DOD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS
INFORMATION FOR THE DOD 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. 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 must be reviewed by the Beneficiary Advisory Panel (BAP) before the Director may make a final decision.

II. Angiotensin Receptor Blockers (ARBs) Drug Class Review

P&T Comments

A. Relative Clinical Effectiveness: The DoD Pharmacy and Therapeutics (P&T) Committee evaluated the relative clinical effectiveness of the seven ARBs marketed in the US [losartan (Cozaar), irbesartan (Avapro), valsartan (Diovan), candesartan (Atacand), telmisartan (Micardis), eprosartan (Teveten) and olmesartan (Benicar] and their respective combinations with hydrochlorothiazide, by considering information regarding their safety, effectiveness, and clinical outcome. The clinical review included consideration of pertinent information from a variety of sources determined by the Committee to be relevant and reliable, including but not limited to sources of information listed in 32 C.F.R. 199.21(e)(1). The Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the Uniform Formulary unless the Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the Uniform Formulary in that therapeutic class.

There has been an increase in the use of ARBs over the past five years and the class is now in the top 10 of Military Health System (MHS) drug class expenditures. The committee agreed that in the MHS, ARBs are not recommended as first-line agents for treating hypertension due to their higher cost and fewer trials supporting a mortality reduction, compared to diuretics or angiotensin converting enzyme (ACE) inhibitors. The ACE inhibitors and ARBs have similar safety concerns regarding hyperkalemia, elevations of serum creatinine, angioedema, and pregnancy category labeling. The ARBs have an incidence of cough similar to placebo. An ARB is an appropriate agent for hypertension if a patient cannot tolerate an ACE inhibitor.

1.) Efficacy for Hypertension: All seven ARBs are approved by the FDA for treating hypertension. In clinical trials, ARBs lowered systolic blood pressure by 7.5-10 mm Hg and diastolic blood pressure by 4.5 to 6.5 mm Hg,

compared to placebo. The Committee agreed that there is no evidence that any one ARB is more efficacious than the others for lowering blood pressure.

2). *Efficacy for Chronic Heart Failure:* When evaluating the ARBs for treatment of chronic heart failure, the Committee agreed that evidence of a favorable effect on clinical outcomes (i.e., irreversible outcomes such as hospitalization for heart failure or death) is more important than evidence of favorable effects on physiologic outcomes (i.e., reversible outcomes that are surrogate markers of disease, such as changes in pulmonary capillary wedge pressure).

Two ARBs have clinical evidence from large, well-conducted, randomized controlled trials showing a reduction in the risk of hospitalization due to chronic heart failure, a clinically relevant outcome. Based on the results of the Val-HeFT trial, the FDA approved valsartan for use in patients with heart failure who are intolerant of ACE inhibitors. The CHARM trials with candesartan support its use in chronic heart failure, although at the time of the meeting the FDA had not yet approved candesartan for this indication. (Note: Candesartan was approved for heart failure on 22 Feb 05, following the DoD P&T committee meeting). The Committee agreed that there was no evidence that either valsartan or candesartan were preferable relative to the other for the treatment of chronic heart failure. Since none of the other ARBs have outcome studies showing a reduction in clinically relevant outcomes related to chronic heart failure, the Committee agreed that valsartan and candesartan were preferable to the other five ARBs for the treatment of heart failure.

3.) *Efficacy for Type 2 Diabetic Nephropathy*: When evaluating the ARBs for treatment of type 2 diabetics with nephropathy, the Committee agreed that evidence of a favorable effect on clinical outcomes (i.e., irreversible outcomes such as development of end stage renal disease, the need for dialysis or renal transplantation, or death) is more important than evidence of favorable effects on physiologic outcomes (i.e., reversible outcomes that are surrogate markers of disease, such as changes in the urinary albumin to creatinine ratio, urinary albumin excretion rate, or glomerular filtration rate).

Based on the results of the RENAAL and IDNT trials, the FDA has approved two ARBs, losartan and irbesartan, respectively, for treatment of diabetics who have an elevated serum creatinine and proteinuria. The Committee agreed that there was no evidence that either losartan or irbesartan were preferable relative to the other for the treatment of renal nephropathy in type 2 diabetics. Since none of the other ARBs have outcome studies showing a reduction in clinically relevant outcomes related to type 2 diabetic nephropathy, the Committee agreed that losartan and irbesartan were preferable to the other five ARBs for the treatment of type 2 diabetic nephropathy.

4.) *Safety/Tolerability:* The Committee agreed that there is no evidence that any one ARB is preferable to the others with respect to safety or tolerability. These medications are generally well tolerated, with adverse event rates for

all the ARBs similar to placebo in controlled trials. The likelihood of potentially serious adverse events, including hyperkalemia, elevations of serum creatinine, and angioedema, do not appear to differ among agents. Drug interaction profiles are similar. All ARBs are 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.

Conclusion: The P&T Committee concluded that:

(1) all seven ARBs have similar relative clinical effectiveness for treating hypertension;

(2) candesartan and valsartan have similar relative clinical effectiveness for treating chronic heart failure;

(3) losartan and irbesartan have similar relative clinical effectiveness for treating type 2 diabetics with nephropathy;

(4) all seven ARBs have similar safety and tolerability profiles. Valsartan, candesartan, losartan and irbesartan have higher clinical utility (overall clinical usefulness) relative to the three ARBs that are indicated solely for treating hypertension (telmisartan, eprosartan, and olmesartan).

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to accept the conclusion that valsartan, candesartan, losartan, and irbesartan have increased clinical utility (due to their evidence for uses in addition to hypertension) relative to the three ARBs that are only indicated for treating hypertension (telmisartan, olmesartan, and eprosartan) and concluded that there is no evidence that any one ARB is more efficacious than the others for lowering blood pressure..

B. Relative Cost Effectiveness: In considering the relative cost effectiveness of pharmaceutical agents in this class, the Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). To determine the relative cost-effectiveness of the agents within the ARB therapeutic class, two separate economic analyses were performed, a pharmacoeconomic analysis and budget impact analysis (BIA). The preceding conclusion from the Committee that all seven ARBs showed similar relative clinical effectiveness for treating hypertension; that candesartan and valsartan showed similar relative clinical effectiveness for treating chronic heart failure, and that losartan and irbesartan showed similar relative clinical effectiveness for treating type 2 diabetic nephropathy was incorporated into the models. Given the results of the clinical analysis, a series of cost-minimization analyses (CMA) were conducted which revealed: that candesartan was more cost-effective relative to valsartan for the treatment of heart failure; that irbesartan was more cost-effective relative to losartan for treatment of type 2 diabetic nephropathy; and that irbesartan was more cost-effective relative to the other ARBs for the treatment of

hypertension. Moreover, it was determined that eprosartan was not cost-effective relative to the other hypertension ARBs (telmisartan and olmesartan).

The results of the CMA were subsequently incorporated into a BIA, which accounts for other factors and costs associated with a potential decision to recommend one or more ARBs status be changed from formulary to non-formulary such as: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and costs incurred while switching patients from non-formulary agents to formulary agents. The results of the budget impact analyses further confirmed the results from the cost minimization analyses. Eprosartan was found not to be cost-effective relative to the other hypertension ARBs.

Conclusion: The Committee concluded that eprosartan was not cost-effective relative to the other ARBs for treating hypertension. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ARBs, and other relevant factors, the Committee recommended that eprosartan's status be changed from formulary to non-formulary, with candesartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan maintaining formulary status with the formulary cost share.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to recommend formulary status for candesartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan, and non-formulary status for eprosartan under the Uniform Formulary.

C. Implementation Plan: Because relatively few patients are receiving eprosartan at any MHS pharmacy point of service (less than 1% of all patients receiving ARBs) the Committee proposed a 30-day transition period for implementation of a decision by the Director, TMA, to classify eprosartan as non-formulary on the Uniform Formulary. Prior to the P&T Committee meeting, the Government had solicited a request for blanket purchase agreement (BPA) price quotes from manufacturers. One manufacturer subsequently filed a protest concerning this class with the Government Accountability Office (GAO). Any decision by the Director, TMA, concerning this class, including an implementation plan, may proceed, however, no award of a BPA, based on these quotes will occur until after the GAO has issued a ruling on the protest. The TMA and PEC web sites will notify all interested parties when GAO has ruled on the protest, and what subsequent decisions have been made.

MTFs are not allowed to have non-formulary pharmaceutical agents on their local formularies. MTFs will be able to fill non-formulary requests for non-formulary agents only if both of the following conditions are met: 1) the prescription is written by a MTF provider and 2) the beneficiary and his or her provider has established medical necessity for the agent. MTFs may (but are not required to) fill a non-formulary prescription written by a non-MTF provider to whom the patient was referred as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee voted to recommend an effective date of 30 days from the final decision date if the Director, TMA, approves the Committee's recommendation.

II. Angiotensin Receptor Blockers (ARBs) drug class review (cont.)

BAP Comments

A. **Relative Clinical Effectiveness***:* The P&T Committee concluded that
(1) all seven ARBs have similar relative clinical effectiveness for treating hypertension;
(2) that candesartan and valsartan have similar relative clinical effectiveness for treating chronic heart failure;
(3) that losartan and irbesartan have similar relative clinical effectiveness for treating type 2 diabetics with nephropathy;
(4) that all seven ARBs have similar safety and tolerability profiles. Valsartan, candesartan, losartan and irbesartan have higher clinical utility (overall clinical usefulness) relative to the three ARBs that are indicated solely for treating hypertension (telmisartan, eprosartan, and olmesartan).

Considering the relative clinical effectiveness determinations of the ARBs, the P&T Committee, based upon its collective professional judgment, accepted the conclusion that valsartan, candesartan, losartan, and irbesartan have increased clinical utility (due to their evidence for uses in addition to hypertension) relative to the three ARBS that are only indicated for treating hypertension (telmisartan, olmesartan, and eprosartan), and concluded that there is no evidence that any one ARB is more efficacious than the others for lowering blood pressure.

B. **Relative Cost Effectiveness:** The P&T Committee, based upon its collective professional judgment, concluded that eprosartan was not cost-effective relative to the other ARBs for treating hypertension.

C. **Uniform Formulary Recommendation:** Considering the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ARBs, and other relevant factors, the P&T Committee recommended that eprosartan's status be changed from formulary to non-formulary, with candesartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan maintaining formulary status with the formulary cost share under the Uniform Formulary as stated in 1A and 1B above.

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

D. **Implementation Plan*:*** The P&T Committee recommended an effective implementation date of 30 days from the final decision date if the Director, TMA, approves the Committee's recommendation.

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

III. Proton Pump Inhibitors (PPIs) drug class review

P&T Comments

A. **Relative Clinical Effectiveness*:*** The P&T Committee evaluated the relative clinical effectiveness of all the FDA approved proton pump inhibitors available in the US. The PPI therapeutic class was defined as omeprazole (Prilosec, Zegerid & generics), lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix), and esomeprazole (Nexium). The clinical review included consideration of pertinent information from a variety of sources determined by the Committee to be relevant and reliable, including but not limited to sources of information listed in 32 C.F.R. 199.21(e)(1). The Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the Uniform Formulary unless the Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the Uniform Formulary in that therapeutic class.

PPIs are among the top 10 MHS drug class expenditures. The Committee agreed that in the MHS, PPIs are not recommended as first-line agents for treating Gastro Esophageal Reflux Disease (GERD), and they are not intended for the immediate relief of infrequent GERD symptoms. For GERD symptom relief, PPIs are best used after lifestyle modification, antacid and H2-blocker therapies have failed. PPIs are first-line therapy for Peptic Ulcer Disease (PUD), whether non-steroidal anti-inflammatory drug (NSAID)-induced, associated with *Helicobacter pylori* infection, or due to a hypersecretory condition.

1.) *Efficacy:* Although FDA indications differ slightly amongst the PPIs, the vast majority of studies found no significant difference in efficacy in treating GERD and PUD. Minor differences in clinical utility, such as pediatric indication, possible need for dosage adjustment in hepatic failure, and availability of alternative dosage forms were noted. After a review of head-to-head trials and meta-analyses, the P&T Committee concluded that all of the PPIs show similar efficacy when equivalent doses are used.

2.) *Safety/Tolerability:* The P&T Committee found that PPIs were not significantly different with respect to major contraindications, drug interactions, and adverse drug events. The dropout rates in clinical trials due to adverse events were comparable amongst the five PPIs. All PPIs are pregnancy category B, except omeprazole, which is category C.

Conclusion: The P&T Committee concluded that all PPIs have similar relative clinical effectiveness for treating GERD and PUD. All five PPIs have similar safety and tolerability profiles.

COMMITTEE ACTION*:* The P&T Committee, based upon its collective professional judgment, concluded that all five PPIs demonstrate similar relative clinical effectiveness.

B. **Relative Cost Effectiveness*:*** In considering the relative cost effectiveness of pharmaceutical agents in this class, the Committee evaluated the costs of the agents in relation to the safety, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). Two analyses were used to determine the relative cost-effectiveness of agents within the PPI therapeutic class; a pharmacoeconomic analysis using cost-minimization techniques, and a budget impact analysis (BIA). Cost-minimization (CMA) was chosen for the pharmacoeconomic analysis because the clinical analysis determined the outcomes of interest (effectiveness, safety, and tolerability) to be similar among all the PPIs.

Results of the CMA showed omeprazole to be the most cost-effective PPI across all points of service (MTFs, Retail, Mail), followed by rabeprazole, lansoprazole, and pantoprazole. It was determined that esomeprazole was not cost effective relative to the other PPIs.

The results of the CMA were then incorporated into a BIA, which accounts for other factors and costs associated with a potential decision regarding formulary status of PPIs within the Uniform Formulary. These factors included: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and switch costs. The results of the budget impact analysis further confirmed the results of the CMA. Esomeprazole was found not to be cost effective relative to the other PPIs.

Conclusion: The P&T Committee concluded that esomeprazole was not cost effective relative to the other PPIs. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the PPIs and other relevant factors, the P&T Committee recommended that esomeprazole's status be changed from formulary to non-formulary, with rabeprazole, lansoprazole, and pantoprazole maintaining formulary status with the formulary cost share, and omeprazole maintaining formulary status with a generic cost share.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to recommend non-formulary status for

esomeprazole, with rabeprazole, lansoprazole, and pantoprazole maintaining formulary status at the formulary cost share, and omeprazole maintaining formulary status at the generic cost share.

C. **Implementation Plan*:*** Because a substantial number of patients are currently receiving esomeprazole from one of the three MHS pharmacy points of service (138,739 patients, 13.4 % of all patients receiving PPIs) the P&T Committee proposed a 90-day transition period for implementation of the decision to change esomeprazole to a non-formulary drug on the Uniform Formulary. Patients wishing to fill prescriptions for esomeprazole at retail network pharmacies or the TMOP would then have to pay the non-formulary cost share unless medical necessity for esomeprazole is established by the beneficiary and/or his or her provider.

Prior to the implementation of the Uniform Formulary, the former DoD P&T Committee had made a decision that prescriptions for esomeprazole could not be filled through the TMOP, unless medical necessity was validated. If the Director, TMA, concurs in the Committee's recommendation, prescriptions for esomeprazole may be filled through the TMOP, but will require payment of the non-formulary cost share of $22. Beneficiaries who already have a medical necessity validation on file at the TMOP are required to re-establish medical necessity for esomeprazole under the medical necessity criteria approved by the Director, TMA, in order to receive esomeprazole at the formulary cost share.

MTFs will not be allowed to have esomeprazole on their local formularies. MTFs will be able to fill non-formulary requests for esomeprazole only if both of the following conditions are met: 1) the prescription must be written by a MTF provider and 2) the beneficiary and his or her provider must establish medical necessity for esomeprazole. MTFs may (but are not required to) fill an esomeprazole prescription written by a non-MTF provider to whom the patient was referred by the MTF as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee voted to recommend an effective date of 90 days from the final decision date, the date that DoD P&T Committee minutes are signed by the Director, TMA, approving the Committee's recommendation.

III. Proton Pump Inhibitor (PPI) drug class review (cont)

BAP Comments

***A*. Relative clinical effectiveness**: The P&T Committee, based upon its collective professional judgment, concluded that all PPIs have similar relative clinical effectiveness for treating Gastro Esophageal Reflux Disease (GERD) and Peptic Ulcer Disease (PUD). All five PPIs have similar safety and tolerability profiles.

B.* Relative Cost Effectiveness:* The P&T Committee, based upon its collective professional judgment, concluded that esomeprazole was not cost effective relative to the other PPIs.

C. Uniform Formulary Recommendation: Considering the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations of the PPIs, the P&T Committee recommended that esomeprazole's status be changed from formulary to non-formulary, with rabeprazole, lansoprazole, and pantoprazole maintaining formulary status with the formulary cost share, and omeprazole maintaining formulary status with a generic cost share under the Uniform Formulary as stated in 1A and 1B above.

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

D. Implementation Plan*:* The P&T Committee recommended an effective date of 90 days from the final decision date, the date that DoD P&T Committee minutes are signed by the Director, TMA, approving the Committee's recommendation.

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

IV. Prior Authorizations Review

P&T comments

The DoD P&T Committee reviewed existing prior authorizations and recommended rules for new FDA approved drugs in drug classes for which prior authorizations already exist. This would provide a consistent benefit and avoid circumstances

under which prior authorizations exist for very similar medications but cannot be applied to newly approved medications of the same type only after several months of unrestricted use. The PEC would report changes to prior authorizations following these general rules at the next scheduled DoD P&T Committee meeting.

DoD Pharmacy and Therapeutics Committee Action*:* The P&T Committee made the following recommendation: Any new drug in the following classifications that may become available for use in treatment will be subject to the same prior authorization as the existing agents.

- *PDE-5 inhibitors* for erectile dysfunction
- *Injectable gonadotropins* for infertility treatment
- *Antifungals* for onychomycosis
- *Growth hormone agents*

IV. Prior Authorizations Review

BAP comments

Application of PAs to newly FDA-approved drugs within the same class*:*** The P&T Committee recommended the following: Any new drug in the following classifications that may become available for use in treatment will be subject to the same prior authorization as the existing agents.

- *PDE-5 inhibitors* for erectile dysfunction
- *Injectable gonadotropins* for infertility treatment
- *Antifungals* for onychomycosis
- *Growth hormone agents*

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