DOD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

INFORMATION FOR THE UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL

I. Uniform Formulary Review Process

Under 10 U.S.C. § 1074g, as implemented by 32 C.F.R. 199.21, the DoD P&T Committee is responsible for developing the Uniform Formulary (UF). Recommendations to the Director, TMA, on formulary status, pre-authorizations, and the effective date for a drug's change from formulary to non-formulary status receive comments from Beneficiary Advisory Panel (BAP), which must be reviewed by the Director before making a final decision.

II. Antilipidemic (LIP-1) Drug Class Review

P&T Comments

A. Relative Clinical Effectiveness: Information regarding the safety, effectiveness, and clinical outcomes of the Antilipidemic 1 drugs was considered. The Committee's review focused primarily on the drugs' ability to lower low-density lipoprotein concentrations (LDL), to raise high-density lipoprotein concentrations (HDL), and to reduce clinical outcomes including all-cause mortality, cardiovascular mortality, myocardial infarction (MI), stroke, and need for revascularization. Differences in the drugs' 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 drugs' 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 (Lescol), fluvastatin extended release (Lescol XL), pravastatin (Pravachol, generics), lovastatin (Mevacor, generics), lovastatin extended release (Altoprev), atorvastatin (Lipitor) 10 and 20 mg (corresponding Caduet doses which include atorvastatin 10 or 20 mg), simvastatin (Zocor, generics) 10, 20, and 40 mg, ezetimibe/simvastatin (Vytorin) 10/10 mg, and rosuvastatin (Crestor) 5 mg.
- The following statins are considered intensive %LDL lowering statins: atorvastatin (Lipitor) 40 and 80mg (corresponding Caduet doses which include atorvastatin 40 and 80 mg), rosuvastatin (Crestor) 10, 20, and 40 mg, simvastatin (Zocor, generics) 80 mg, and ezetimibe/simvastatin (Vytorin) 10/20, 10/40, and 10/80 mg.
- When equipotent doses are used, the statins achieve similar %LDL lowering (e.g., atorvastatin (Lipitor) 20 mg, simvastatin (Zocor, generics) 40 mg and ezetimibe/simvastatin (Vytorin) 10/10 mg all attain 41 to 45% LDL lowering). Rosuvastatin (Crestor) 40 mg and ezetimibe/simvastatin (Vytorin) 80/10 mg are the only statins capable of attaining >55% LDL lowering.
- Based on a previous model conducted by the PEC that evaluated National Health and Nutrition Examination Survey (NHANES) data, 80 to 85% of the DoD population requiring a statin is expected to attain their LDL goal on simvastatin (Zocor, generics) doses ≤40mg. Simvastatin (Zocor, generics) 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 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 (Lipitor) 20 mg, simvastatin (Zocor, generics) 40 mg and ezetimibe/simvastatin (Vytorin) 10/10 mg can achieve an 8 to 9% increase in HDL concentrations, but at doses of atorvastatin 80 mg and ezetimibe/simvastatin 40/10 mg, only a 5-6% increase in HDL is achieved.
- 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 (Lipitor), simvastatin (Zocor, generics), and pravastatin (Pravachol, generics) 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 (Lipitor) 10 mg (ASCOT-LLA and CARDS trials), lovastatin (Mevacor) 20 to 40 mg (AFCAPS, TexCAPS trials), pravastatin (Pravachol, generics) 40 mg (WOSCOPS), and simvastatin (Zocor, generics) 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 (Lipitor) 10 to 80 mg (GREACE, TNT), lovastatin (Mevacor, generics) 40 to 80 mg (Knatterud et al), pravastatin (Pravachol, generics) 40 mg (LIPID, CARE), simvastatin (Zocor, generics) 20 to 40 mg (4S), and fluvastatin (Lescol) 40mg (administered bid) (LIPS).

- TNT: In the Treat to Target (TNT) trial, low dose atorvastatin (Lipitor) 10 mg was compared to intensive dose atorvastatin (Lipitor) 80 mg for 5 years in 10,000 patients with stable CHD. Intensive dose atorvastatin (Lipitor) 80 mg was associated with significantly fewer patients reaching the primary composite outcome (which included non-fatal MI) vs. atorvastatin (Lipitor) 10 mg (28.1% vs. 33.5%, $p<0.001$). There was no benefit of intensive dose atorvastatin (Lipitor) 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 (Lipitor) 80 mg was compared to low to moderate dose simvastatin (Zocor, generics) 20 to 40 mg. In contrast to TNT, intensive dose atorvastatin (Lipitor) did not show a benefit in the primary composite endpoint (CHD death, hospitalized non-fatal MI, resuscitated

cardiac arrest); (9.3% of atorvastatin (Lipitor) patients reached the primary endpoint, vs. 10.4% of simvastatin (Zocor, generics) 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 (Pravachol, generics) 40 mg was compared to intensive dose atorvastatin (Lipitor) 80 mg for two years in over 4,000 recently hospitalized (< 10 days) patients with ACS. Significantly fewer patients receiving intensive dose atorvastatin (Lipitor) 80 mg reached the primary composite endpoint (all cause death, MI, unstable angina requiring hospitalization, stroke) than moderate dose pravastatin (Pravachol, generics) 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 (Lipitor) 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 (Zocor, generics) 40 to 80 mg vs. delayed initiation (after four months) of low dose simvastatin (Zocor, generics) 20 mg. The long delay in statin administration, and not the individual statin evaluated, likely contributed to the negative results.

Rosuvastatin (Crestor) and ezetimibe/simvastatin (Vytorin): There are no published trials assessing the benefits of rosuvastatin (Crestor) on clinical outcomes; one large trial (JUPITER) is in progress. While there are no clinical trials specifically assessing the Vytorin formulation, there is evidence for clinical benefits of the simvastatin (Zocor, generics) component from the Scandinavian Simvastatin Survival Study (4S) and Heart Protection Study (HPS) trials. There is no evidence to suggest that addition of ezetimibe (Zetia) to simvastatin (Zocor, generics) would negate the clinical benefits of the simvastatin (Zocor, generics) 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 (LFTs).
  - Transient elevations of aspartate aminotransferase and alanine aminotransferase (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 the 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 (Crestor) 40 mg was associated with a 4 to 5% incidence of proteinuria. This was higher than the incidence reported with rosuvastatin (Crestor) doses ≤20 mg (1 to 4%), atorvastatin (Lipitor) 10 to 80 mg (0.4% to 2%), simvastatin (Zocor, generics) 20 to 80 mg (0.6% to 4%), or pravastatin (Pravachol, generics) 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 >10x 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 (Zocor, generics), pravastatin (Pravachol, generics), lovastatin (Mevacor, generics) and fluvastatin (Lescol) that did not differ from placebo (0.023% with the statins vs. 0.015% with placebo).

- Rosuvastatin (Crestor) 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). 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 incidence rate to determine differences in myotoxicity between the statins.
    - Cerivastatin (Baycol) had the highest reporting rate of rhabdomyolysis (72.88 per 1 million US prescriptions) when 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 (Crestor) at 13.54 reports per 1 million prescriptions, compared to simvastatin (Zocor) (8.71), fluvastatin (Lescol) (3.44), lovastatin (Mevacor, generics) (Mevacor) (2.76), atorvastatin (Lipitor) (1.67) and pravastatin (Pravachol) (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 (Mevacor, generics), 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. The impact of these patients is 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 (Mevacor, generics) (Mevacor) are approved for use in children as young as 10 years with rare heterozygous familial hypercholesterolemia.

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 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 (Crestor) 40 mg. Rosuvastatin (Crestor) 40 mg should only be initiated in patients failing to reach target LDL goals with rosuvastatin (Crestor) 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 (Lipitor). None of the pleiotropic markers (e.g., C-reactive protein,) have 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 (Crestor) 40 mg was shown to cause plaque regression in the ASTEROID trial, and atorvastatin (Lipitor) 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 (Crestor) for which there is no published study.

5.) *Efficacy and safety of Ezetimibe (Zetia):*

- Ezetimibe (Zetia) lowers LDL by a mechanism distinct to that of the statins, as it inhibits absorption of dietary cholesterol.
- Use of ezetimibe (Zetia) 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 (Zetia) 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 (Zetia) 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 (Zetia), 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 (Zetia) 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 (Zetia) in the MHS.

6.) *Efficacy and safety of ezetimibe/simvastatin (Vytorin):*

- The combination of simvastatin with ezetimibe (Vytorin) provides additional efficacy for LDL lowering.
- Doses of ezetimibe/simvastatin (Vytorin) greater than 10/20 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 (Zocor, generics) alone.
- The efficacy profiles of ezetimibe/simvastatin (Vytorin) reflect 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 (Niaspan) is associated with a reduced risk of GI adverse events and hepatotoxocity compared to niacin immediate release (Niacor) 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 (Niaspan) are limited to those patients who can tolerate the flushing and GI disturbances.

8.) *Clinical issues with lovastatin/niacin extended release (Advicor), atorvastatin/amlodipine (Caduet), lovastatin extended release (Altoprev), and fluvastatin extended release (Lescol XL)*

- Lovastatin/niacin extended release (Advicor) is difficult to initiate and titrate, since it is available in a fixed dose formulation.
- Atorvastatin/amlodipine (Caduet) contains a statin in combination with the dihydropyridine calcium channel blocker amlodipine. Amlodipine (Norvasc) was designated non-formulary under the UF in Aug 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 (Altoprev) does not offer additional LDL lowering or safety benefits over lovastatin (Mevacor, generics). Unlike lovastatin, Altoprev is available in a 60 mg tablet, but does not attain a >45% LDL lowering.

- Fluvastatin extended release (Lescol XL) 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 (Lescol) 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 (Zetia). Providers were also concerned with the safety profile of rosuvastatin (Crestor).

COMMITTEE ACTION: The P&T Committee voted to accept the clinical effectiveness conclusions stated in III(A) below.

B. Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the Antilipidemic I (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 C.F.R. 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 (Lipitor) 40 and 80 mg; rosuvastatin (Crestor) 10, 20, and 40 mg; ezetimibe/simvastatin (Vytorin) 10/20, 10/40, and 10/80 mg; and simvastatin (Zocor, generics) 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 (Zocor, generics)— 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 (Lipitor) was more effective but considerably more costly compared to low dose (20-40mg) simvastatin (Zocor, generics). The results of this analysis support use of high dose atorvastatin (Lipitor) only in patients who cannot be successfully treated to goal with simvastatin (Zocor, generics).

For the low to moderate % LDL lowering agents (≤ 45%) in the LIP-1 class [simvastatin (Zocor, generics) 5, 10, 20, and 40 mg, atorvastatin (Lipitor) 10 and 20 mg; rosuvastatin (Crestor) 5 mg; ezetimibe/simvastatin (Vytorin) 10/10 mg; and all strengths of pravastatin (Pravachol, generics), fluvastatin (Lescol), fluvastatin extended release (Lescol XL), lovastatin (Mevacor, generics), lovastatin extended release (Altoprev), niacin/lovastatin (Advicor), niacin extended release (Niaspan), niacin immediate release (Niacor), and ezetimibe (Zetia)], the cost-effectiveness of the agents within this subclass was evaluated using the Annual Cost per 1% LDL Decrease model. In pharmacoeconomic terms, lovastatin (Mevacor, generics), lovastatin ER (Altoprev), simvastatin (Zocor, generics), and rosuvastatin (Crestor) 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 (Caduet), 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 (Caduet), it was compared to the combination of atorvastatin (Lipitor) 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 (Caduet) was considerably more costly compared to the combination of atorvastatin (Lipitor) 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 (Pravachol, generics), ezetimibe (Zetia), and niacin extended release (Niaspan), 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 (Lipitor) and ezetimibe/simvastatin (Vytorin) 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.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to accept the LIP-1 relative cost-effectiveness analysis. The P&T

Committee concluded that the Uniform Formulary scenario that included atorvastatin (Lipitor), ezetimibe/simvastatin (Vytorin), and simvastatin (Zocor, generics) 80 mg as the high % LDL lowering agents on the UF was the most cost effective UF scenario.

C. Implementation Plan: MTFs will not be allowed to have Crestor (rosuvastatin) or Caduet (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 Antilipidemic (LIP1) 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 an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

III. Antilipidemic (LIP-1) Drug Class Review (cont.)

BAP Comments

A. Relative Clinical Effectiveness:

The Committee concluded:

1. across equipotent doses, the statins achieve similar %LDL lowering, with rosuvastatin (Crestor) 40 mg and ezetimibe/simvastatin (Vytorin) 80/10 mg as the only statins capable of achieving 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 (Lipitor) (Lipitor), pravastatin (Pravachol) and simvastatin (Zocor, generics) 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 (Lipitor) (Lipitor) 10 mg, lovastatin (Mevacor, generics) 20 to 40 mg, pravastatin (Pravachol, generics) 40 mg, and simvastatin (Zocor, generics) 40 mg;
6. in trials assessing the secondary prevention of coronary heart disease (CHD), beneficial effects on clinical outcomes have been noted with atorvastatin (Lipitor) (Lipitor) 10 to 80 mg, lovastatin (Mevacor, generics) 40 to 80 mg, pravastatin

(Pravachol, generics) 40 mg, simvastatin (Zocor, generics) 20-40 mg, and fluvastatin (Lescol) 40mg (administered BID);

7. in one trial assessing acute coronary syndrome (ACS) patients, beneficial effects on clinical outcomes were noted with atorvastatin (Lipitor) (Lipitor) 80 mg when it was compared to pravastatin (Pravachol, generics) 40 mg (PROVE-IT 2004);
8. there are no published trials assessing the benefits of rosuvastatin (Crestor) 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 (Lescol), pravastatin (Pravachol, generics_, and rosuvastatin (Crestor) 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 (Crestor) 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 (Zetia) 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 (Vytorin) 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 (Niaspan) is required in the MHS as its primary benefit is to raise HDL by 25%;
18. lovastatin/niacin extended release (Advicor), atorvastatin/amlodipine (Caduet), lovastatin extended release (Altoprev), and fluvastatin extended release (Lescol XL) do not offer additional clinical benefits over the other Antilipidemic 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; and
20. based on clinical issues alone, none of the Antilipidemic (LIP-1) agents are sufficiently less effective than the others agents within the class to be classified as non-formulary.

B. Relative Cost Effectiveness: The P&T Committee concluded that the Uniform Formulary scenario that included atorvastatin (Lipitor), ezetimibe/simvastatin (Vytorin), and simvastatin (Zocor, generics) 80 mg as the high % LDL lowering agents on the UF was the most cost effective UF scenario.

C. Uniform Formulary Recommendation: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the Antilipidemic I agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that atorvastatin (Lipitor), fluvastatin immediate & extended release (Lescol, Lescol XL), pravastatin (Pravachol, generics), simvastatin (Zocor, generics), lovastatin immediate & extended release (Mevacor, generics; Altoprev), lovastatin/niacin (Advicor), ezetimibe/simvastatin (Vytorin), niacin immediate & extended release (Niacor, Niaspan), and ezetimibe (Zetia) be maintained as formulary on the UF and that rosuvastatin (Crestor) and atorvastatin/amlodipine (Caduet) be classified as non-formulary.

BAP Comment:	☐ Concur ☐ Non-concur Additional Comments and Dissentions:

D. Implementation Plan: The P&T Committee recommended an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

BAP Comment:	☐ Concur ☐ Non-concur Additional Comments and Dissentions:

IV. Thiazolidinedione (TZD) Drug Class Review

P&T Comments

A. **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.

2) *Efficacy for Glycemic Control*

Rosiglitazone (Avandia) and pioglitazone (Actos) and their fixed-dose combinations with metformin or glimepiride are FDA-approved for treating patients with type 2 diabetes mellitus (T2DM). The primary efficacy measures evaluated included hemoglobin A1c (A1c) 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 (Avandia) monotherapy reduces A1c by 0.6% to 1.5% and FPG by 33 mg/dL to 55 mg/dL, while pioglitazone (Actos) monotherapy reduces A1c 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 (Avandia) and pioglitazone (Actos) monotherapy included 802 patients. The trial showed similar reductions in A1c 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 A1c were reported: -0.90% (95% Confidence Interval [CI] -1.42% to -0.38%) with rosiglitazone (Avandia) 4 mg once daily (QD); -0.99% (95% CI -1.32% to -0.66%) with pioglitazone (Actos) 30 mg QD. Similar point estimates and overlapping confidence intervals were reported for rosiglitazone (Avandia) 8 mg QD and pioglitazone (Actos) 45 mg QD for reductions in both A1c and FPG. [Chiquette 2004]
- *Combination Therapy* – When a TZD is added on to another antidiabetic drug, greater reductions in A1c 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: A1c decreased by 1.3% with rosiglitazone (Avandia) plus glimepiride vs. 1.4% with pioglitazone (Actos) 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 A1c were

reported: [-1.05 (95% Confidence Interval -1.2 to -0.9) with rosiglitazone (Avandia) 4 mg QD plus other antidiabetic drugs vs. -1.16 (95% CI -1.4 to -0.0) with pioglitazone (Actos) 30 mg QD plus other antidiabetic drugs]. Similar reductions in A1c and FPG, with overlapping confidence intervals, were reported for rosiglitazone (Avandia) 8 mg QD plus other antidiabetic drugs vs. pioglitazone (Actos) 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 (Avandia) and pioglitazone (Actos). 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 (Avandia) nor pioglitazone (Actos) are superior to the other in reducing A1c or FPG.

3) *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 T2DM, when available.

- *Microvascular Complications* – There are no clinical trials with either rosiglitazone (Avandia) or pioglitazone (Actos) that evaluate the effects of long-term TZD therapy on prevention of microvascular complications. However, both TZDs reduce A1c, and reductions in A1c are correlated with a reduced risk of microvascular events, as previously shown in the United Kingdom Prospective Diabetes Study (UKPDS).
- *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 (Actos) on clinical outcomes in over 5,000 patients. After three years, there was no significant difference with pioglitazone (Actos) 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 (Avandia) 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 (Avandia), and design limitations of the one published trial with pioglitazone (Actos), PROACTIVE, there is insufficient evidence to determine whether one TZD is superior to the other in preventing the clinical complications of diabetes.

4) *Safety and Tolerability*

- *Hypoglycemia* – One meta-analysis compared the differences in the incidence of hypoglycemia between rosiglitazone (Avandia) and pioglitazone (Actos). The pooled risk differences were compared with each drug vs. placebo, and the results were similar for each TZD; rosiglitazone (Avandia) risk difference vs. placebo 3% (95% CI 0% to 5%) and pioglitazone (Actos) 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 (Avandia) 4% (95% CI 2% to 5%), pioglitazone (Actos) 4% (95% CI 2% to 7%). [State of Oregon 2006]
- *Heart Failure* – Both rosiglitazone (Avandia) and pioglitazone (Actos) have been linked to development of heart failure; neither are recommended for use in patients with New York Heart Association (NYHA) Class III or IV heart failure Product labeling for both rosiglitazone (Avandia) and pioglitazone (Actos) 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 (Avandia) 2.39% vs. pioglitazone (Actos) 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 (Avandia) vs. 2.0 kg with pioglitazone (Actos)—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 (Avandia) and pioglitazone (Actos).

- *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. Glaxo SmithKline issued a "Dear Doctor Letter" on 5 Jan 2006 regarding the association of rosiglitazone (Avandia) with new onset and worsening macular edema. Takeda, the manufacturer of pioglitazone (Actos), 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 (Actos) than rosiglitazone (Avandia), due to metabolism of the former by CYP3A4 enzymes. However, the clinical significance of the drug-drug interactions with pioglitazone (Actos) may be counterbalanced by the availability of multiple metabolic pathways. Of note, use of pioglitazone (Actos) 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 (Actos).
- *Withdrawal Due to Adverse Effects* – Drug discontinuations due to adverse effects were similar for rosiglitazone (Avandia) and pioglitazone (Actos) 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 (Avandia) vs. 4.8% with pioglitazone (Actos). [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 (Avandia) and pioglitazone (Actos). 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 (Actos) than rosiglitazone (Avandia), 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.

5) *Effects on Lipid Parameters*

The TZDs exhibit other actions that can have unintended consequences in T2DM patients. Treatment with rosiglitazone (Avandia) and pioglitazone (Actos) 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 T2DM patients

require treatment with lipid lowering therapy. CHD is the number one cause of death in T2DM patients.

- Two head-to-head trials (one as monotherapy, the other as add-on therapy with other diabetic medications) reported that rosiglitazone (Avandia) adversely effected the lipid panel, as reflected by increases in TC (by 15-16%), LDL (by 17-23%), and TG (by 15-18%). In contrast, pioglitazone (Actos) showed a favorable effect on the lipid profile, due 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 (Actos) 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 (Avandia) therapy resulted in increases in TC (10-21%), LDL (7-15%), and HDL (2-3%), but did not affect TGs. Pioglitazone (Actos) increased HDL (2-5%) and reduced LDL (0.4 to 0.5%). Reductions in TG were more pronounced with pioglitazone (Actos), but a statistically significant difference was noted only for pioglitazone (Actos) in the Canadian analysis. Both TZDs were associated with modest increases in HDL (by 2-5%); the marked difference between rosiglitazone (Avandia) and pioglitazone (Actos) 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 (Actos) appears to have a more favorable effect on lipid parameters than rosiglitazone (Avandia). The clinical significance of this difference has yet to be determined.

6) *Other Factors*

- Rosiglitazone (Avandia) is dosed either once or twice daily, while pioglitazone (Actos) is dosed once daily.
- Rosiglitazone (Avandia) binds primarily to PPAR gamma receptors, while pioglitazone (Actos) 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 (Avandia) nor pioglitazone (Actos) 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 (Actos) 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 (Actos) and no preference between the two.

Overall Clinical Effectiveness Conclusion – The Committee concluded that: (1) neither rosiglitazone (Avandia) or pioglitazone (Actos) appear 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 (Avandia) or pioglitazone (Actos) appear 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 (Actos); (5) rosiglitazone (Avandia) appears to have a less favorable effect on lipid parameters than pioglitazone (Actos), 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 (Actos) and no preference; (7) neither rosiglitazone (Avandia) or pioglitazone (Actos)—or their respective combination products—appear sufficiently less clinically effective than the other to warrant classification as non-formulary based on clinical issues alone.

COMMITTEE ACTION: The P&T Committee voted to accept the overall clinical effectiveness conclusions stated above.

B. 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 C.F.R. 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 T2DM, 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 Actos (pioglitazone) was more cost-effective compared to Avandia (rosiglitazone) for a 1 of 1 position on the UF, whereas Avandia (rosiglitazone) was more cost-effective compared to Actos (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 Uniform Formulary. 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 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.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to accept the TZD cost analysis presented by the PEC. The P&T Committee concluded that the UF scenario that maintained rosiglitazone (Avandia), pioglitazone (Actos), rosiglitazone/metformin (Avandamet), pioglitazone/metformin (Actoplus Met), and rosiglitazone/glimepiride (Avandaryl) on the UF formulary was the most cost effective UF scenario considered.

C. Implementation Plan: Since no agents were recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

COMMITTEE ACTION: *N/A*

V. Thiazolidinedione (TZD) Drug Class Review (cont.)

BAP Comments

A. Relative Clinical Effectiveness: The Committee concluded that: (1) neither rosiglitazone (Avandia) or pioglitazone (Actos) appear 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 (Avandia) or pioglitazone (Actos) appear 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 (Actos); (5) rosiglitazone (Avandia) appears to have a less favorable effect on lipid parameters than pioglitazone (Actos), 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 (Actos) and no preference; (7) neither rosiglitazone (Avandia) or pioglitazone (Actos)—or their respective combination products—appear sufficiently less clinically effective than the other to warrant classification as non-formulary under the Uniform Formulary based on clinical issues alone

B. Relative Cost Effectiveness: 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.

C. Uniform Formulary Recommendation: The P&T Committee, based upon its collective professional judgment, voted to accept the TZD cost analysis presented by the PEC. The P&T Committee concluded that the UF scenario that maintained rosiglitazone (Avandia), pioglitazone (Actos), rosiglitazone/metformin (Avandamet), pioglitazone/metformin (Actoplus Met), and rosiglitazone/glimepiride (Avandaryl) on the UF formulary was the most cost effective UF scenario considered.

BAP Comment:	☐ Concur ☐ Non-concur Additional Comments and Dissentions:

VI. Histamine-2 Antagonists and other gastrointestinal (GI) protectants Drug Class Review

A. Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the H2 antagonists and other gastrointestinal (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 (VA), as well as the 1999 American College of Gastroenterology (ACG) guidelines for the treatment of GERD, conclude 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 (Tagamet, generics) 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 (Carafate, generics)* – Sucralfate does not affect gastric acid pH, but is thought to act by forming a non-absorbable physical barrier over mucosal ulcerations. At least 10 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 (Cytotec, generics)* – 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 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 (Tagamet, generics). 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 (Carafate, generics)* – 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 (Cytotec, generics)* – 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 (Tagamet, generics) 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 (Carafate, generics) include a tablet and oral suspension, while misoprostol is only available in a tablet. Ranitidine (Zantac, generics) 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 (Zantac, generics) is the most widely prescribed H2 antagonist in the MHS, accounting for 67% of all H2 antagonist prescriptions, followed by famotidine (Pepcid, generics, 22%), cimetidine (Tagamet, generics, 8%) and nizatidine (Axid, generics, 3%).
- *Pediatrics* – Ranitidine (Zantac, generics) and famotidine (Pepcid, generics) are indicated for use in children as young as two years of age; nizatidine (Axid, generics) is indicated in children older than 11 years, and cimetidine (Tagamet, generics) is indicated for use in children older than 15 years of age.
- *Pregnancy* – The four H2 antagonists and sucralfate (Carafate, generics) are rated as pregnancy category B. Misoprostol (Cytotec, generics) is rated as pregnancy category X.

Overall Clinical Effectiveness Conclusion – The Committee voted that: (1) the four H2 antagonists ranitidine (Zantac, generics), cimetidine (Tagamet, generics), famotidine (Pepcid, generics), and nizatidine (Axid, generics) are widely considered interchangeable for treatment of gastroesophageal reflux disease (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 (Tagamet, generics) has evidence for use in non-gastrointestinal conditions; (3) ranitidine (Zantac, generics) 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 (Pepcid, generics) and nizatidine (Axid, generics) have similar dosing intervals, drug interaction profiles and formulations as ranitidine (Zantac), but are less

frequently prescribed in the MHS; (5) cimetidine (Tagamet, generics) 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 (Cytotec, generics) 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 (Carafate, generics) has a unique mechanism of action (physical barrier formation) and offers an alternative to proton pump inhibitors (PPIs) and H2 antagonists for stress ulcer prophylaxis.

COMMITTEE ACTION – The P&T Committee voted to accept the clinical effectiveness conclusions stated above.

B. Relative Cost Effectiveness:

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

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 (Axid, generics). Not surprisingly, nizatidine (Axid, generics) 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 (Cytotec, generics) and sucralfate (Carafate, generics), 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 to accept the H2 antagonists & other GI protectants cost analysis.

C***OMMITTEE ACTION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the H2 antagonists & other GI protectants, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that the H2 antagonists ranitidine (Zantac, generics), cimetidine (Tagamet, generics), famotidine (Pepcid, generics) and nizatidine (Axid, generics); the prostaglandin analog misoprostol (Cytotec, generics); and the mucosal protective agent sucralfate (Carafate, generics) should be maintained on the UF and that no agents from this class be classified as non-formulary.

C. Implementation Plan: Since no agents were recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

COMMITTEE ACTION: *N/A*

VII. Histamine-2 Antagonists and other gastrointestinal (GI) protectants Drug Class Review (cont.)

BAP Comments

A. Relative Clinical Effectiveness: The Committee voted that: (1) the four H2 antagonists ranitidine (Zantac, generics), cimetidine (Tagamet, generics), famotidine (Pepcid, generics), and nizatidine (Axid, generics) are widely considered interchangeable for treatment of gastroesophageal reflux disease (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 (Tagamet, generics) has evidence for use in non-gastrointestinal conditions; (3) ranitidine (Zantac, generics) 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 (Pepcid, generics) and nizatidine (Axid, generics) have similar dosing intervals, drug interaction profiles and formulations as ranitidine (Zantac), but are less frequently prescribed in the MHS; (5) cimetidine (Tagamet, generics) 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 (Cytotec, generics) 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 (Carafate, generics) has a unique mechanism of action (physical barrier formation) and offers an alternative to proton pump inhibitors (PPIs) and H2 antagonists for stress ulcer prophylaxis.

B. Relative Cost Effectiveness: The P&T Committee, based upon its collective professional judgment, voted to accept the H2 antagonists & other GI protectants cost analysis presented by the PEC. The P&T Committee concluded that the H2 antagonists ranitidine (Zantac, generics), cimetidine (Tagamet, generics), famotidine (Pepcid, generics) and nizatidine (Axid, generics); the prostaglandin analog misoprostol (Cytotec, generics); and the mucosal protective agent sucralfate (Carafate, generics) should be maintained on the UF.

C. Uniform Formulary Recommendation: The P&T Committee, based upon its collective professional judgment, voted to recommend that the H2 antagonists ranitidine (Zantac, generics), cimetidine (Tagamet, generics), famotidine (Pepcid, generics) and nizatidine (Axid, generics); the prostaglandin analog misoprostol (Cytotec, generics); and the mucosal protective agent sucralfate (Carafate, generics) should be maintained on the UF and that no agents from this class be classified as non-formulary.

BAP Comment:	☐ Concur ☐ Non-concur Additional Comments and Dissentions:

VIII. PRIOR AUTHORIZATION (PA) REQUIREMENT FOR BYETTA

A. Clinical And Cost Background: Byetta is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin (Glucophage, generics) and a sulfonylurea, but have not achieved adequate glycemic control. Pharmacologically, Byetta 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. Byetta 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. Byetta 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, Byetta decreased 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 Byetta with a sulfonylurea may increase the risk of hypoglycemia, and the sulfonylurea dose may need to be reduced. Concurrent use of Byetta and metformin (Glucophage, generics) is relatively unlikely to cause hypoglycemia. Because it slows gastric emptying, Byetta 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 1 hour prior to Byetta. Byetta 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 Byetta in clinical trials also complained of significantly more jitteriness, dizziness, and headache than those receiving placebo.

Byetta 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 Byetta 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 Pharmacoeconomic Center, about 90% of MHS patients who received a first prescription for Byetta 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 Byetta (8,681 out of a total of 9,634 patients). In other words, about 10% of MHS patients starting Byetta 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 Byetta. While there may be alternative explanations for some of these cases, it appears that some of these patients are receiving Byetta as a weight-loss medication and/or in a setting of "pre-diabetes." Many health plans have PA requirements for Byetta, primarily based on its FDA indication.

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

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

- In the MHS, up to 10% of Byetta usage may be for appears likely to be used for indications not covered by TRICARE and/or not supported by clinical evidence. The use of Byetta for weight loss may increase based on continued coverage in the lay press increasing familiarity with the medication. Overall, utilization of Byetta is increasing.
- Modifications to the Pharmacy Data Transaction Service (PDTS) scheduled for completion by Dec 06 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 (prior authorization 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 Byetta.

C. Implementation Plan & Criteria: 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.

BAP Comment:	☐ Concur ☐ Non-concur Additional Comments and Dissentions:

The Committee agreed that the following PA criteria should apply 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

BAP Comment:	☐ Concur ☐ Non-concur Additional Comments and Dissentions: