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. ANTILIPIDEMICS II (LIP-2s)

P&T Comments

A. Relative Clinical Effectiveness:

1) Formulations

a) Fibric Acid Derivatives

i) Products

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

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

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

ii) FDA approval process

The newer fenofibrate formulations received FDA approval via a 505b(2) application. Under this process, newer products are approved by

demonstrating bioequivalence to the original new drug application of the innovator fenofibrate 200 mg product. The newer formulations are marketed in varying dosage strengths lower than 200 mg. However, bioequivalence is similar between innovator fenofibrate 200 mg, IDD-P micronized fenofibrate (Triglide) 160 mg, nanocrystallized fenofibrate (Tricor) 145 mg, and micronized fenofibrate (Antara) 130 mg.

b) Omega-3 Fatty Acids

i) Products

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

Prescription omega-3 fatty acids (Omacor) – Omacor is a marine-derived omega-3 polyunsaturated fatty acid product that was approved by the FDA in 2004. It is the first and only prescription fish oil product available. Each 1-gram Omacor capsule contains 90% omega-3 acid esters, consisting of 465 mg (46%) EPA, 375 mg (38%) DHA), 6% other omega-3 acid esters, and 10% omega-6 fatty acids.

ii) FDA indication

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

Prescription omega-3 fatty acids (Omacor) – Omacor is currently approved only as an adjunct to diet in patients with very high TG levels (>500 mg/dL).

iii) Off-label uses

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

c) Bile Acid Sequestrants

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

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

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

2) Efficacy

a) *Efficacy Measures*

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

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

b) *Fibric Acid Derivatives*

i) *Lipoprotein efficacy*

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

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

ii) *Clinical outcomes*

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

- *Helsinki Heart Study 1987 (HHS)* – HHS was a double-blind placebo-controlled study conducted in 4,000 Finnish men (average age 47 years) who did not have CHD (primary prevention trial). After five years, gemfibrozil 600 mg BID resulted in a significant reduction (34%) in nonfatal myocardial infarction (MI) and CHD death, compared to placebo. There was no difference between gemfibrozil and placebo in all-cause mortality.
- *Veteran Affairs High density lipoprotein cholesterol Intervention Trial 2001 (VA-HIT)* – VA-HIT was a secondary prevention trial conducted in over 2,000 male VA patients who had a history of CHD (average age 64 years). After five years, compared to placebo, treatment with gemfibrozil 600 mg BID resulted in a significant reduction (22%) in the risk of nonfatal MI or CHD death. There was no difference in death due to any cause. Thirty percent of the study participants were diabetic, and when this subpopulation was analyzed, significant reductions in the composite of nonfatal MI, stroke and CHD death were seen.
- *Fenofibrate Intervention and Event Lowering in Diabetes 2005 (FIELD)* – The FIELD trial was a randomized double-blinded placebo-controlled trial which included 9,975 type 2 diabetic participants, 2,131 of whom had cardiovascular disease. Patients were treated with fenofibrate 200 mg QD or placebo for 5 years. Patients were not receiving statins at the start of the study, but could start antilipidemic therapy, including statins, during the trial.

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

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

iii) Efficacy conclusion

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

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

b) Omega-3 fatty acids

i) Lipoprotein efficacy

Fish oil supplements: placebo-controlled trials – One meta-analysis of 36 crossover and 32 parallel studies of dietary and supplemental omega-3 fatty acids reported that a 3- to 4-gram daily dose resulted in a reduction of TG by 25-34%, and an increase in LDL by 4-11%, regardless of source or formulation.

Prescription omega-3 fatty acids (Omacor): placebo-controlled trials – Ten prospective, randomized clinical trials have examined the effects of the marketed Omacor formulation on TG and LDL concentrations in patients with elevated TG levels. Overall, Omacor 4 grams daily resulted in a 20-45% reduction in TG levels when compared to placebo. The TG-lowering response appears to correlate with baseline TG levels (e.g. patients with higher baseline TG levels will generally have a greater TG-lowering response).

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

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

iii) Prescription omega-3 fatty acids (Omacor) vs. other lipid-lowering therapies – The TG-lowering effects of Omacor are slightly lower than

those achieved with fibric acid derivatives or niacin. Omacor is associated with similar increases in HDL compared to fibric acid derivatives and niacin.

iv) Clinical outcomes

- *Fish oil supplements: systematic reviews/meta-analyses* – The effects of dietary or supplemental omega-3 fatty acids on cardiovascular disease outcomes have been evaluated in several meta-analyses and systematic reviews, with conflicting results reported. Some reports suggest a beneficial effect when omega-3 fatty acids are used for either primary or secondary cardiovascular disease prevention. In contrast, a 2004 Cochrane review of randomized controlled trials (RCTs) and cohort studies found no strong evidence that dietary or supplemental omega-3 fatty acids reduced total mortality, cardiovascular events, or cancer.
- *Fish oil supplements: placebo-controlled trial (GISSI-Prevenzione)* – In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto miocardico (GISSI)-Prevenzione Trial, an omega-3 fatty acid with a different ratio of EPA and DHA than Omacor was evaluated. Fish oil supplementation was associated with a 15% reduction in the risk of the composite endpoint of death, nonfatal MI, and stroke in 11,324 survivors of a recent MI. There was a 20% reduction in all-cause mortality, which was driven by a 45% reduction in sudden death. There was no difference in nonfatal MI between the groups. Limitations to the study include the open label study design, a dropout rate nearing 30% by study completion, use of a fish oil supplement different than Omacor, and high dietary intake of fish (which in itself has cardiovascular benefits).
- *Prescription omega-3 fatty acids (Omacor): placebo-controlled trial* – One placebo-controlled, double-blinded trial evaluated the effect of Omacor on cardiovascular outcomes. In this study, 300 patients with acute MI were randomly assigned to receive Omacor 4 grams daily or corn oil placebo for a median time period of 1.5 years. There was no statistically significant difference in the rate of cardiac events (cardiac death, resuscitation, recurrent MI, and unstable angina) between groups (28% with Omacor vs. 24% with placebo, hazard ratio 1.19, 95% CI 0.76-1.86). The lack of difference was attributed to the small size and short duration of the trial, as well as the inclusion of Norwegian patients whose diets already contained a high content of fish.
- *Prescription omega-3 fatty acids (Omacor) vs. fish oil supplements* – There are no head-to-head trials of Omacor versus fish oil supplements.
- *Prescription omega-3 fatty acids (Omacor) vs. other lipid-lowering therapies* – Niacin and gemfibrozil both have clinical trial evidence supporting long-term benefits on cardiovascular outcomes.

v) Efficacy conclusion: Randomized clinical trials showed a reduction in TG levels of 20-45% with Omacor 4 grams once daily. However, Omacor has

also been associated with increases in LDL, which may offset beneficial reductions in TG. Concomitant use of a statin may blunt increases in LDL.

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

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

c) *Bile Acid Sequestrants*

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

- *Cholestyramine (Questran, Questran Light, generics)* – The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was a large placebo-controlled trial that compared cholestyramine 24 g QD to placebo in preventing coronary artery disease (CAD) in 3,806 men with primary hypercholesterolemia. Treatment with cholestyramine resulted in greater reductions in TC and LDL than placebo (TC -17% with cholestyramine vs. -1% with placebo; LDL -26% with cholestyramine vs. -5% with placebo ($p<0.001$).

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

- *Colesevelam (Welchol)* – One double-blind study compared various doses of colesevelam to placebo for 24 weeks in 494 patients with primary hypercholesterolemia. LDL levels decreased by 18% at the highest dose; all colesevelam doses reduced LDL significantly versus placebo ($p<0.001$). There were small, non-clinically significant increases in HDL and TG.

- *Colestipol (Colestid, generics)* – One large placebo-controlled trial with colestipol published in 1978 reported a 12% reduction in TC; LDL values were not reported.

- *Cholestyramine or colestipol (Colestid, generics) vs. placebo* – In 1972, a study of 45 adults with hyperlipidemia examined the cholesterol lowering activity and safety of colestipol monotherapy or cholestyramine monotherapy versus placebo. After one year of therapy, colestipol and cholestyramine had a similar effect on TC (40% reduction).

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

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

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

3) Safety / Tolerability

a) Fibric Acid Derivatives

i) Myopathy with statin combination therapy

- *Background* – An increased risk of myositis and potentially fatal rhabdomyolysis has been reported with fibric acid derivatives, either as monotherapy or in combination with a statin (particularly cerivastatin); it appears to be dose-related. This risk was first identified via spontaneous reports to the FDA Adverse Event Reporting System (AERS).
- *Gemfibrozil vs. fenofibrate* – Mechanistically, differences in glucuronidation pathways between gemfibrozil and fenofibrate are postulated to account for potential differences in the risk of developing myotoxicity. Gemfibrozil undergoes glucuronidation metabolism through the uridine diphosphate glucuronosyl transferase (UGT) 1A1 and 1A3 pathways, which results in competition with the statins. Fenofibrate is eliminated via UGT 1A9 and 2B7 pathways, which do not appear to interfere with statin glucuronidation.
- *FDA retrospective review* – A retrospective data analysis of the FDA AERS database found that half of the cases of statin-induced

rhabdomyolysis identified were associated with concomitant medications affecting statin metabolism, and of these more than one third were associated with fibric acid derivatives, gemfibrozil in particular. Many of these reports involved cerivastatin, which has now been withdrawn from the market.

Another study evaluating the FDA AERS database analyzed the reporting rate (not incidence rate) of myotoxicity between fenofibrate plus a statin vs. gemfibrozil plus a statin. Based on 606 adverse event reports compiled from 1998 to 2002, the reporting rate (rhabdomyolysis cases per million U.S. prescriptions) was 0.58 for fenofibrate and 8.6 with gemfibrozil. This study excluded cerivastatin, which has now been withdrawn from the market. Limitations include varying definitions of myotoxicity, lack of verification of data, and the use of spontaneous reporting rates, which are subject to reporting bias and do not establish a causal relationship.

- *Fenofibrate/statin combination trial* – In 2005, one randomized, double-blinded 18-week trial (n=600) evaluated safety of monotherapy with low-dose simvastatin (20 mg) versus combination therapy with a standard dose of fenofibrate plus simvastatin 20 mg. The incidence of myalgia in the combination group was 2.2% vs. 2.4% with simvastatin. There were no reports of rhabdomyolysis.
- *Clinical practice guidelines* – Professional organizations have not favored one fibric acid derivative over the other with respect to safety of use in combination with statins. The most recent joint guidelines (2003) from the American College of Cardiology, the American Heart Association, and the National Heart Lung and Blood Institute conclude that there is a risk with all fibric acid derivative/statin combinations, not just gemfibrozil plus statins.

ii) Minor adverse effects

- *Lab abnormalities* – Both gemfibrozil and fenofibrate have been associated with abnormal liver function tests when administered as monotherapy. Increases in serum creatinine ranging from 8 to 18% have been reported with fenofibrate in patients with normal or impaired renal function. Product labeling advises monitoring of serum creatinine during therapy with either fenofibrate or gemfibrozil.
- *Gemfibrozil vs. fenofibrate: minor adverse effects* – Gastrointestinal (GI) complaints (e.g., nausea, vomiting, and diarrhea) are most common for both fenofibrate and gemfibrozil. Although they occur in fewer than 5% of patients taking fibric acid derivatives, they appear to occur more often with gemfibrozil than with fenofibrate, based on pooled data from product labeling. The head-to-head efficacy trial mentioned earlier (conducted in 21 patients) did not report adverse events.

- *Fenofibrate formulations: minor adverse effects* – There are no head-to-head trials assessing differences in adverse effects among the newer fenofibrate formulations. Differences in fenofibrate formulations are primarily related to decreases in particle size designed to address bioavailability issues, allowing the most recent products (Tricor, Antara and Triglide) to offer once daily dosing and be taken without regard to meals. These differences do not appear to equate to differences in GI adverse effects, although comparative data are not available.

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

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

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

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

b) Omacor

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

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

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

c) Bile Acid Sequestrants

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

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

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

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

iii) *Special populations*

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

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

4) Other Factors

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

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

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

c) *Bile Acid Sequestrants* – Cholestyramine (Questran, Questran Light, generics) is only available in a powder form, which some patients find unpalatable. Cholestyramine and colestipol are available as powders or granules for oral suspension, with colestipol also available in tablet form. Both colestipol (Colestid, generics) and colesevelam (Welchol) require large daily tablet

burdens (up to sixteen tablets per day for colestipol and seven for colesevelam).

5) Place in Therapy

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

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

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

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

   a) *Fibric Acid Derivatives*

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

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

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

      iv) Monotherapy with either fibric acid derivatives or statins has been associated with an increased risk of myalgia, myositis, and rhabdomyolysis. This risk appears to be increased with gemfibrozil/statin

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

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

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

b) Omega-3 Fatty Acids

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

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

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

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

c) Bile Acid Sequestrants

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

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

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

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

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

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

B. LIP-2s – Relative Cost Effectiveness

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

Results from the fibric acid derivative CMA revealed: 1) gemfibrozil (Lopid, generics) was the most cost-effective fibric acid derivative, and 2) IDD-P fenofibrate (Triglide) was by far the most cost effective fenofibrate. Among the bile acid sequestrants, the CMA showed that colesevelam (Welchol) was not cost-effective in the treatment of hyperlipidemia when compared to other available agents. The results for the prescription omega-3 fatty acids (Omacor) CEA showed that omega-3 fatty acids (Omacor) was not cost effective in the treatment of hypertriglyceridemia when compared to gemfibrozil (Lopid), fenofibrate, and niacin. At this time, there is insufficient evidence to support a clinical benefit for omega-3 fatty acids (Omacor) in prevention of CHD. For this reason, the cost effectiveness of omega-3 fatty acids (Omacor) was not evaluated for this consequence or clinical outcome. Based on the results of the clinical review and the pharmacoeconomic evaluations, a budget impact analysis (BIA) of various UF scenarios for the LIP-2s was conducted. The goal of the BIA was to aid the Committee in determining which group of LIP-2s best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS.

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

COMMITTEE ACTION: The P&T Committee voted to accept the relative cost effectiveness analysis of the LIP-2 class.

C. Uniform Formulary Recommendation

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

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the Pharmacy and Therapeutics Committee may also designate that the drug be cost-shared at the

generic rate." The objective is to maximize use of IDD-P fenofibrate (Triglide) in the retail network and mail order, given its significantly lower cost relative to other fenofibrate products. Lowering the cost-share for brand name IDD-P fenofibrate (Triglide) will provide a greater incentive for beneficiaries to use the most cost effective fenofibrate formulation in the purchased care arena

D. Implementation Plan:

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

III. ANTILIPIDEMICS II (LIP-2s) (cont.)

BAP Comments

A. Uniform Formulary Recommendation: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the LIP-2s, and other relevant factors, the P&T Committee recommended that: 1) fenofibrate (Lofibra, generics), IDD-P fenofibrate (Triglide), cholestyramine/ aspartame (Questran Light, generics), cholestyramine/sucrose (Questran, generics), colestipol (Colestid, generics), and gemfibrozil (Lopid, generics) be maintained as formulary on the Uniform Formulary; 2) micronized fenofibrate (Antara), nanocrystallized fenofibrate (Tricor), colesevelam (Welchol), and prescription omega-3 fatty acids (Omacor) be classified as non-formulary; and 3) the normal brand formulary cost-share of $9.00 for IDD-P fenofibrate (Triglide) be lowered to the generic formulary cost-share of $3.00.

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

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

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

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

IV. 5-ALPHA REDUCTASE INHIBITORS (5-ARIs)

P&T Comments

A. **Relative Clinical Effectiveness:**

1) FDA-approved indications

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

2) Efficacy Measures

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

3) Efficacy

i. *Long term placebo-controlled trials* – The most extensive data supporting long term efficacy and safety of the 5-ARIs are from two large randomized, double-blind, placebo-controlled trials. The four-year Proscar Long-Term Efficacy and Safety Study (PLESS) [McConnell et al, 1998] showed a significant reduction in symptom scores, Qmax, TPV, risk of AUR, and risk of BPH-related surgery with finasteride, compared to placebo. Data for dutasteride comes from pooled analyses of three identical parallel-group trials (ARIA 3001, 3002, 3003) [Roehrborn et al, 2002]. All three trials had a 2-

year double-blinded phase comparing dutasteride to placebo, followed by a 2-year open-label extension phase during which all patients were treated with dutasteride. At the end of the 2-year double-blind phase, dutasteride significantly reduced symptom scores, Qmax, TPV, risk of AUR, and risk of BPH-related surgery with finasteride, compared to placebo.

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

ii. *Systematic reviews and meta-analysis* – Two systematic reviews [Clifford et al, 2000; Edwards et al, 2002] and one meta-analysis [AUA Guideline, 2003] concluded that finasteride offers consistent improvement in terms of symptom relief, urinary flow rate, and decreased risk of AUR and the need for prostatic surgery, compared to placebo. No systematic reviews or meta-analyses are available for dutasteride.

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

Unpublished summary data from a second head-to-head trial, the Enlarged Prostate International Comparator Study (EPICS), were furnished by the manufacturer of dutasteride [data on file, GlaxoSmithKline]. EPICS compared dutasteride 0.5 mg and finasteride 5 mg in men with BPH. Following a 4-week placebo run-in period, 1630 men were randomized to dutasteride (n=813) or finasteride (n=817) for twelve months. After 1 year similar improvements from baseline were seen with dutasteride vs. finasteride, respectively, with respect to changes in symptom scores (-5.8 vs.- 5.5), reductions in TPV (-26.3% vs. -26.7%) and Qmax (2.0 vs. 1.7 mL/sec). No statistically significant differences in outcome measures between treatment groups were reported.

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

iv. *Prostate cancer* – There is limited evidence concerning the potential use of 5-ARIs for prostate cancer prevention. The only large, long-term trial [Thompson et al, 2003] reported a 24.8% reduction in the prevalence of prostate cancer in patients receiving finasteride vs. placebo; however, a higher percentage of high-grade prostate cancer tumors was reported with finasteride, compared to placebo. It is not known whether or not dutasteride produces the same effect.

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

4) Safety and Tolerability

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

ii. *Overall adverse events* – The most common adverse effects are related to sexual dysfunction. Similar incidences of sexual adverse events and gynecomastia have been reported with finasteride and dutasteride. In general, clinical trials report rates of decreased libido of 2 to10%, erectile dysfunction 3 to16%, ejaculatory disorders 0 to 8%, and gynecomastia 1 to 2%. The

incidence of sexual dysfunction is generally higher during the first six to twelve months of treatment and diminishes with chronic dosing.

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

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

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

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

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

5) Therapeutic Interchangeability

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

6) 5-ARIs – Overall Clinical Effectiveness Conclusion

The P&T Committee concluded that:

a) There is insufficient evidence to conclude that there are significant differences in efficacy between finasteride and dutasteride. Indirect comparisons from long-term efficacy trials suggest similar decreases in total prostate volume, increases in urinary flow rate, improvement in symptoms, and similar reductions in the risk of AUR and BPH-related surgery.

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

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

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

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

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

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

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

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

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

B. Relative Cost Effectiveness: The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the 5-ARI medications differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of BPH. As a result, several cost minimization analyses (CMAs) were performed to compare the relative cost effectiveness of the 5-ARIs by condition set. The CMAs compared the weighted average cost per day of treatment for each drug product across all three points of service. In addition, a cost effectiveness analysis was conducted evaluating the cost per BPH surgery avoided for each of the 5-ARIs.

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

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

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

COMMITTEE ACTION: The DOD P&T Committee to accept the 5-ARI relative cost effectiveness analysis as presented by the PEC.

C. Uniform Formulary Recommendation: In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the 5-ARIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that finasteride (Proscar, generics) be maintained as formulary on the UF and that dutasteride (Avodart) be classified as non-formulary.

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

V. 5-ARI (cont.)

BAP Comments

A. **Uniform Formulary Recommendation:** In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the 5-ARIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that finasteride (Proscar, generics) be maintained as formulary on the UF and that dutasteride (Avodart) be classified as non-formulary.

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

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

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

VI. DRUG CLASS REVIEW - PROTON PUMP INHIBITORS (PPIs)

A. Relative Clinical Effectiveness:

1) FDA-Approved Indications and Other Uses

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

In practice, most of the agents have published data showing effectiveness for use in any of the acid related disorders and are commonly prescribed to treat all acid

related conditions, regardless of FDA indication. Omeprazole (Prilosec, generics), lansoprazole (Prevacid), and esomeprazole (Nexium) are indicated for use in children.

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

2) Efficacy Measures

Comparative efficacy was evaluated on a disease state basis based on FDA indicated uses of the PPIs. The emphasis was on objective clinical endpoints (ulcer healing, esophagitis healing, maintenance of healing / prevention of disease, and symptomatic resolution) rather than surrogate endpoints (such as pH measurements, supplemental antacid use and serum drug levels), given the uncertain relationship of surrogate endpoints to clinical outcomes.

3) Clinical Evidence

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

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

4) Efficacy

i. Erosive esophagitis (EE) healing

Evidence from head-to-head trials suggests the majority of patients obtain complete healing of erosive disease within 8 weeks of treatment on any PPI, with most patients achieving symptom relief within 4 weeks of initiating treatment.

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

Two trials comparing esomeprazole and lansoprazole reported differences favoring esomeprazole, with one trial reporting statistically significant differences in healing and symptom resolution at 4 weeks that disappeared by 8 weeks and the other reporting a small but statistically significant difference in healing and symptom resolution at 4 weeks and healing at 8 weeks. Another head-to-head trial of esomeprazole and lansoprazole showed no significant difference in healing or symptom resolution at the same time points.

Two trials comparing esomeprazole and omeprazole reported differences favoring esomeprazole; both trials compared esomeprazole 40 mg to omeprazole 20 mg, which are not equivalent doses. Two adequately powered later trials, one comparing esomeprazole 40 mg to omeprazole 20 mg and one comparing esomeprazole 20 mg to omeprazole 20 mg, failed to show statistically significant differences in healing rates at 4 and 8 weeks or symptom resolution at 4 weeks.

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

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

ii. Maintenance of healing in erosive esophagitis

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

Conclusion – There is sufficient evidence to support the use of PPIs for maintenance of initial healing and symptomatic relief of EE for as long as 5 years. However, the evidence is insufficient to conclude that one PPI is superior to others for maintenance of EE healing.

iii. Ulcer healing and maintenance of healing

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

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

iv. Endoscopy negative reflux disease

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

Six trials show efficacy of various healing or maintenance doses of PPIs for initial resolution of heartburn (the primary outcome in all of the trials). Three other trials compare on-demand use of a PPI to placebo or an active comparator (e.g., a histamine-2 blocker), as continuation therapy after initial resolution of symptoms.

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

v. H. pylori eradication with multi-drug regimens

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

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

vi. Efficacy in Pediatric Patients

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

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

5) Safety / Tolerability

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

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

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

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

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

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

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

e) *Other factors* – Lansoprazole (Prevacid), esomeprazole (Nexium) and omeprazole/sodium bicarbonate (Zegerid) have dosage forms that can be used in pediatric patients or patients with swallowing difficulties. All three are available as packets for oral suspension; lansoprazole (Prevacid) is also

available as an orally disintegrating tablet. Omeprazole (Prilosec, generics) capsules contain enteric-coated granules commonly used to prepare a bicarbonate-based extemporaneous suspension.

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

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

6) PPIs – Overall Clinical Effectiveness Conclusion:

The P&T Committee concluded that:

a) Based on head-to-head and other controlled trials, PPIs have similar efficacy in a wide range of acid related disorders and are highly therapeutically interchangeable. Although some trials appear to demonstrate superior efficacy for healing of EE with esomeprazole, actual differences are small and inconsistent among trials. Evidence for clinical efficacy is similar enough to consider all agents equally effective in healing of EE.

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

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

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

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

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

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

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

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

B. Proton Pump Inhibitors (PPIs) – Relative Cost Effectiveness

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

1) C7301: Two or fewer PPIs are selected for the UF and one PPI is selected for the BCF. ($\leq$2 UF, 1 BCF)

2) C7302: Three or four PPIs are selected for the UF and one PPI is selected for the BCF. (3-4 UF, 1 BCF)

3) C7303: Three or four PPIs are selected for the UF and two PPIs are selected for the BCF. (3-4 UF, 2 BCF)

4) C7304: Five or more PPIs are selected for the UF and one PPI is selected for the BCF. ($\geq$5 UF, 1 BCF)

5) C7305: Five or more PPIs are selected for the UF and two PPIs are selected for the BCF. ($\geq$5 UF, 2 BCF)

6) C7306: Two PPIs (generic omeprazole and one other PPI) are selected for the UF and generic omeprazole is the only PPI selected for the BCF. In addition, a PA process requires all new PPI users to complete an adequate trial of generic omeprazole before any other PPI is provided to a new user through an MTF pharmacy, the TMOP, or a TRICARE retail network pharmacy.

7) C7307: Two PPIs (generic omeprazole and one other PPI) are selected for the UF. Generic omeprazole will be selected to the BCF and the other PPI may be selected

for the BCF. In addition, a PA process requires all new PPI users to complete an adequate trial of generic omeprazole or the second UF PPI before any third tier PPI is provided to a new user through an MTF pharmacy, the TMOP, or a TRICARE retail network pharmacy.

Results from the PPI CMAs showed three important findings: 1) as expected, the more restrictive the UF scenario, the lower the cost per day of treatment; 2) for the three condition sets that evaluated UF scenarios with two or fewer UF agents(C7301, C7306, and C7307), omeprazole and esomeprazole were the most cost effective agents; and 3) for the two condition sets that evaluated UF scenarios with 3 to 4 UF agents (C7302 and C7303), omeprazole, esomeprazole, pantoprazole, and rabeprazole were the most cost effective agents.

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

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

COMMITTEE ACTION: The DOD P&T Committee voted to accept the PPI relative cost effectiveness analysis as presented by the PEC.

C. Uniform Formulary Recommendation: In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that: 1) omeprazole (Prilosec, generics) and esomeprazole (Nexium) be maintained as formulary on the UF with a prior authorization requiring a trial of either agent for new patients; 2) that rabeprazole (Aciphex), lansoprazole (Prevacid), pantoprazole (Protonix), and omeprazole/sodium bicarbonate (Zegerid) be classified as non-formulary with a PA requiring a trial of either omeprazole (Prilosec, generics) or esomeprazole (Nexium) for new patients; and 3) that the normal brand formulary cost-share of $9.00 for esomeprazole (Nexium) be lowered to the generic formulary cost-share of $3.00.

The authority for the last recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the Pharmacy and Therapeutics Committee may also designate that the drug be cost-shared at the generic rate." Lowering the cost-share for brand name esomeprazole (Nexium) will provide a greater incentive for beneficiaries to use esomeprazole rather than the less

cost effective branded products—rabeprazole (Aciphex), lansoprazole (Prevacid), pantoprazole (Protonix), or omeprazole/sodium bicarbonate (Zegerid)—in the purchased care arena.

(a) PPIs – PA Criteria

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

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

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

D. Implementation Period

The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The P&T Committee believed the considerable cost avoidance associated with this recommendation warranted a more aggressive implementation period. Furthermore, the P&T Committee was anxious to extend the $3.00 cost-share for esomeprazole (Nexium) to beneficiaries as soon as possible. The implementation period will begin immediately following approval by the Director, TMA.

VII. Proton Pump Inhibitors (cont.)

BAP Comments

A. **Uniform Formulary Recommendation:** In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that: 1) omeprazole (Prilosec, generics) and esomeprazole (Nexium) be maintained as formulary on the UF with a prior authorization requiring a trial of either agent for new patients; 2) that rabeprazole (Aciphex), lansoprazole (Prevacid), pantoprazole (Protonix), and omeprazole/sodium

bicarbonate (Zegerid) be classified as non-formulary with a PA requiring a trial of either omeprazole (Prilosec, generics) or esomeprazole (Nexium) for new patients; and 3) that the normal brand formulary cost-share of $9.00 for esomeprazole (Nexium) be lowered to the generic formulary cost-share of $3.00.

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

(a) PPIs – PA Criteria

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

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

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

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

B. **Implementation Plan:** The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The P&T Committee believed the considerable cost avoidance associated with this recommendation warranted a more aggressive implementation period. Furthermore, the P&T Committee was anxious to extend the $3.00 cost-share for esomeprazole (Nexium) to beneficiaries as soon as possible. The implementation period will begin immediately following approval by the Director, TMA.

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

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

A. ARBs – Relative Clinical Effectiveness

The ARB drug class was previously evaluated for UF status in Feb 05. The P&T Committee focused on efficacy differences with respect to labeled indications, particularly in those areas where a benefit in clinical outcomes (e.g., death, hospitalization for heart failure, decreased need for dialysis or renal transplantation) was demonstrated. The primary areas evaluated were efficacy for hypertension, chronic heart failure (HF), and type 2 diabetic nephropathy.

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

1) Efficacy

a) Efficacy Measures

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

b) Hypertension

All seven ARBs are approved by the FDA for treating hypertension. One meta-analysis evaluating the ARBs (with the exception of olmesartan) examined data from over 51 clinical trials enrolling over 12,000 patients with

hypertension. The meta-analysis reported that treatment with any ARB reduced systolic blood pressure by 7.5-10 mm Hg and diastolic blood pressure (DBP) by 4.5 to 6.5 mm Hg, compared to placebo (placebo-corrected values). Pooled clinical trial data from seven studies with olmesartan (Benicar) enrolling over 2,600 patients show similar BP reductions to the other six ARBs.

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

c) *Hypertension and Clinical Outcomes*

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

Candesartan (Atacand) was found to reduce non-fatal stroke in the SCOPE trial in elderly patients when compared to placebo. When valsartan (Diovan) was compared to amlodipine (Norvasc) in the VALUE trial, there were no differences noted in cardiovascular mortality or all-cause mortality between the two drugs, however, there were fewer MIs, fatal strokes, and nonfatal strokes with amlodipine. The beneficial results with amlodipine were attributed to a greater percentage of patients achieving target BP goals vs. valsartan (64% vs. 58%). In the Jikei Heart Study, valsartan was found to reduce cardiovascular events and strokes, compared to placebo, in a Japanese population.

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

e) Chronic Heart Failure

There are no head to head trials comparing the ARBs for use in chronic heart HF. Two large, randomized, placebo-controlled trials, one each with valsartan

(Diovan) and candesartan (Atacand), demonstrated a reduction in the risk of hospitalization due to chronic HF, a clinically relevant outcome.

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

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

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

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

f) Type 2 Diabetic Nephropathy

Patients with type 2 diabetes frequently progress from microalbuminuria to overt proteinuria, with decreasing GFR and eventual development of ESRD. However, the most common cause of death in diabetic patients is due to cardiovascular complications.

i) Microalbuminuria

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

Placebo- or active-controlled trials – Benefits on physiologic outcomes in patients with microalbuminuria have been shown with candesartan (Atacand), irbesartan (Avapro), telmisartan (Micardis) and valsartan (Diovan) in small studies with placebo or active comparators (usually an ACE inhibitor or calcium channel blocker). There is no published data

evaluating efficacy of eprosartan (Teveten) or olmesartan (Benicar) in either microalbuminuria or nephropathy.

ii) Nephropathy

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

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

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

g) Post Myocardial Infarction

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

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

2) Safety / Tolerability

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

These medications are generally well-tolerated, with adverse event rates for all the ARBs similar to placebo in controlled trials. The likelihood of potentially serious adverse events, including hyperkalemia, elevations of serum Cr, and angioedema, does not appear to differ among agents. Drug interaction profiles are similar. All

ARBs are rated pregnancy category C during the first trimester, and pregnancy category D during the second and third trimesters, based on the occurrence of fetal abnormalities with ACE inhibitors. The P&T Committee agreed that there is no evidence that any one ARB is preferable to the others with respect to safety or tolerability.

3) Other Factors

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

4) DoD Utilization

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

5) Therapeutic Interchangeability

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

6) Clinical Coverage

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

7) ARB Overall Clinical Effectiveness Conclusion

The DoD P&T Committee concluded that:

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

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

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

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

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

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

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

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

B. ARBs – Relative Cost Effectiveness

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the ARB medications differed in regards to efficacy, safety, or tolerability in the treatment of hypertension. However, several products did have additional clinical outcomes data and FDA approved indications for the treatment of chronic HF (candesartan and valsartan) and type 2 diabetic nephropathy (losartan and irbesartan). The clinical review determined that a UF scenario with an agent from these two additional subgroups would be clinically advantageous. As a result, several cost-minimization analyses (CMAs) were performed to determine the relative cost effectiveness of the agents by condition set (3 or fewer agents on the UF, 4 – 5 agents on the UF, and 6 or more agents on the UF) and by indication (hypertension, chronic HF, and type 2 diabetic nephropathy). The CMAs compared the weighted average cost per day of treatment for each drug product across all three points of service.

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

Based on the results of the clinical review and the pharmacoeconomic evaluations, a budget impact analysis (BIA) of various formulary scenarios was conducted to

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

Cost Effectiveness Conclusion –The Committee accepted the conclusions stated above and determined from the BIA that the Uniform Formulary scenario that included candesartan (Atacand), candesartan/HCTZ (Atacand HCT), losartan (Cozaar), losartan/HCTZ (Hyzaar), telmisartan (Micardis), and telmisartan/HCTZ (Micardis HCT) was the most cost effective UF scenario.

COMMITTEE ACTION: The DoD P&T Committee to accept the ARB relative cost effectiveness analysis as presented by the PEC.

C. Uniform Formulary Recommendations

In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ARBs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that candesartan (Atacand), candesartan/HCTZ (Atacand HCT), losartan (Cozaar), losartan/HCTZ (Hyzaar), telmisartan (Micardis), and telmisartan/HCTZ (Micardis HCT) be maintained as formulary on the UF and that eprosartan (Teveten), eprosartan/HCTZ (Teveten HCT), irbesartan (Avapro), irbesartan/HCTZ (Avalide), olmesartan (Benicar), olmesartan/HCTZ (Benicar HCT), valsartan (Diovan) and valsartan/HCTZ (Diovan HCT) be classified as non-formulary.

D. **Uniform Formulary Implementation Period**

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

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

BAP Comments

A. Uniform Formulary Recommendations. In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ARBs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that candesartan (Atacand), candesartan/HCTZ (Atacand HCT), losartan (Cozaar), losartan/HCTZ (Hyzaar), telmisartan (Micardis), and telmisartan/HCTZ (Micardis HCT) be maintained as formulary on the UF and that eprosartan (Teveten), eprosartan/HCTZ (Teveten HCT), irbesartan (Avapro), irbesartan/HCTZ (Avalide), olmesartan (Benicar), olmesartan/HCTZ (Benicar HCT), valsartan (Diovan) and valsartan/HCTZ (Diovan HCT) be classified as non-formulary.

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

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

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