40 mg, and fluvastatin 40 mg (administered BID).

7) In one trial assessing acute coronary syndrome (ACS) patients, beneficial effects on clinical outcomes were noted with atorvastatin 80 mg when it was compared to pravastatin 40 mg (PROVE-IT 2004).

8) There are no published trials assessing the benefits of rosuvastatin on clinical outcomes.

9) There is no evidence that increases in liver function tests (ALT) or minor adverse events (GI disturbances, headaches, rash, itching) are less likely to occur with one statin vs. another, and these adverse effects are dose-related.

10) Concerns of proteinuria and myotoxicity remain with rosuvastatin; the overall incidence of rhabdomyolysis occurs rarely with statins.

11) Fluvastatin, pravastatin, and rosuvastatin have the most favorable drug-drug interaction profiles,

12) There is insufficient evidence to determine whether one statin is less tolerable than another.

13) In terms of other factors, the statins can be initiated at maximum doses, with the exception of rosuvastatin 40 mg.

14) There is insufficient evidence to determine the clinical applicability of differences between the statins in terms of pleiotropic effects or effects on markers of atherosclerotic progression (intravascular ultrasound or carotid intima media thickness).

15) Ezetimibe offers an additional 15-20% LDL lowering by a mechanism distinct to that of the statins, but has not yet been evaluated for clinical outcomes.

16) Ezetimibe/simvastatin provides added efficacy in terms of LDL lowering and has a safety and efficacy profile reflecting that of its two individual components.

17) Niacin extended release is required in the MHS as its primary benefit is to raise HDL by 25%.

18) Lovastatin/niacin extended release, atorvastatin/amlodipine, lovastatin extended release, and fluvastatin extended release do not offer additional clinical benefits over the other LIP-1 agents and have low utilization in the MHS (<5,000 Rxs/month dispensed).

19) A survey of MTF providers, including cardiologists, was overwhelmingly in support of simvastatin for treating the 80-85% of MHS patients requiring LDL lowering ≤45%, and also supported use of ezetimibe.

20) Based on clinical issues alone, none of the LIP-1 agents are sufficiently less effective than the others agents within the class to be classified as non-formulary.

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

B. LIP-1 Relative Cost Effectiveness

The P&T Committee evaluated the relative cost-effectiveness of the LIP-1 agents in relation to the effectiveness, 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). A series of cost-effectiveness analyses were used to determine the relative cost-effectiveness of agents within the LIP-1 therapeutic class.

For the high % LDL lowering agents (>45%, intensive) in the LIP-1 class (atorvastatin 40 and 80 mg; rosuvastatin 10, 20, and 40 mg; ezetimibe/simvastatin 10/20, 10/40, and 10/80 mg; and simvastatin 80 mg), four separate cost-effectiveness models were constructed.

1) The Annual Cost per 1% LDL Decrease model compared the cost-effectiveness of the high % LDL lowering agents on annual cost per 1% LDL decrease using a decision analytical model.
2) The Annual Cost per Patient Treated to Goal model compared the cost-effectiveness of these agents on annual cost per patient successfully treated to NCEP goal using a Monte Carlo simulation model.
3) The Medical Cost Offset Model compared the cost-effectiveness of these agents based on their predicted outcomes and total predicted health care expenditures for CHD and CHD risk-equivalent patients.
4) The Cost per Event-Free Patient model, based on the results of the IDEAL Trial, compared the cost-effectiveness of the agents included in that trial – high-dose (80mg) atorvastatin (Lipitor) vs. low-dose (20-40 mg) simvastatin – using a decision analytic model.

The results of the first three cost-effectiveness analyses showed ezetimibe/simvastatin (Vytorin) to be the most cost effective high % LDL lowering agent. The results of the fourth analysis revealed that high-dose (80 mg) atorvastatin was more effective but considerably more costly compared to low dose (20-40mg) simvastatin. The results of this analysis support use of high dose atorvastatin only in patients who cannot be successfully treated to goal with simvastatin.

For the low to moderate % LDL lowering agents ($\leq$ 45%) in the LIP-1 class (simvastatin 5, 10, 20, and 40 mg, atorvastatin 10 and 20 mg; rosuvastatin 5 mg; ezetimibe/simvastatin 10/10 mg; and all strengths of pravastatin, fluvastatin, fluvastatin extended release lovastatin, lovastatin extended release, niacin/lovastatin, niacin extended release, niacin immediate release, and ezetimibe), the cost-effectiveness of the agents within this subclass was evaluated using the Annual Cost per 1% LDL Decrease model. In pharmacoeconomic terms, lovastatin, lovastatin extended release, simvastatin, and rosuvastatin were located along the cost efficiency frontier and were considered to be the optimal agents. Although these agents differed in terms of cost-effectiveness relative to each other, they were more cost-effective than (dominated) the other agents evaluated.

With respect to atorvastatin/amlodipine, an earlier review did not show additional clinical benefit for amlodipine versus other dihydropyridine CCBs. Single ingredient amlodipine (Norvasc) is non-formulary under the UF. In order to assess the cost effectiveness of atorvastatin/amlodipine, it was compared to the combination of atorvastatin and a UF dihydropyridine calcium channel blocker, based on the weighted average cost per day of therapy. The results of this analysis revealed that atorvastatin/amlodipine was

considerably more costly compared to the combination of atorvastatin and a UF dihydropyridine calcium channel blocker, regardless of point of service.

To account for other factors and costs associated with a UF decision (market share migration, switch costs, non-formulary cost shares, and medical necessity processing fees), a budget impact analysis was performed. The goal of the BIA was to assist the Committee in determining which group of high % LDL lowering LIP-1 agents best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The BIA focused on high % LDL lowering agents because 1) simvastatin could meet the vast majority of the needs of patients requiring low % LDL lowering agents; 2) some low % LDL lowering agents were considered to be clinically necessary (pravastatin, ezetimibe, and niacin extended release); and 3) of the remaining low % LDL lowering agents, nothing would be gained clinically or economically by making them non-formulary, especially considering their low market share. Based on the BIA results and other clinical and cost considerations, the Committee agreed that the UF scenario that included the high % LDL lowering agents atorvastatin and ezetimibe/simvastatin on the UF best achieved this goal when compared to other alternative UF scenarios, and thus was determined to be more cost-effective relative to other UF scenarios.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstention, and 0 absent) to accept the LIP-1 relative cost-effectiveness analysis as presented by the PEC. The P&T Committee concluded that the Uniform Formulary scenario that included atorvastatin, ezetimibe/simvastatin, and simvastatin 80 mg as the high % LDL lowering agents on the UF was the most cost effective UF scenario.

COMMITTEE ACTION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the LIP-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 1 opposed, 1 abstained, and 0 absent) to recommend that atorvastatin, fluvastatin immediate and extended release, pravastatin, simvastatin, lovastatin immediate and extended release, lovastatin/niacin, ezetimibe/simvastatin, niacin immediate and extended release, and ezetimibe be maintained as formulary on the UF and that rosuvastatin and atorvastatin/amlodipine be classified as non-formulary under the UF.

C. LIP-1 UF Medical Necessity Criteria

Based on the clinical evaluation of the LIP-1 agents, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general medical necessity criteria for rosuvastatin:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.
3) Treatment with the formulary alternatives has resulted, or is likely to result, in therapeutic failure.
4) The patient previously responded to rosuvastatin and changing to a formulary alternative would incur unacceptable clinical risk.

The P&T Committee noted that some specific situations in which rosuvastatin might be considered medically necessarily were 1) if a patient requires a high % LDL lowering agent in order to meet his or her LDL goal *and* requires a non-CYP3A4-metabolized statin due to potential drug interactions, or 2) if a patient requires a high % LDL lowering agent in order to met his or her LDL goal *and* is not able to reach that goal with any of the formulary high % LDL lowering agents. The P&T Committee also noted that criterion #4 would apply rarely, since changes in statin therapy are unlikely to present a risk of destabilization or serious adverse effects in the vast majority of patients and since rosuvastatin does not offer any significant safety advantages compared to other statins other than not being metabolized through CYP3A4.

Based on the clinical evaluation of the LIP-1 agents, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following medical necessity criterion for atorvastatin/ amlodipine:

1) Use of formulary alternatives is contraindicated.

The P&T Committee noted that the other conditions for establishing medical necessity provided for in the UF rule do not apply to atorvastatin/amlodipine since the components of this product are available as single ingredients and there is no evidence to support improved efficacy, safety, or tolerability with the combination product vs. its individual components given separately. Amlodipine, a dihydropyridine calcium channel blocker used for hypertension and coronary artery disease, has not been shown to enhance the lipid-lowering effects of atorvastatin. The P&T Committee further noted that since single ingredient amlodipine is non-formulary under the UF, the closest therapeutic alternative to atorvastatin/amlodipine on the UF would be atorvastatin or another UF statin plus a UF dihydropyridine calcium channel blocker [felodipine (Plendil, generics), nifedipine extended release (Adalat CC, Procardia XL, generics), or nisoldipine (Sular)].

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 1 absent) to approve the medical necessity criteria outlined above.

D. LIP-1 Implementation Plan:

Because of contractual considerations associated with the statin drug class affecting MTFs and TMOP, the P&T Committee recommended an effective date no sooner than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have rosuvastatin or atorvastatin/amlodipine 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) medical necessity is established. MTFs may (but are not required to) fill a prescription for non-formulary LIP-1 agents written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 opposed, 2 abstained, 0 absent) an effective date no sooner than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

E. LIP-1 BCF Review and Recommendations

The P&T Committee had previously determined that one or more low to moderate % LDL lowering agents and no more than one high % LDL lowering agent could be considered for addition to the BCF. Based on the relative clinical effectiveness and cost effectiveness of the agents and taking into account the following considerations, the P&T Committee recommended the following LIP-1 agents for BCF status:

- *Simvastatin* – Simvastatin provides LDL-lowering of up to 40 to 45% at doses ≤ 40 mg/day; can be used to treat 85% of MHS patients who require a statin; has shown proven mortality benefits in primary and secondary prevention trials [HPS; 4S]; is labeled for pediatric use in patients as young as 10 years of age; has an acceptable adverse event profile compared to other statins; and is familiar to MHS providers as evidenced by its current high utilization in the MHS.
- *Pravastatin* – Pravastatin is one of three statins not metabolized via the CYP3A4 system, which is necessary in order to avoid drug interactions in special populations *requiring* treatment with interacting medications (e.g., HIV/AIDS patients, solid organ transplant patients); has shown proven mortality benefits in primary and secondary prevention trials [WOSCOPS, CARE, LIPID]; is labeled for pediatric use in patients as young as 8 years of age; and has the highest utilization in the MHS of the three non-CYP3A4-metabolized statins.
- *Ezetimibe/simvastatin*– The combination of simvastatin and ezetimibe provides additional efficacy for LDL lowering; the 45% to more than 55% LDL lowering attainable with doses higher than 10/20 mg can be used to treat the estimated 15 to 20% of patients who cannot meet goal with simvastatin alone.
- *Niacin extended release* – Niacin is the only agent in the class that has been shown to raise HDL by 25%; has shown proven benefits for mortality, MI, and stroke [Coronary Drug Project]; and has a lower risk for GI adverse events and hepatotoxicity compared to other niacin formulations.

The Committee commented that while atorvastatin is recommended to remain on the UF, MTFs are strongly advised to avoid adding it to local formularies. Simvastatin doses of 20 to 40 mg provide similar efficacy for LDL lowering as atorvastatin but 10 to 20 mg, at a much lower cost due to generic availability. Patient migration from simvastatin to atorvastatin, particularly for patients requiring lower doses, will erode the cost-savings anticipated to occur as generic prices for simvastatin continue to decrease without providing additional clinical benefit. One possible exception to this may be ACS patients, in whom atorvastatin may be preferable based on the results of the PROVE-IT trial (for most patients, this would most likely entail use of 80 mg dose of atorvastatin, based on the lower LDL goals in this patient population).

COMMITTEE ACTION: The P&T Committee voted (15 for, 1 opposed, 1 abstained, 0 absent) to recommend simvastatin, pravastatin, ezetimibe/simvastatin and niacin extended release as the BCF selections in this drug class.

10. CLASS OVERVIEWS. ATTENTION-DEFICIT / HYPERACTIVITY DISORDER AND NARCOLEPSY MEDICATIONS; SEDATIVE HYPNOTICS I (NON-BENZODIAZEPINE SEDATIVE HYPNOTICS); SEDATIVE HYPNOTICS II

Portions of the clinical reviews for each class were presented to the Committee. The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review, and for developing the appropriate cost effectiveness models. Both the clinical and economic analyses of these three classes will be completed during the November 2006 meeting; no action necessary.

11. ADJOURNMENT

The second day of the meeting adjourned at 1600 hours on 16 August 2006. The dates of the next meeting are 14-16 November 2006.

Patricia Buss

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

List of Appendices

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

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	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 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	Pending approval	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) - excludes gelcaps and effervescent tablets	Pending approval	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	Pending approval	Pending approval
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 July 06	27 Sept 06 (60 days)
May 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 drospironone (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 July 06	24 Jan 07 (180 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 July 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 July 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)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	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 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)
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)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	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 05	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
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

ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; 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])

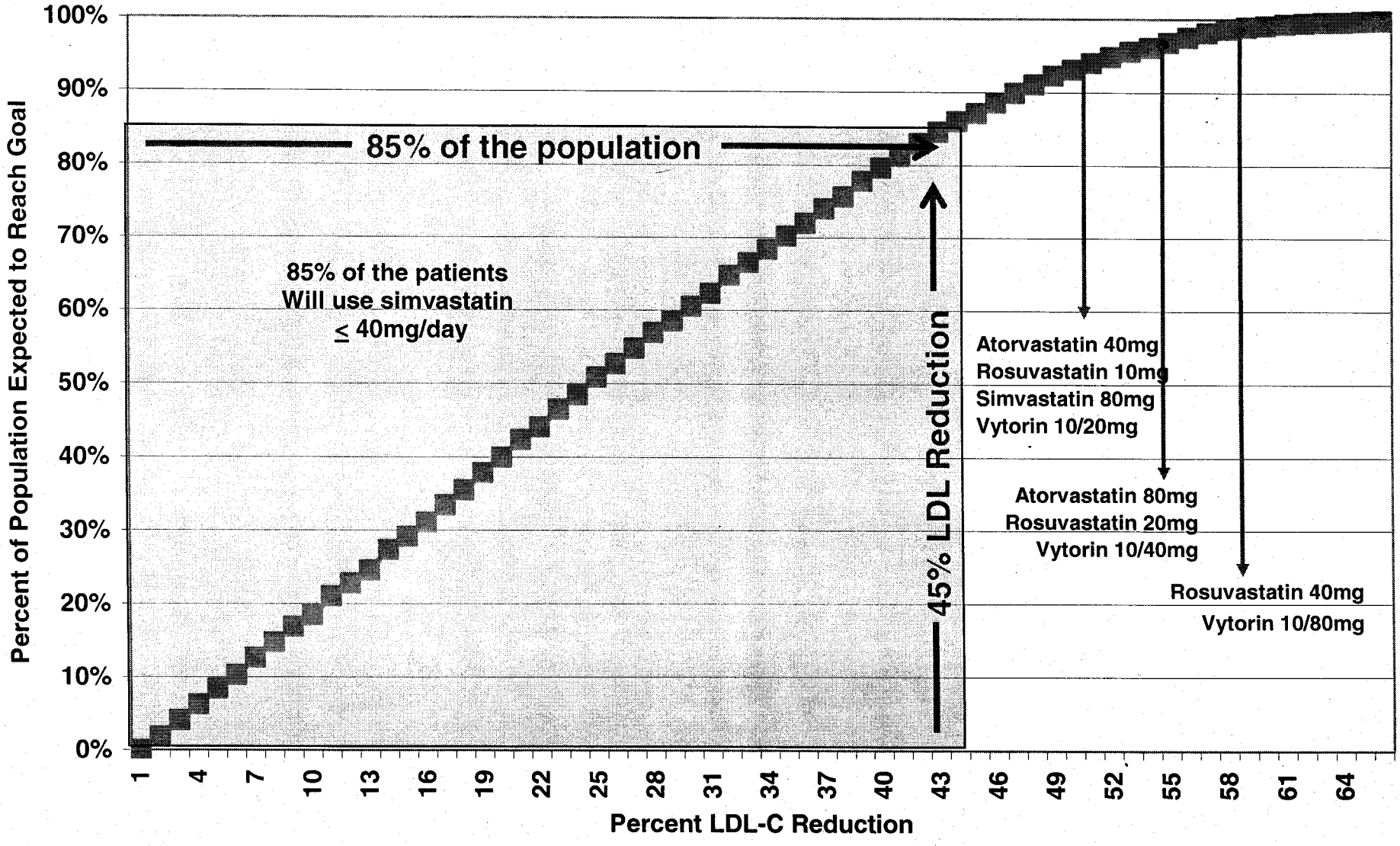
Appendix B – Table 2. Newly Approved Drugs. August 2006 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	**FDA Approval Date & FDA-Approved Indications**	**Committee Recommendation**
Dasatinib tabs (Sprycel; BMS) oral multi-kinase inhibitor	Jun 06 ▪ Treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib (Gleevec) ▪ Treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy	No UF recommendation at this meeting. Consideration of UF status deferred until oral cancer medications reviewed. Quantity limits recommended: ▪ TMOP o Days supply limit 45 days o 20 mg: 180 tabs per 45 days o 50 mg: 180 tabs per 45 days o 70 mg: 90 tabs per 45 days ▪ Retail Network o Days supply limit 30 days o 20 mg: 120 tabs per 30 days o 50 mg: 120 tabs per 30 days o 70 mg: 60 tabs per 30 days
Selegiline transdermal system (Emsam; BMS / Somerset) MAO A/B inhibitor	Mar 06 ▪ Acute and longer-term treatment of major depressive disorder in adult patients	No UF recommendation at this meeting. Consideration of UF status deferred until MAO inhibitors reviewed.
Rasagiline tabs (Azilect; Teva) MAO B inhibitor	May 06 ▪ Treatment as monotherapy of early Parkinson's Disease and combination use with levodopa in patients with moderate to advanced stages of Parkinson's Disease	No UF recommendation at this meeting. Consideration of UF status deferred until Parkinson's medications reviewed.
Methylphenidate transdermal system (Daytrana; Shire/Noven) amphetamine	Apr 06 ▪ Treatment of attention deficit hyperactive disorder (ADHD) in children 6-12 yrs of age	No UF recommendation at this meeting. Consideration of UF status deferred until ADHD / narcolepsy drug class reviewed in Nov 06.
Lubiprostone caps (Amitiza; Sucampo / Takeda) chloride channel activator	Jan 06 ▪ Treatment of chronic idiopathic constipation in adults	No UF recommendation at this meeting. Consideration of UF status deferred until drug class reviewed.

Appendix C – Table 3. Table of Abbreviations

ACS	acute coronary syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BPA	blanket purchase agreement
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CHD	coronary heart disease
CI	confidence interval
CMA	cost minimization analysis
CYP450	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DM	diabetes mellitus
DoD	Department of Defense
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FY	fiscal year
GERD	gastrointestinal reflux disease
GI	gastrointestinal
H2	histamine-2
HDL	high density lipoprotein
HbA1c	glycosylated hemoglobin A1c
IV	intravenous
LDL	low density lipoprotein
MI	myocardial infarction
MHS	Military Health System
MTF	military treatment facility
NSAID	non-steroidal anti-inflammatory drug
PA	prior authorization
P&T	Pharmacy and Therapeutics
PDTS	Pharmacy Data Transaction Service
PEC	Pharmacoeconomic Center
PPARs	peroxisome proliferator-activated receptors
PPIs	proton pump inhibitor
QD	once daily
QID	four times daily
TC	total cholesterol
TG	triglyceride
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
TZD	thiazolidinedione
ULN	upper limit of normal
UF	Uniform Formulary

Figure 1. Estimated Percent of Population Expected to Reach ATP-III LDL Goals with Increasing LDL Reduction
(NHANES3 Data Modeling by DoD PEC)



Appendix E – Table 4. Expected Mean LDL Reductions, by Statin and Dose

Expected Mean LDL Reduction	Statin					
	Lovastatin	**Pravastatin**	**Simvastatin**	**Fluvastatin**	**Atorvastatin**	**Rosuvastatin**
	IR - Mevacor, generics ER - Altoprev	Pravachol, generics	Zocor, generics	IR - Lescol, generics ER - Lescol XL	Lipitor	Crestor
25 to 30%	20 mg	20 mg	10 mg	40 mg		
30 to 40%	40 – 80 mg	40 mg	20 mg	80 mg (ER only)	10 mg	
40 to 45%	IR: 80 mg (40 mg x 2) ER: 60 mg	80 mg	40 mg or Vytorin 10/10 mg		20 mg	5 mg
45 to 50%	Please note: ezetimibe (Zetia) or niacin generally decrease LDL up to an additional 15%		80 mg or Vytorin 10/20 mg		40 mg	10 mg
50 to 55%			Vytorin 10/40 mg		80 mg	20 mg
>55%			Vytorin 10/80 mg			40 mg

IR = immediate release; ER = extended release
Vytorin = ezetimibe/simvastatin