

**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. ADRENERGIC BETA-BLOCKING AGENTS (ABAs)**

*P&T Comments*

**A. ABAs - Relative Clinical Effectiveness:**

The P&T Committee evaluated the relative clinical effectiveness of the ABAs marketed in the U.S. by considering information regarding their safety, effectiveness, and clinical outcomes. The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 CFR 199.21(e)(1).

The P&T Committee focused on the clinical effectiveness of the ABAs for treating cardiovascular disorders, in particular chronic HF; non-cardiovascular uses were not evaluated. Use of the ABAs for hypertension and acute myocardial infarction were only briefly discussed, since all of the older ABAs are available in generic formulations, and have been commercially available for decades. Additionally other antihypertensive drug classes are now available that are widely used (e.g., ACE inhibitors, ARBs, calcium channel blockers).

- 1) *Pharmacology* - With respect to pharmacology, the ABAs differ in their selectivity for the beta ( $\beta$ ) and alpha ( $\alpha$ ) receptors. ABAs with  $\beta$ 1-selectivity include atenolol (Tenormin, generics), metoprolol succinate (Toprol XL, generics), metoprolol tartrate (Lopressor, generics) and bisoprolol (Zebeta). Cardioselectivity is postulated to reduce adverse pulmonary effects, however selectivity is dose dependent. Carvedilol (Coreg IR and generics; Coreg CR) and labetalol (Trandate, generics) are non-selective ABAs that have equal affinity for  $\beta$ 1 and  $\beta$ 2 receptor, and also exhibit  $\alpha$ -blocking properties, which decreases peripheral vascular resistance via vasodilation.
- 2) *FDA-Approved Indications* – All of the ABAs and the ABA/diuretic combinations are approved for treating hypertension, with the exception of sotalol (Betapace, Betapace AF, generics). Both metoprolol tartrate (Lopressor, generics) and

metoprolol succinate (Toprol XL, generics) are approved for angina. With regards to chronic HF, carvedilol (Coreg IR and generics; Coreg CR) and metoprolol succinate (Toprol XL) are indicated for use to reduce the risk of death, however there are slight differences in the package labeling. Both Coreg IR and Coreg CR are approved for use in patients with mild to severe HF and to reduce the risk of death following myocardial infarction (MI) in patients with left ventricular systolic dysfunction (LVSD). Metoprolol succinate (Toprol XL, generics) is approved for treating patients with mild to moderately severe HF. Bisoprolol (Zebeta) is not approved for treating HF, but has evidence of a mortality benefit from one clinical trial (see efficacy section).

- 3) *Labetolol (Trandate, generics)* – Labetolol is similar to carvedilol in that it is a non-selective ABA that also exhibits  $\alpha$  receptor blocking properties. However the Committee agreed that clinical comparisons to carvedilol (Coreg IR, generics; Coreg CR) would not be considered, since labetalol has not been evaluated in the treatment of chronic HF. Niche uses for labetalol include intravenous use for hypertensive urgency/emergency, and use for pregnancy.
- 4) *Sotalol (Betapace, Betapace, AF, generics)* – Unlike the other ABAs, sotalol is the only ABA that is not approved for treating hypertension. Two branded formulations are available; Betapace is FDA-approved for treating ventricular arrhythmias, while Betapace AF is specifically labeled for use in maintaining normal sinus rhythm (NSR) in atrial fibrillation and contains instructions for initiating therapy. The Committee did not further evaluate sotalol, as both Betapace and Betapace AF are available in generic formulations.
- 5) *Carvedilol extended release (Coreg CR)* – The Committee evaluated the pharmacokinetic and pharmacodynamic differences between carvedilol extended release (Coreg CR) and carvedilol IR (Coreg IR, generics). Coreg CR is a capsule containing beads with differing release mechanisms. The Committee agreed that with the exception of the time to max concentration (which is delayed with carvedilol extended release), Coreg CR and Coreg IR show similar kinetic profiles.
- 6) *Efficacy for hypertension* – The Oregon Health & Science University's Drug Effectiveness Review Program (DERP) first reviewed the beta blockers in 2005, with an update published in 2007. DERP concluded that the ABAs are equally effective at controlling blood pressure in patients with hypertension. No ABA has been shown to be more efficacious than another, either as initial therapy or when added on to a diuretic, ACE inhibitor or ARB.
- 7) *Efficacy for chronic HF* – The P&T Committee focused on the use of metoprolol succinate (Toprol XL, generics), metoprolol tartrate (Lopressor, generics), carvedilol (Coreg IR and generics; Coreg CR) and bisoprolol (Zebeta, generics) for chronic HF. Both formulations of carvedilol are FDA-approved for HF, but the Coreg CR indication was granted solely based on data from Coreg IR clinical trials.

- a) *Placebo controlled trials* – Placebo controlled trials conducted with bisoprolol (CIBIS-II, metoprolol succinate (MERIT-HF), and carvedilol IR (US Carvedilol Trial) showed reductions in mortality of approximately 30%. Treatment with carvedilol IR showed a 35% reduction in mortality in patients with severe HF (left ventricular ejection fraction <20%) in the COPERNICUS trial. The CAPRICORN trial supported the use of carvedilol IR as it reduced the risk of death by 23% in post-MI patients with LVSD. FDA-approval for carvedilol extended release (Coreg CR) was based on the clinical trial data with carvedilol IR (Coreg IR, generics); Coreg CR has not been evaluated in a clinical trial for HF.
  - b) *Head-to-head trials* – Clinical outcomes were evaluated with carvedilol IR (Coreg IR and generics) vs. metoprolol tartrate (Lopressor, generics) in the COMET trial, which enrolled over 3,000 patients with mild to moderate HF. After 58 months, treatment with carvedilol resulted in a significant 17% reduction in mortality and a significant 29% reduction in fatal and non-fatal MI. The superiority of carvedilol over metoprolol tartrate seen in this trial has generated controversy, due to concerns of potential non-equivalent dosage comparisons. Metoprolol succinate (Toprol XL, generics) was not available to the COMET investigators, and has not been evaluated directly with carvedilol.
  - c) *National Guidelines* – The 2005 American College of Cardiology/American Heart Association guidelines specifically mention that three ABAs, metoprolol succinate (Toprol XL, generics), carvedilol (Coreg IR and generics; Coreg CR), and bisoprolol (Zebeta; generics), have shown a benefit in reducing mortality in patient with chronic HF. Patients with Stage C HF should receive one of these three ABAs.
- 8) *Safety and tolerability* - With respect to safety and tolerability, the adverse event profile of the ABAs is well known, and generally recognized as a class effect. In a retrospective study conducted in 268 patients enrolled in a HF clinic, no difference was seen in the percentage of patients started on either carvedilol IR or metoprolol succinate who were switched to the other drug due to tolerability problems with dizziness, fatigue, or dyspnea.
- With respect to safety differences between carvedilol IR and carvedilol extended release, conflicting results have been seen. In one comparative trial in patients with hypertension, the overall incidence of adverse events was lower with carvedilol extended release than carvedilol IR. However a higher incidence of adverse events with carvedilol CR was seen at the 80 mg dose vs. 25 mg carvedilol IR in patients with HF.
- 9) *Other Factors* – Differences in adherence between carvedilol IR and carvedilol extended release were evaluated by the P&T Committee. Carvedilol IR requires twice daily dosing, while carvedilol extended release is dosed once daily, which theoretically should improve patient adherence. Systematic reviews conducted with several drug classes other than the ABAs report adherence rates of 79% +/- 14% with QD dosing, vs. 69% +/- 15% with BID dosing. Whether this increase

in adherence translates into improved outcomes for the ABAs used for chronic HF remains unclear.

One manufacturer-sponsored study evaluating differences in compliance rates between carvedilol extended release and carvedilol IR found no difference between the two drugs in 269 patients with HF after 5 months of therapy (Coreg CR: 89.3% +/- 20.8 vs. Coreg IR: 88.1% +/- 24.1%). The clinical applicability of these results is difficult to determine, due to the open-label design of the Coreg CR arm, and the supervised setting of a HF clinic.

*10) Clinical Coverage* – In order to meet the needs of the majority of patients in DoD, the P&T Committee agreed that an ABA with evidence of a mortality benefit in chronic HF must be included on the BCF. The DoD P&T Committee also agreed that an ABA/diuretic combination did not require inclusion on the BCF.

*11) Therapeutic Interchangeability* – With respect to treating hypertension, the ABAs have a high degree of therapeutic interchangeability. With respect to treating chronic HF, there is a high degree of therapeutic interchangeability between carvedilol, metoprolol succinate, and bisoprolol, which have been shown to reduce mortality.

*12) ABA overall clinical effectiveness conclusion* - The DoD P&T Committee concluded that:

- a) Labetolol (Trandate, generics) was not clinically comparable to carvedilol (Coreg IR and generics; Coreg CR) despite exhibiting alpha blocking properties, as it has not been evaluated for chronic HF.
- b) Sotalol (Betapace, Betapace AF, generics) was not clinically comparable to the other ABAs, as it is not FDA-approved for treating chronic HF.
- c) For treating hypertension, there is no evidence of clinically relevant differences in efficacy between the ABAs, when titrated to effect.
- d) For treating chronic HF, metoprolol succinate (Toprol XL, generics), carvedilol (Coreg IR and generics; Coreg CR), and bisoprolol (Zebeta, generics) have been shown to reduce mortality. Bisoprolol is not FDA-approved for this indication. Based on the available evidence, there is no data to suggest that there are differences in the reduction in mortality between carvedilol, metoprolol succinate, or bisoprolol.
- e) Clinically relevant differences in the safety and tolerability profile of the ABAs are not apparent. There is insufficient evidence to determine if there are clinically relevant differences in the adverse event profile between carvedilol IR and carvedilol extended release.
- f) Despite the convenience of once daily dosing of carvedilol extended release (Coreg CR), there is no compelling clinical evidence to suggest a benefit of Coreg CR over carvedilol IR (Coreg IR and generics).
- g) Based on clinical issues alone, there are no compelling reasons to classify any of the ARBs as non-formulary on the UF.

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

## **B. ABAs – Relative Cost Effectiveness**

- A.** The P&T Committee evaluated the relative cost effectiveness of the ABAs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

For the economic evaluation, the ABAs were functionally divided into three groups, based on predominant use: 1) ABAs for hypertension, 2) ABAs for chronic HF, and 3) ABAs used for other conditions (e.g., severe hypertension; arrhythmias).

The ABAs for hypertension include acebutolol (Sectral, generics), atenolol (Tenormin, generics), betaxolol (Kerlone, generics), metoprolol tartrate (Lopressor, generics), nadolol (Corgard, generics), penbutolol (Levatol, generics), pindolol (Visken, generics), propranolol IR and ER (Inderal, Inderal LA, generics), timolol (Blocadren, generics), and their diuretic combinations of atenolol chlorthalidone (Tenoretic, generics), bisoprolol/HCTZ (Ziac, generics) metoprolol tartrate/HCTZ (Lopressor HCT, generics), nadolol/bendroflumethiazide (Corzide, generics), propranolol/HCTZ (Inderide, generics) and timolol-HCTZ (Timozide) (which has now been discontinued).

The ABAs for heart failure include bisoprolol (Zebeta, generics), metoprolol succinate (Toprol XL, generics), carvedilol IR (Coreg IR, generics), and carvedilol extended release (Coreg CR).

Lastly, the ABA group for other conditions includes sotalol (Betapace, Betapace AF) for ventricular arrhythmias and maintenance of NSR in patients with atrial fibrillation/flutter and labetalol (Normodyne, generics) for hypertension and severe hypertension.

The relative clinical effectiveness evaluation concluded that: 1) for hypertension, ABAs are highly clinically interchangeable when titrated to effect, and 2) for chronic HF, there is insufficient evidence to suggest clinically significant differences between agents [e.g. metoprolol succinate (Toprol XL, generics) vs. carvedilol (Coreg IR and generics; Coreg CR) vs. bisoprolol (Zebeta, generics)] or between different dosage forms approved for chronic HF (e.g. carvedilol IR vs. carvedilol CR). As a result, cost minimization analyses (CMA) were conducted for each subgroup to compare the relative cost effectiveness of these agents.

Results from the cost-effectiveness analyses revealed:

*For hypertension,*

- 1) The three most cost-effective agents are atenolol (Tenormin, generics), metoprolol tartrate (Lopressor, generics), and propranolol IR (Inderal, generics), which account for 90% of the hypertensive ABA utilization.

- 2) The other agents are more costly and have lower utilization relative to the top three, but all of these agents are generically available and are considered to be cost-effective.

*For heart failure,*

- 1) Carvedilol IR (Coreg IR, generics) is the most cost-effective ABA followed closely by (ranked from most to least cost-effective) bisoprolol (Zebeta, generics), metoprolol succinate (Toprol XL, generics), and carvedilol extended release (Coreg CR).
- 2) The system-wide weighted average cost per day for carvedilol extended release (Coreg CR) was only slightly higher than that of carvedilol IR (Coreg IR, generics), and thus was determined to be cost-effective relative to the other ABAs for chronic HF.

*For other conditions,*

- 1) Sotalol (Betapace, generics), sotalol AF (Betapace AF, generics), and labetalol (Normodyne, generics) are all available in generic formulations and are cost-effective.

A budget impact analysis (BIA) was performed to examine the potential budget impact of a UF scenario with carvedilol extended release (Coreg CR) designated as formulary on the UF versus a one with carvedilol extended release designated as non-formulary on the UF. The BIA showed that the scenario that designated carvedilol extended release (Coreg CR) as formulary on the UF resulted in significantly lower MHS expenditures versus the scenario which designated carvedilol extended release (Coreg CR) as non-formulary on the UF.

*Cost Effectiveness Conclusion* – The P&T Committee concluded for consideration of UF status that:

- 1) All ABAs used primarily to treat hypertension are cost-effective, with atenolol (Tenormin, generics), metoprolol tartrate (Lopressor, generics), and propranolol IR (Inderal, generics) being the most cost-effective.
- 2) All of the ABAs with clinical evidence for heart failure are cost-effective, with carvedilol IR (Coreg IR, generics) being the most cost-effective agent.
- 3) The ABAs for other indications, sotalol (Betapace, generics), sotalol AF (Betapace AF, generics), and labetalol (Normodyne, generics) are cost-effective.

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

### **C. ABAs - Uniform Formulary Recommendation**

In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the NAs, and other relevant factors, the P&T

Committee, based upon its collective professional judgment, voted to recommend that:

Atenolol (Tenormin, generics), atenolol-chlorthalidone (Tenoretic, generics), metoprolol tartrate (Lopressor, generics), metoprolol succinate (Toprol XL, generics), propranolol (Inderal, generics), propranolol-HCTZ (Inderide, generics), propranolol ER (Inderal LA, generics), timolol (Blocadren, generics), timolol/HCTZ (Timoziide) bisoprolol (Zebeta, generics), bisoprolol/HCTZ (Ziac, generics), nadolol (Corgard, generics), nadolol/bendroflumethiazide (Corzide, generics), acebutolol (Sectral, generics), betaxolol (Kerlone, generics), penbutolol (Levatol, generics), carvedilol IR (Coreg IR, generics), and carvedilol extended release (Coreg CR) be designated formulary on the UF.

**D. Implementation Plan: Not applicable**

**III. ADRENERGIC BETA-BLOCKING AGENTS (ABAs)**

*BAP Comments*

**A. Uniform Formulary Recommendation:** In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that:

Atenolol (Tenormin, generics), atenolol-chlorthalidone (Tenoretic, generics), metoprolol tartrate (Lopressor, generics), metoprolol succinate (Toprol XL, generics), propranolol (Inderal, generics), propranolol-HCTZ (Inderide, generics), propranolol ER (Inderal LA, generics), timolol (Blocadren, generics), timolol/HCTZ (Timoziide) bisoprolol (Zebeta, generics), bisoprolol/HCTZ (Ziac, generics), nadolol (Corgard, generics), nadolol/bendroflumethiazide (Corzide, generics), acebutolol (Sectral, generics), betaxolol (Kerlone, generics), penbutolol (Levatol, generics), carvedilol IR (Coreg IR, generics), and carvedilol extended release (Coreg CR) be designated formulary on the UF.

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|---------------------|---|
| <i>BAP Comment:</i> | <input type="checkbox"/> Concur <input type="checkbox"/> Non-concur |
|                     | Additional Comments and Dissentions:                                |

**IV. BPH ALPHA BLOCKERS (BPH-ABs)**

*P&T Comments*

**A. BPH-ABs - Relative Clinical Effectiveness:**

- 1) *FDA-approved indications* – Terazosin (Hytrin, generics), doxazosin (Cardura, generics), alfuzosin (Uroxatral), and tamsulosin (Flomax) are FDA-approved for treating the signs and symptoms of BPH.
- 2) *Efficacy measures* - The primary outcome measures used to assess BPH AB efficacy are changes in symptom scores [e.g., American Urological Association Symptom Index (AUA-SI) or international prostate symptom score (IPSS)], and urinary flow rate (Qmax). In clinical trials, a decrease in symptom score of three or more points is generally considered clinically significant, although men self-rate decreases of one to two points as slightly improved symptoms. A change in urinary flow rate of 2 to 3 mL/sec is considered clinically significant.

3) *Efficacy*

- a) *Meta-analyses/systematic reviews* – A meta-analysis [AUA 2003], systematic reviews [Djavan 1999, Clifford & Farmer 2000, Wilt 2002,2003], and pooled analysis concluded that the ABs were effective, and consistently improved lower urinary tract symptoms (LUTS) and Qmax compared to placebo. The ABs produced comparable improvements in LUTS and Qmax.
- b) *Placebo-controlled studies* - Placebo-controlled studies have demonstrated improvements in total symptom score from baseline of about 30% to 50% for the ABs vs. about 10% to 30% for placebo. On average, terazosin (Hytrin, generics) reduced AUA-SI score by 3 points; tamsulosin (Flomax) by 3 points [Wilt 2002, 2003]; doxazosin (Cardura, generics) by 3 points at 1 year [Kirby 2003] and 2 points at 4 years, [McConnell 2003]; and alfuzosin (Uroxatral) by 2 points short-term [MacDonald 2005], more than placebo. Improvements in Qmax for the ABs were about 5% to 15% greater than placebo [Djavan 1999, Clifford & Farmer 2000, Wilt 2002, 2003, Roehrborn 2001].

A rapid response (within 2 weeks) was seen with most ABs. Improvement with tamsulosin (Flomax) has been observed after the first dose, with peak effects occurring after one week [Djavan 1999, 2004]. Alfuzosin (Uroxatral) has also demonstrated improvement after the first-dose [Djavan 1999, Roehrborn 2001].

- c) *Head-to-head trials* - Head-to-head trials and indirect comparative studies (e.g., meta-analysis and systematic reviews) between ABs when used at equivalent doses do not show clinically relevant difference in efficacy, in terms of symptom relief and urodynamic improvements. Overall, for the ABs, total symptom score improved by 30% to 40% relative to baseline and Qmax by 16% to 29%.
- d) *Newly published clinical trials* - Since the prior August 2005 DoD P&T Committee review, only two randomized controlled trials and three quality of life (QoL) studies were identified.
  - *Nordling 2005* – The first trial was a double-blind, placebo-controlled trial that indirectly compared alfuzosin 10 mg or 15 mg (Uroxatral) or tamsulosin 0.4 mg (Flomax) to placebo. Although alfuzosin and tamsulosin were not directly compared to each other, significant symptoms improvement occurred when both treatments were administered at the recommended doses (i.e., alfuzosin 10 mg, tamsulosin 0.4 mg)



compared to placebo. The IPSS change from baseline was similar with both agents.

- *Roehrborn 2006* - The second double-blinded, placebo-controlled study demonstrated that alfuzosin (Uroxatral) prevented/slowed the overall clinical progression of BPH after 2 years, but did not reduce the risk of acute urinary retention or need for surgery. Alfuzosin (Uroxatral) reduced AUA-SI score by 1 point, and improved QoL compared to placebo.
- *Elhilali 2006, Flannery 2006, Hartung 2006* - Three non controlled open-labeled studies conducted in the primary care setting suggested that both alfuzosin (Uroxatral) and tamsulosin (Flomax) improved QoL measures in addition to improving LUTS.
- *Conclusion for new information since 2005* - No newly published U.S. head-to-head trials were identified since the 2005 review was conducted. Review of the clinical literature since 2005 does not add substantial new information or support changes in current clinical practice for the treatment of LUTS in men with BPH.

e) *Efficacy conclusion*- Based on limited head-to-head trials and indirect comparisons between the agents the following conclusions can be made:

- The existing evidence does not support clinically significant differences in efficacy between terazosin (Hytrin, generics), doxazosin (Cardura, generics), tamsulosin (Flomax), and alfuzosin (Uroxatral).
- All the ABs produce clinically significant symptom improvements when compared to placebo. Results of the AUA meta-analysis suggest terazosin (Hytrin, generics), doxazosin (Cardura, generics), alfuzosin (Uroxatral), and tamsulosin (Flomax) are similar in efficacy, based on partial relief of symptoms and improvement in the AUA-SI-Score. Other systematic reviews, meta-analyses, and clinical trials agree with the AUA meta-analysis.
- There are no published head-to-head trials directly comparing alfuzosin (Uroxatral) with tamsulosin (Flomax). One trial published since 2005 [Nordling] that indirectly compared alfuzosin (Uroxatral) or tamsulosin (Flomax) with placebo reported significant symptom improvement with both treatments. Existing evidence does not support clinically significant differences in efficacy between alfuzosin (Uroxatral) and tamsulosin (Flomax).

#### 4) *Safety / Tolerability*

a) *Adverse reactions* – The most commonly reported adverse events with the ABs during placebo controlled and open label uncontrolled studies are vasodilatory in nature (e.g., dizziness, asthenia/fatigue, headache, and hypotension). The incidence of vasodilatory effects with alfuzosin (Uroxatral) and tamsulosin (Flomax) are relatively low. Postural hypotension occurred in approximately 3% of patients treated with tamsulosin (Flomax) and in less than 1% of patients

treated with alfuzosin (Uroxatral). Asthenia and dizziness were reported in a higher percentage of tamsulosin (7-8%) and alfuzosin (3-4%) treated patients compared to placebo. Adverse events associated with ABs are dose dependent, with a higher incidence reported with higher doses compared to low dose or placebo.

- b) *Discontinuation rates* – Discontinuation rates due to adverse events range between 4% to 10% for tamsulosin (Flomax) and alfuzosin (Uroxatral), which is comparable to placebo. For terazosin (Hytrin, generics) and doxazosin (Cardura, generics), the percentage of patients who discontinued treatment due to adverse events was 8% to 20%.
- c) *Syncope and orthostatic hypotension* – The package labeling for all four ABs contain a warning for syncope and orthostatic hypotension; however, these events are more prevalent with terazosin (Hytrin, generics) and doxazosin (Cardura, generics). As a result, terazosin and doxazosin require dose titration when treatment is initiated. In clinical trials, tamsulosin (Flomax) and alfuzosin (Uroxatral) either do not decrease BP to a clinically significant extent, or reduce BP similar to placebo. Tamsulosin and alfuzosin may be better options for patients with BPH who cannot tolerate a BP reductions, or orthostatic changes in BP, heart rate, or peripheral vascular responsiveness.
- d) *Sexual Dysfunction* – The package labeling for tamsulosin (Flomax) carries a warning concerning the risk of priapism. Although alfuzosin (Uroxatral) labeling does not contain a warning for priapism, post-marketing cases have been reported. Data from the AUA meta-analysis estimated that the rate of ejaculatory dysfunction with tamsulosin (Flomax) was 10%. The incidence of ejaculatory dysfunction with alfuzosin (Uroxatral), terazosin (Hytrin, generics), and doxazosin (Cardura, generics), were approximately 1% in placebo-controlled trials.
- e) *Drug-drug interactions* – Drug interactions are more of an issue with alfuzosin (Uroxatral) and tamsulosin (Flomax) compared to doxazosin (Cardura, generics) and terazosin (Hytrin, generics). Alfuzosin is contraindicated for concomitant use with potent cytochrome P450 (CYP) 3A4 inhibitors such as ketoconazole (Nizoral), itraconazole (Sporanox), and ritonavir (Norvir). Tamsulosin (Flomax) has potential drug interactions with cimetidine and warfarin.
- f) *Drug-drug interactions with phosphodiesterase Type 5 (PDE-5) inhibitors*– PDE-5 inhibitors (sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis)] are mild vasodilators, which may decrease BP. Concomitant use of PDE-5 inhibitors with any AB may evoke orthostatic hypotension.
- g) *Special populations* – Terazosin (Hytrin, generics) and doxazosin (Cardura, generics) are rated pregnancy category C, while alfuzosin (Uroxatral) and tamsulosin (Flomax) are rated pregnancy category B. No AB is indicated for use in women. Doxazosin (Cardura, generics) should be used with caution in patients with hepatic failure. Alfuzosin (Uroxatral) is contraindicated in patients with moderate or severe hepatic insufficiency (Child-Pugh categories B and C), and

caution is recommended in patients with severe renal insufficiency. Alfuzosin (Uroxatral) should be used with caution in patients with a history of QT prolongation or who are receiving concomitant medications with the potential for QT prolongation. The effect of terazosin (Hytrin, generics), doxazosin (Cardura, generics), and tamsulosin (Flomax) on the QT interval has not been studied. Allergic reactions with tamsulosin (Flomax) have been reported in patients with sulfa allergy.

- h) *Dose titration* – Each time there is a period of noncompliance with terazosin (Hytrin, generics) or doxazosin (Cardura, generics), dosage titration from the lowest dose will be necessary to avoid potential problems with orthostatic hypotension. Dosage titration after noncompliance episodes is not necessary with alfuzosin (Uroxatral) or terazosin (Flomax).
- i) *Intraoperative Floppy Iris Syndrome (IFIS)* –Tamsulosin (Flomax) can cause a potential intraoperative complication, IFIS, during cataract surgery. IFIS was a recently described phenomenon affecting cataract surgery at the time of the 2005 review. To date, several case reports and observational studies have connected IFIS with tamsulosin (Flomax) use [Blouin 2007, Chang 2005, Chadha 2007, Cheung 2007, Parssinen 2006, Oshika 2007, Takmaz 2007]. The literature has a few anecdotal case reports of IFIS occurring with alfuzosin (Uroxatral) [Blouin 2007, Settas 2006], terazosin (Hytrin, generics), and doxazosin (Cardura, generics) [Chadha 2007, Parmar 2005]. Data from the FDA Adverse Event Reporting System (AERS) identified isolated cases suggestive of IFIS with tamsulosin (Flomax), doxazosin (Cardura, generics), terazosin (Hytrin, generics), and the 5-alpha reductase inhibitor finasteride (Proscar), and has included this as a precaution in all AB package labeling.
- j) *Safety and tolerability conclusion*- Vasodilatory adverse events were reported most commonly with the ABs during placebo-controlled and open label uncontrolled trials. Dizziness and asthenia most commonly lead to discontinuation of therapy. Alfuzosin (Uroxatral) and tamsulosin (Flomax) appear well-tolerated; there are only a few differences in safety considerations (e.g., drug interactions with CYP3A4 inhibitors; precautions for QT prolongation). Data from the clinical trials published since 2005 did not add substantial new information as to safety, tolerability or adverse events.

#### 5) *Other Factors*

*Provider Input:* Results from a survey sent to MTF providers indicated that alfuzosin (Uroxatral) and tamsulosin (Flomax) had similar effectiveness, safety and tolerability profiles.

#### 6) *Therapeutically Interchangeability*

Terazosin (Hytrin, generics) and doxazosin (Cardura, generics) the non-uroselective ABs, have a low degree of therapeutic interchangeability with alfuzosin (Uroxatral) and tamsulosin (Flomax), the uroselective AB, in terms of safety/tolerability. The non-uroselective agents have a high incidence of discontinuation rates and vasodilatory effects than the non-uroselective agents.

For the uroselective ABs alfuzosin (Uroxatral) and tamsulosin (Flomax), there is a high degree of therapeutic interchangeability with regards to efficacy, safety, and tolerability.

7) *Clinical Coverage*

Neither alfuzosin (Uroxatral) nor tamsulosin (Flomax) offers a unique benefit over the other. It is not likely that a patient who did not have an adequate response with one uroselective AB would have a better response with the other. Either alfuzosin (Uroxatral) or tamsulosin (Flomax) could be expected to meet the needs of the majority of the DoD patients requiring a uroselective agent.

There is no evidence to suggest switching between the four ABs would provide additional benefit to patients who fail treatment due to lack of effectiveness. Patients with an inadequate response to the ABs would be candidates for a 5-alpha reductase inhibitor or surgery. To meet the needs of the majority of the patients in DoD, one non-uroselective AB and one uroselective AB (for patients who can not tolerate a non-uroselective AB) is required.

8) *Clinical Effectiveness Conclusion* - The P&T Committee concluded that:

- a) Based on randomized placebo-controlled trials, terazosin (Hytrin, generics), doxazosin (Cardura, generics), tamsulosin (Flomax), and alfuzosin (Uroxatral) were found to produce clinically significant and comparable symptom improvements when compared to placebo.
- b) Based on limited head-to-head trials and indirect comparisons between the agents, existing evidence does not support clinically significant differences in efficacy between alfuzosin (Uroxatral) and tamsulosin (Flomax).
- c) There appear to be few differences in the incidence of adverse effects with alfuzosin (Uroxatral) and tamsulosin (Flomax), based on placebo-controlled trials and limited comparative data. Both agents are well tolerated. The most common adverse events are vasodilatory effects.
- d) There appear to be major differences in withdrawal rates due to adverse events between non-uroselective [terazosin (Hytrin, generics) and doxazosin (Cardura, generics)] and the uroselective agents [alfuzosin (Uroxatral), and tamsulosin (Flomax)]. Withdrawal rates reported in clinical trials were low overall for alfuzosin and tamsulosin.
- e) The package labeling for alfuzosin (Uroxatral) contains cautions for QT prolongation effects. The effect of tamsulosin (Flomax) on the QT interval has not been studied.
- f) Alfuzosin (Uroxatral) is contraindicated for use with potent CYP3A4 inhibitors such as ketoconazole (Nizoral), itraconazole (Itraconazole), and ritonavir (Norvir). Tamsulosin (Flomax) has potential drug interactions with cimetidine and warfarin.
- g) Doxazosin (Cardura, generics) should be used with caution in men with hepatic failure. Alfuzosin (Uroxatral) is contraindicated in men with moderate to severe

hepatic impairment (Child-Pugh categories B and C). Tamsulosin (Flomax) does not require dosage adjustment in men with moderate hepatic dysfunction.

- h) Package labeling for all four ABs contains information regarding the potential for IFIS. For patients receiving alfuzosin (Uroxatral) and tamsulosin (Flomax) consultation with an ophthalmologist is recommended prior to cataract surgery.
- i) Terazosin (Hytrin, generics) and doxazosin (Cardura, generics) have a low degree of therapeutic interchangeability with alfuzosin (Uroxatral) and tamsulosin (Flomax) in terms of safety/tolerability due to the higher incidence of discontinuation rates and vasodilatory effects seen with the non-uroselective ABs.
- j) Alfuzosin (Uroxatral) and tamsulosin (Flomax) have a high degree of therapeutic interchangeability; either drug could be expected to meet the needs of the majority of DoD BPH patients requiring an uroselective agent.
- k) Review of the clinical literature since 2005 does not add substantial new information or support changes in current clinical practice for the treatment of LUTS in men with BPH, or for safety profiles between the uroselective ABs.
- l) Based on clinical issues alone, there are no compelling reasons to classify any of the AB agents as non-formulary under the UF.

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

**B. BPH-ABs - Relative Cost Effectiveness:** The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the uroselective AB medications differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of BPH. As a result, a CMA was performed to compare the relative cost effectiveness of potential UF uroselective ABs scenarios. The CMA compared the weighted average cost per day of treatment for each potential UF scenario across all three points of service. The potential UF uroselective ABs scenarios considered were derived from the following condition sets:

- 1) One selective BPH-AB will be selected to the UF and the BCF. In addition, a PA process would require all new selective BPH-AB users to complete an adequate trial of the UF selective BPH-AB before the non-formulary selective BPH-AB is provided to a new user through an MTF pharmacy, the TMOP, or a TRICARE retail network pharmacy. (1 UF, 1 BCF, with PA)
- 2) One selective BPH-AB will be selected to the UF and up to one selective BPH-AB will be included on the BCF. (1 UF, 0-1 BCF).
- 3) Two or more selective BPH-ABs will be selected to the UF and up to one selective BPH-AB will be included on the BCF. (2+ UF, 0-1 BCF)

Results from the AB CMA showed that: 1) UF scenario, under condition set #1, with alfuzosin (Uroxatral) as the one uroselective agent on the UF and BCF in conjunction with Step Therapy to be the most cost-effective UF scenario considered; 2) UF scenario, under condition set #2, with alfuzosin (Uroxatral) as the one uroselective

agent on the UF and BCF without Step Therapy was the next most cost-effective UF scenario considered. However, under this UF scenario, without Step Therapy, the weighted average cost per day of therapy increased by 53% over the most cost-effective UF scenario; 3) any condition set that included tamsulosin (Flomax) on the UF was more costly compared to baseline's (what DoD pays today) weighted average cost per day of therapy.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost-shares). The goal of the BIA was to aid the Committee in determining which uroselective AB best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS. The results of the BIA paralleled those of the cost effectiveness analysis. The UF scenario, under condition set #1, with alfuzosin as the one uroselective agent on the UF and BCF in conjunction with Step Therapy was the most cost-effective UF scenario.

**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 alfuzosin (Uroxatral) as the only uroselective agent on the UF and BCF in conjunction with a step therapy/PA was the most cost effective scenario.

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

**C. BPH-ABs - Uniform Formulary Recommendation:** In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that:

Alfuzosin (Uroxatral) be maintained as the uroselective formulary AB, and that terazosin (Hytrin, generics) and doxazosin (Cardura, generics) be maintained as the non-uroselective formulary ABs; and 2) tamsulosin (Flomax) be classified as non-formulary under the UF with a PA requiring a trial of alfuzosin (Uroxatral) for new patients.

#### **D. BPH Alpha Blockers – PA Criteria**

The P&T Committee agreed that the following PA criteria should apply to tamsulosin (Flomax). 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 either tamsulosin (Flomax) or alfuzosin (Uroxatral) 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:

- b) The patient has tried alfuzosin (Uroxatral) and had an inadequate response or was unable to tolerate treatment due to adverse effects.
- c) Treatment with alfuzosin (Uroxatral) is contraindicated.

The P&T Committee noted that in order for a patient to receive tamsulosin (Flomax) 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 tamsulosin (Flomax) would NOT automatically receive it at the formulary cost-share.

**COMMITTEE ACTION:** The P&T Committee voted to recommend the PA criteria outlined above.

**E. BPH-ABs – UF Implementation Plan:**

The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

**COMMITTEE ACTION:** The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

**V. BPH-ABs (cont.)**

**BAP Comments**

**A. Uniform Formulary Recommendation:** In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the BPH-ABs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that Alfuzosin (Uroxatral) be maintained as the uroselective formulary AB, and that terazosin (Hytrin, generics) and doxazosin (Cardura, generics) be maintained as the non-uroselective formulary ABs; and 2) tamsulosin (Flomax) be classified as non-formulary under the UF with a PA requiring a trial of alfuzosin (Uroxatral) for new patients.

The P&T Committee agreed that the following PA criteria should apply to tamsulosin (Flomax). Coverage would be approved if a patient met any of the following criteria:

- 1) Automated PA criteria:
  - d) The patient has received a prescription for either tamsulosin (Flomax) or alfuzosin (Uroxatral) 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:
  - e) The patient has tried alfuzosin (Uroxatral) and had an inadequate response or was unable to tolerate treatment due to adverse effects.

f) Treatment with alfuzosin (Uroxatral) is contraindicated.

|                     |   |
|---------------------|---|
| <i>BAP Comment:</i> | <input type="checkbox"/> Concur <input type="checkbox"/> Non-concur |
|                     | Additional Comments and Dissentions:                                |

**B. Implementation Plan:** The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

|                     |   |
|---------------------|---|
| <i>BAP Comment:</i> | <input type="checkbox"/> Concur <input type="checkbox"/> Non-concur |
|                     | Additional Comments and Dissentions:                                |

## VI. TARGETED IMMUNOMODULATORY BIOLOGICS (TIBs)

### A. TIBS - Relative Clinical Effectiveness:

The P&T Committee evaluated the relative clinical effectiveness of the targeted immunomodulatory biologics (TIBs) currently marketed in the United States. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

The TIB class is comprised of five medications covered as part of the DoD pharmacy benefit: adalimumab (Humira), anakinra (Kineret), etanercept (Enbrel), efalizumab (Raptiva), and alefacept (Amevive). Three similar biologic agents are not part of the pharmacy benefit due to their intravenous (IV) route of administration: abatacept (Orencia), infliximab (Remicade), and rituximab (Rituxan). Like Enbrel and Humira, Remicade is approved for multiple indications and in many respects directly



competes with these two self-administered multiple indication agents. The IV agents were included in the review for comparative purposes only. (See Table 2.)

**Table 2: FDA-Approved Indications for Targeted Immunomodulatory Biologics (TIBs)**

| Brand  | Generic    | Manufacturer | How Given | How Given |     |     |    | Plaque psoriasis | Crohn's Disease | UC |
|--|------------|--------------|-----------|-----------|-----|-----|----|------------------|-----------------|----|
|  |            |              |           | RA        | JRA | PsA | AS |                  |                 |    |
| Enbrel   | Etanercept | Amgen/Wyeth  | SQ        | X         | X   | X   | X  |                  |                 |    |
| Humira   | Adalimumab | Abbott       | SQ        | X         |     | X   | X  |                  | X               |    |
| Kineret  | Anakinra   | Amgen        | SQ        | X         |     |     |    |                  |                 |    |
| Raptiva  | Efalizumab | Genentech    | SQ        |           |     |     | X  |                  |                 |    |
| Amevive  | Alefacept  | Astellas     | IM/IV     |           |     |     | X  |                  |                 |    |
| <i>Not part of outpatient pharmacy benefit</i> |            |              |           |           |     |     |    |                  |                 |    |
| Remicade                                       | Infliximab | Centocor     | IV        | X         |     | X   | X  | X                | X               |    |
| Orencia  | Abatacept  | BMS          | IV        | X         |     |     |    |                  |                 |    |
| Rituxan**                                      | Rituximab  | Genentech    | IV        | X         |     |     |    |                  |                 |    |

RA = rheumatoid arthritis; JRA = juvenile rheumatoid arthritis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; UC = ulcerative colitis; NHL = ; SQ = subcutaneous; IM = intramuscular; IV = intravenous

\* The Food and Drug Administration is currently considering adalimumab (Humira) for the treatment of JRA and plaque psoriasis.

\*\* Rituxan is also approved for non-Hodgkin's lymphoma.

Since the FDA lacks regulatory authority to approve generic versions of biologic medications, generic formulations for the TIBs are not likely to appear in the near future. The TIB class accounted for approximately \$136 million dollars in MHS expenditures in FY 2007, primarily at the retail point of service (66%), followed by MTFs (19%) and mail order (15%). This estimate does not accurately represent utilization of the IV agents (e.g., Remicade), since these medications are commonly administered in clinic or office settings and are included on outpatient pharmacy profiles only in MTFs that choose to maintain such a record. The cost of treatment with these agents is high (on the order of \$10,000 to \$20,000 annually). There were approximately 11,500 unique TIB utilizers in the MHS in the most recent quarter (Jun to Aug 2007), not including patients receiving IV agents.

The majority of use of TIBs in DoD is for the two multi-indication agents (Enbrel and Humira), not including patients receiving IV agents. Fewer than 4% of DoD TIB utilizers are receiving other TIBs. Over the entire patient population, Enbrel and Humira are consistently used in about a 2:1 ratio, although utilization in the last quarter (Jun to Aug 2007) shows increased uptake of Humira among new users (new users only: 44% use of Humira vs. 54% use of Enbrel, 2% other TIBs).

*1) Pharmacology and Clinical Use*

TIBs are used to treat a variety of serious disease states. Based on an analysis of TIB prescriptions for patients with relevant diagnosis codes in the MHS Mart (M2) over a six-month period (Jan through June 2007), the most commonly treated condition treated with TIBs in DoD is rheumatoid arthritis (RA). About 73% of TIB patients are being treated for RA. Other conditions include psoriasis (15%), psoriatic arthritis (7%), ankylosing spondylitis (4%), as well as Crohn's disease, juvenile rheumatoid arthritis, and ulcerative colitis (all less than 1% each). In most cases the TIBs are indicated as treatment for moderate to severe cases of these conditions, usually following an inadequate response to initial therapy.

The TIBs target various mediators of the inflammation cascade, effectively retarding the extent and severity of inflammation at the local level. Enbrel, Humira, and Remicade all act through inhibition of tumor necrosis factor-alpha (TNF- $\alpha$ ). Humira and Remicade are monoclonal antibodies; they bind specifically to TNF- $\alpha$ , blocking interaction with the p55 and p75 cell surface TNF receptors. Enbrel is a soluble receptor to TNF- $\alpha$  that binds circulating TNF- $\alpha$  and lymphotoxin- $\alpha$ , preventing interaction with cell surface receptors. Kineret (which is FDA-indicated only for RA) is a human recombinant protein that competitively blocks the interleukin (IL)-1 receptor, blocking inflammatory and immunological responses.

The other TIBs affect T cell (Amevive, Raptiva, Orencia) or B cell (Rituxan) involvement in autoimmune and inflammatory processes. Amevive and Raptiva are FDA-indicated only for the treatment of plaque psoriasis, while the IV agents Orencia and Rituxan are FDA-indicated only for RA.

Dosing of the various agents varies from every 8 weeks via IV infusion (Remicade) to daily subcutaneous dosing (Kineret). (See Table 3) The two multi-indication self-administered TIBs, Enbrel and Humira, are given every 1 or 2 weeks (see Table 2). Three major areas of uncertainty about actual dosing of the TIBs (which may affect safety, tolerability, and efficacy as well as cost) are: 1) the percent of RA patients who receive weekly rather than every other week dosing with Humira; 2) the percent of plaque psoriasis patients who continue to receive twice weekly dosing with Enbrel 50 mg following the 12-week induction phase; and 3) the percent of patients who receive higher or more frequent doses of Remicade for the treatment of RA and Crohn's disease.

**Table 3: Dosing and Administration of the TIBs**

| Brand  | Generic    | Dosing  |
|--|------------|---|
| Enbrel   | Etanercept | <b>RA, PsA, AS</b> – 25 mg twice weekly or 50 mg once weekly SQ<br><b>JRA</b> (4-17 years) – 0.8 mg/kg per week (maximum 50 mg per week), given once or twice per week SQ<br><b>Plaque psoriasis</b> – 50 mg twice weekly SQ for 3 months, then decrease to 50 mg SQ weekly   |
| Humira   | Adalimumab | <b>RA</b> – 40 mg every other week SQ, may increase to 40 mg q week for monotherapy<br><b>PsA, AS</b> – 40 mg every other week SQ<br><b>Crohn's</b> – 160 mg at week 0, 80 mg at week 2, then 40 mg every other week beginning week 4   |
| Kineret  | Anakinra   | <b>RA</b> – 100 mg daily SQ (consider 100 mg every other day SQ in patients with severe renal insufficiency or end stage renal disease)   |
| Raptiva  | Efalizumab | <b>Plaque psoriasis</b> – Initial 0.7 mg/kg SQ injection, then 1 mg/kg weekly SQ injections (not to exceed 200 mg)  |
| Amevive  | Alefacept  | <b>Plaque psoriasis</b> – 15 mg once weekly IM; continue for 12 weeks; after a 12-week interval, may retreat with an additional 12-week course if CD4+ T lymphocyte counts are >250 cells/ $\mu$ L  |
| <i>Not part of outpatient pharmacy benefit</i> |            |   |
| Remicade                                       | Infliximab | <b>RA (adult)</b> – 3 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks (may increase to maximum of 10 mg/kg every 4 weeks)<br><b>RA (pediatric; 6-17 years)</b> – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks<br><b>Crohn's</b> – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks (may increase to 10 mg/kg)<br><b>PsA</b> – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks<br><b>AS</b> – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 6 weeks<br><b>UC, plaque psoriasis</b> – 5 mg/kg IV infusion at 0, 2, 6 weeks, then every 8 weeks<br>Doses > 5 mg/kg per day are contraindicated in patients with moderate to severe heart failure. |
| Orencia  | Abatacept  | <b>RA</b> – IV based on body weight <60 kg = 500 mg; 60-100 kg = 750 mg; >100 kg = 1000 mg); initial dose at 0, 2, 4 weeks, then every 4 weeks  |
| Rituxan  | Rituximab  | <b>RA</b> – 1000 mg IV infusion on days 1 and 15 in combination with methotrexate. Safety and efficacy of retreatment not established.  |

RA = rheumatoid arthritis; JRA = juvenile rheumatoid arthritis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; UC = ulcerative colitis;

## 2) *Efficacy*

A recent well-done systematic review of the drugs in this class is available from the Oregon Health & Science University's DERP. The January 2007 review included published clinical trials through August 2006. The review took a "best evidence" approach, with a primary focus on health outcomes (symptoms, quality of life, functional capacity, hospitalizations, and mortality). Radiological changes were considered as a secondary, intermediate measure.

Many TIB trials, particularly in rheumatologic conditions, included treatment with disease-modifying antirheumatic drugs (DMARDs), particularly methotrexate (MTX), either as monotherapy or in combination with a TIB. (Although the term DMARD technically includes the TIBs, which slow disease progression in RA, it is used in this evaluation to refer solely to non-biologic agents that slow disease progression in RA, such as methotrexate, sulfasalazine, gold salts, and hydroxychloroquine.) Since there are no head-to-head RCTs comparing two or more TIBs, comparisons between TIBs in any given disease state primarily rest on the results of placebo- and/or active-controlled RCTs.

As part of its evaluation of the TIB class, the P&T Committee considered summary efficacy and safety data and conclusions from the DERP review, along with more recently published clinical data following the same general approach. Unpublished data provided by pharmaceutical manufacturers as part of their Academy of Managed Care Pharmacy "dossiers" were also considered when little published data were available (published trials have undergone peer review and are generally considered more reliable than unpublished data). Additional information (typically from open label extension trials or observational studies) was also considered to address questions concerning switching between the TIBs (e.g., in patients refractory to treatment), long-term efficacy and safety, and effects on quality of life and productivity.

Few published guidelines to date attempt to establish the place of specific TIBs in the treatment of the disease states addressed in this evaluation.

### a) *Rheumatoid Arthritis*

A prominent RA efficacy measure is the number of patients attaining a American College of Rheumatology (ACR) 20, 50, or 70 response, based on at least a 20, 50, or 70% reduction compared to baseline in tender / swollen joint counts plus improvements in at least three other specified measures of pain, overall effect, or laboratory measures of inflammation. DERP reviewers chose an ACR 50 response as the outcome measure for adjusted indirect comparisons of randomized placebo controlled trials because it was felt to translate to a clinically significant improvement in health-related quality of life.

Based both on trials included in the DERP review and more recently published trials, there is good-to-fair evidence from meta-analyses and large placebo-controlled RCTs supporting the efficacy of Enbrel, Humira, and

Kineret for the treatment of RA. The same is true for the IV agents Remicade, Orencia, and Rituxan. Amevive and Raptiva lack evidence for the treatment of RA. In general, combination treatment with TIBs plus MTX offered better efficacy than TIBs or MTX alone. The same was true of the DMARD sulfasalazine based on one trial. Beneficial effects on QOL and productivity were associated with improvements in clinical response.

Meta-analysis results from the DERP review suggested no significant difference in efficacy among Enbrel, Humira, and Remicade for the treatment of RA. Point estimates favored the TNF inhibitors (Enbrel, Humira, and Remicade) over the IL-1 inhibitor Kineret, although differences were statistically significant only for ACR 20 and not ACR 50 response. A recent high-quality meta-analysis [Nixon et al, 2007] similarly reported comparable efficacy among Enbrel, Humira, and Remicade for the treatment of RA. An analysis comparing Kineret to the TNF inhibitors as a class concluded that the TNF inhibitors were statistically significantly more efficacious than Kineret (OR 1.96, 95% CI 1.03 to 4.01 for ACR 20; OR 1.93, 95% CI of 1.05 to 3.50 for ACR 50).

Numerous studies have shown clinical benefit in patients switching from one TIB to another, including patients switching from Remicade to Enbrel, Enbrel to Remicade, Enbrel to Humira, Remicade to Humira, and TNF inhibitors to Rituxan or Orencia. In general, clinical response was seen with the second TIB regardless of the reason for switching—albeit at lower rates than in TIB-naïve patients—with no increase in adverse events. This appeared to be true both for switches between TNF inhibitors and from a TNF inhibitor to another TIB. Data on the efficacy of switching to a third TNF inhibitor are mixed.

Another important aspect of overall efficacy concerns the impact of TIBs and other DMARDs on delaying the progressive structural destruction of peripheral joints seen in RA. A common measure is the Total Sharp Score (TSS), which is based on evaluation of x-rays of hands and feet scored for joint erosions and joint space narrowing. Optimally, treatment would both control RA symptoms and delay (or even halt) radiographic disease progression.

Long-term data supporting maintenance of effects on clinical measures (e.g., ACR response) is available for all the TIBs used for the treatment of RA; however, the length of follow-up varies. The longest-term data are available for Enbrel and Humira (4 to 7 years). Both of these TIBs have evidence supporting delay in radiographic progression for up to 2 years. Remicade and Orencia have 1-year data supporting sustained effects on clinical measures and radiographic progression. Kineret has data supporting sustained effects on clinical measures for up to 1 year, but radiographic data only out to 6 months; Rituxan lacks radiographic data but has data supporting sustained effect on clinical measures for up to 2 years (following one course of therapy).

*b) Juvenile Rheumatoid Arthritis*

Enbrel is the only TIB with published evidence that demonstrates efficacy for the treatment of juvenile rheumatoid arthritis (JRA) and the only TIB indicated for this condition. Evidence is limited to a single placebo-controlled RCT; similar results are reported in a retrospective analysis of registry data from Germany in pediatric patients with various forms of arthritis. A small, uncontrolled open-label study provides insufficient evidence for Remicade.

Unpublished evidence suggesting efficacy for Humira in JRA is available from the manufacturer; FDA approval of Humira for this indication is pending.

There is some uncontrolled or observational evidence with Remicade, Enbrel, and Humira for the treatment of JRA-associated uveitis.

c) *Ankylosing Spondylitis*

Ankylosing spondylitis (AS) causes inflammation of the spine and large joints, resulting in stiffness and pain and often progressive disability. Clinical measures are based on improvement in symptoms such as pain, morning stiffness, fatigue, and mobility. Non-biologic DMARDs are not consistently helpful for the treatment of AS.

Based both on trials included in the DERP review and more recently published trials, sufficient evidence exists to support efficacy of Humira, Enbrel, and Remicade for treatment of AS symptoms over a period of one to three years, compared to placebo. It is not known if long-term treatment with TNF inhibitors or other biologics can alter the progression of AS. There is insufficient evidence to conclude that there are differences in comparative efficacy.

One trial provided evidence of successful switching from Remicade to Enbrel in patients with loss of efficacy or adverse events on Remicade. There are insufficient data to generalize these results across all treatments.

d) *Psoriatic Arthritis*

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis. Approximately 10 to 30% of psoriasis patients will develop PsA; the psoriasis usually predates the arthritis by many years. Many RA measures are also used in PsA.

Based both on trials included in the DERP review and more recently published trials, evidence from seven placebo-controlled trials supports efficacy of Enbrel (two trials), Remicade (two trials), and Humira (three trials) in the treatment of PsA. There is insufficient evidence to conclude that there are differences in comparative efficacy among these three agents. A high-quality meta-analysis of placebo-controlled trials [Woolacott et al, 2007] showed very similar treatment effects between Enbrel and Remicade.

Long-term data out to 2 years is available for all three agents, including evidence supporting sustained effects on clinical measures of response and radiographic progression.

One trial with Raptiva (which is FDA indicated only for the treatment of plaque psoriasis) reported negative results in PsA: no statistically significant difference in ACR 20 response was seen at 12 weeks, compared to placebo.

e) *Plaque Psoriasis*

In psoriasis, an environmental trigger is thought to evoke an inflammatory response and subsequent hyperproliferation of keratinocytes, associated with activation of T cells which migrate from the vasculature into the dermal tissues.

A prominent clinical measure of disease severity is the Psoriasis Area and Severity Index (PASI), which incorporates measures of scaling, erythema, and induration of the head, trunk, upper and lower limbs, weighted by severity and affected body surface area. PASI 50/75/90/100 scores represent improvements from baseline in PASI score and are typically reported as the percentages of patients achieving a certain PASI improvement. A PASI 75 response is considered to be the benchmark for current therapies, particularly the biologics.

Based both on trials included in the DERP review and more recently published trials, evidence from published placebo-controlled RCTs supports efficacy of Humira (one trial), Amevive (two trials), Raptiva (four trials), Enbrel (for trials), and Remicade (three trials) in the treatment of plaque psoriasis.

Due to lack of direct comparative data, it is difficult to draw conclusions regarding comparative efficacy. However, PASI 75 response rates appear consistently higher for Remicade compared to the other TIBs used for the treatment of plaque psoriasis, although some evidence suggests diminishing effect with Remicade as continuous use approaches 1 year. PASI 75 response rates for Amevive, Raptiva, and Enbrel appear similar in 12- to 24-week trials.

Evidence for Humira in psoriasis includes one published RCT [Gordon et al, 2006] and additional unpublished data available from the manufacturer. FDA approval of Humira for plaque psoriasis is pending.

f) *Crohn's Disease*

Crohn's disease is a chronic inflammatory disease primarily involving the small and large intestine. In its most severe form, it can be associated with the development of deep ulcers and fistulas that can penetrate into adjoining structures or even to the surface skin, leading to infection. The spread of inflammation and thickening of the bowel wall can lead to bowel obstruction. Symptoms may include diarrhea, abdominal pain, anemia, and weight loss. Treatments include 5-aminosalicylic acid, antibiotics, corticosteroids (for patients without fistulas or abscesses), metronidazole (fistulizing disease), immunosuppressives, methotrexate, and TIBs.

Based both on trials included in the DERP review and more recently published trials, there is fair to good evidence from placebo-controlled RCTs

supporting efficacy of Remicade (seven trials) and Humira (four trials) for initial and maintenance treatment of Crohn's disease.

There is insufficient evidence to conclude that there are differences in comparative efficacy between Remicade and Humira for the treatment of Crohn's disease. Both biologics have published data demonstrating persistence of response for up to one year.

One difference is use in children: Remicade, but not Humira, has published evidence and is indicated for the treatment of pediatric Crohn's disease (ages 6 to 17 years).

Enbrel does not appear to be efficacious for Crohn's disease based on one fair-quality placebo-controlled trial [Sandborn et al, 2001]. The manufacturer states that they have discontinued development of Enbrel for this indication. The difference in effect compared to the other two TNF inhibitors may be due to mechanistic differences between the monoclonal antibody agents (Humira and Remicade) and the soluble receptor agent Enbrel.

*g) Ulcerative Colitis*

Ulcerative colitis (UC) is a chronic inflammatory and ulcerative disease arising in the colonic mucosa, characterized most often by bloody diarrhea; fistulas and abscesses do not occur. Treatment includes 5-aminosalicylic acid (enemas or oral), corticosteroids, immunosuppressives (azathioprine), and TIBs.

Remicade is the only TIB currently FDA-indicated for UC, with evidence from three published placebo-controlled RCTs supporting efficacy. No published RCTs were found for other TIBs in the treatment of UC.

*3) Safety and Tolerability*

*a) Overall Adverse Event Profile*

Overall, TIBs were well-tolerated during clinical trials; the most common and consistently reported adverse events (AEs) are injection site or infusion reactions (depending on route). With the exception of injection reactions, the overall rate of AEs and the percentage of patients discontinuing treatment due to AEs (3-16%) were typically comparable to placebo. The incidence of AEs does not appear to increase over time.

Kineret may cause more injection reactions than Humira and Enbrel based on the mean crude incidence of injection reactions calculated by DERP reviewers from clinical trials included in that review: 17.5% for Humira (95% CI 7.1-27.9); 22.4% for Enbrel (95% CI 8.5-36.3); but 67.2% for Kineret (95% CI 38.7-95.7).

Infusion reactions have the potential to be more serious than injection site reactions; severe acute reactions have been reported in a small percentage of patients (~1%) after Remicade infusions.

b) *Rare but Serious Adverse Events*

The primary safety concerns with TIBs are related to the potential for increased risk of serious AEs (e.g., infections, malignancies, autoimmune disorders, etc), most of which are associated with the drugs' effects on the immune system. These effects are rare and cannot be assessed reliably during clinical trials, although the overall incidence of serious AEs tends to be higher with TIBs compared to placebo, and trends in large RCTs approach statistical significance. Current evidence focusing on specific serious adverse events is primarily observational.

Black box warnings concerning the risk of serious infections and the need to test for latent tuberculosis (TB) prior to initiating TIB therapy are included in labeling for Humira and Remicade; similar information appears in labeling for other TIBs. In general, caution is indicated in patients with chronic infections or a history of recurrent infections, and TIBs should be stopped if the patient develops a serious infection.

Other black box warnings for TIBs include the risk of hepatosplenic T-cell lymphoma with Remicade (reported in young Crohn's disease patients on other immunomodulatory medications) and a list of potentially severe reactions primarily associated with the use of Rituxan for conditions other than RA. There are relatively few absolute contraindications for the TIBs: Amevive is contraindicated in patients with HIV; Enbrel is contraindicated in sepsis; and doses of Remicade greater than 5 mg/kg are contraindicated in patients with moderate to severe heart failure.

(i) *Serious Infections*

The most common serious infection appears to be TB. Observational studies have also reported infections with coccidiomycosis, histoplasmosis, pneumocystis carinii, listeriosis, candida, and Legionella. Evidence from RCTs is limited.

- A meta-analysis [Bongartz et al, 2006] that pooled data from Humira and Remicade RA trials (total n >5000) reported a pooled odds ratio for serious infections of 2.0 (95% CI 1.3 to 3.1), with a number needed to harm of 59 (95% CI 39 to 125) over 3 to 12 months.
- A large RCT (n=1084) designed to assess the risk of serious infections with Remicade in RA patients [Westhovens et al, 2006] reported similar rates of serious infections in patients treated with 3 mg/kg Remicade vs. placebo (RR: 1.0; 95% CI 0.3 to 3.1). However, patients treated with 10mg/kg Remicade had a significantly higher rate of serious infections vs. placebo (RR: 3.1 95% CI 1.2 to 7.9).

The DERP review also included five retrospective database analyses and a prospective cohort study that in general supported a higher risk of TB or granulomatous infection in patients treated with Enbrel or Remicade compared to unexposed patients; more recently published studies do not add substantial evidence.



When all data are considered, the P&T Committee agreed that there is fair evidence of an increased risk of serious infections (including TB) for TIBs compared to placebo. There is insufficient evidence to draw conclusions about the comparative risk of serious infection.

*(ii) Malignancies*

The P&T Committee agreed that largely observational evidence indicates a higher risk of lymphoma for patients treated with Remicade or Enbrel. Results of studies addressing other malignancies are mixed. There is insufficient evidence to draw conclusions about comparative risk.

*(iii) Chronic Heart Failure*

Evidence concerning the safety of TIBs in patients with chronic heart HF and the effects of TIBs on the development of chronic HF is mixed. Data from two unpublished Enbrel RCTs and one published Remicade RCT evaluating these TIBs for the *treatment* of chronic HF suggested higher rates of mortality among chronic HF patients treated with Enbrel or Remicade, compared to placebo. However, observational studies have reported *lower* rates of cardiovascular events in RA patients receiving TNF inhibitors compared to those receiving conventional therapy. Caution is indicated.

*(iv) Other*

All TNF inhibitors appear to cause the development of autoantibodies to some extent. Cases of drug-induced lupus, lupus-like syndromes and other autoimmune disorders have been reported with Enbrel, Humira, and Remicade. The relationship among auto-antibody levels, the likelihood of infusion reactions, degree and durability of clinical response, and the development of autoimmune disorders is unclear.

Based on case reports and product labeling, Humira, Enbrel, and Remicade may be associated with demyelination. Hepatotoxicity has been reported with Remicade and Amevive. Potential effects on hematologic parameters requiring laboratory monitoring include neutropenia with Kineret (neutrophil counts monthly for 3 months, then quarterly for 1 year); dose-dependent reductions in CD4+ T lymphocytes reported with Amevive (CD4+ T lymphocyte counts every 2 weeks during the 12-week treatment period); and periodic assessment of platelet counts with Raptiva (monthly to quarterly).

*c) Drug Interactions*

There is little substantive information concerning potential drug interactions with the TIBs. They are in general considered safe for use with the large number of drugs used concomitantly in clinical trials.

In general, additive effects on the immune system appear to preclude concomitant treatment with more than one TIB. A trial assessing a combination of Kineret and Enbrel (plus MTX) appeared to offer no

additional clinical benefit compared to Enbrel plus MTX, but resulted in a substantially higher rate of pancytopenia and serious infections. Similarly, a trial assessing the addition of Orencia to Enbrel appeared to offer minimal additional clinical benefit compared to Enbrel alone, but resulted in a substantially higher rate of adverse events (including serious adverse events and serious infections).

#### 4) *Use in Special Populations*

Overall, TIBs do not appear to have major differences in terms of efficacy or safety/tolerability in specific subsets of patients (e.g., based on age, gender, race, or comorbid conditions), although this has not been extensively studied. A higher risk of mortality among chronic HF patients treated with Enbrel or Remicade has been previously discussed. Caution is in general indicated in elderly patients due to a higher background risk for serious infections and malignancy.

Other differences include varying pregnancy categories (B vs. C) across drugs (Amevive, Orencia, and Rituxan are Category C due either to complete lack of data or some evidence of harm in animal studies); the potential for a higher risk of AEs with Kineret in patients with impaired renal function (Kineret is known to be substantially excreted by the kidney; dose reduction is recommended); and the availability of safety and efficacy data in pediatric patients (Enbrel is the only TIB FDA-indicated for JRA; Remicade is the only TIB indicated for pediatric Crohn's disease [age 6-17]).

#### 5) *Provider Opinion*

Opinions of MTF providers familiar with the use of TIBs were solicited through the Army, Navy, and Air Force specialty leaders for the three specialties in which these agents are primarily used (rheumatology, dermatology, and gastroenterology).

- *Rheumatology* – Factors influencing the decision to choose between Enbrel and Humira were frequency of dosing and the shorter half-life of Enbrel, which was considered useful in patients in whom there was a fear of infectious complications. Responders considered the two equally efficacious, and almost universally reported efficacy with a second TIB in patients who had had an inadequate response to the first TIB. They tended to use Orencia, then Rituxan, in patients failing TNF agents, usually after a trial of two agents. Kineret was not considered useful in RA; responders cited anecdotal use in Still's disease (pediatric and adult).
- *Dermatology* – Responders stated that they usually started with Enbrel for psoriasis (with which they had the most experience) or Humira; many would consider Humira after a 4- to 6-month trial of Enbrel. Some do use Humira as first line. Based on the published data (PASI 75 scores), providers thought that Humira might have greater efficacy, although they also theorized that it might have a higher risk of infection based on its binding of both tissue-bound and soluble TNF. Comments about dosing of Enbrel (i.e., patients staying on the twice-weekly 50 mg dose after the initial treatment period) included a

perception that many patients require the higher dose and that many also require additional therapy (phototherapy, MTX), the possibility that Enbrel may need to be weight-based due to higher TNF production in patients with a high BMI; and the perception that effects of Enbrel may wane over time, requiring that the dose be increased back to 50 mg twice weekly.

Survey responders typically placed Raptiva before Amevive in patients with a contraindication to TNF inhibitors or who had failed Enbrel or Humira. Raptiva was noted to be helpful when treating very heavy or light-weight individuals, since dosing is weight-based; it was also noted as having a potential role in some off-label uses. Remicade was typically reserved for severe or refractory disease or for patients in whom a more rapid onset of improvement is necessary (pustular psoriasis); responders noted that cyclosporine and Remicade are really the only options for acute cases.

- *Gastroenterology* – Responders commented that most are now using Humira for Crohn’s disease to some extent (instead of Remicade); some prefer Humira as the first choice because of easier administration. They perceived that many providers will continue to use Remicade due to lack of guidelines. They noted that the factors affecting their choice of biologic agent for Crohn’s disease were concerns about infusion reactions, antibody formation, need for a concomitant immunosuppressant, and type of disease (with more literature and experience with Remicade for the treatment of fistulizing disease).

Responders did not perceive that there was much (off-label) use of Humira for Crohn’s disease at present, although some providers have commented that they would try it before cyclosporine or colectomy in patients who cannot take Remicade.

*Relative Clinical Effectiveness Conclusion:* The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the following clinical effectiveness conclusion:

- a) Across all disease states reviewed, all of the TIBs FDA-indicated for a particular condition have sufficient evidence from placebo-controlled RCTs to demonstrate efficacy. TIBs are typically added to standard therapy in patients with moderate to severe disease. In general, combination treatment of rheumatologic conditions with TIBs plus MTX offers better efficacy than TIBs or MTX alone. Beneficial effects on QOL and productivity are associated with improvements in clinical response.
- b) There is a lack of direct comparative evidence (head-to-head RCTs) across all disease states. In all disease states except RA, trials were too small in number or too heterogeneous to make indirect comparisons based on meta-analysis of placebo-controlled trials feasible. With two exceptions, treatment effect across agents appeared similar.
- c) In RA, Kineret appears to be less efficacious than the TNF inhibitors (Enbrel, Humira, and Remicade) with respect to effects on symptoms (ACR response), based on indirect comparison of data from placebo-controlled trials.

- d) In psoriasis, PASI 75 scores for Remicade appeared consistently higher than with other TIBs used for psoriasis (Enbrel, Amevive, and Raptiva), although there is insufficient comparative evidence to draw a definitive conclusion. Some evidence suggests diminishing effect with Remicade as continuous use approaches 1 year. PASI 75 response rates for Amevive, Raptiva, and Enbrel appear similar in 12- to 24-week trials. An indication for Humira for the treatment of plaque psoriasis is under consideration by the FDA; one published trial and additional unpublished data available from the manufacturer supports its efficacy for this condition.
- e) The multi-indication self-administered TIBs (Humira and Enbrel) compare favorably to one another. Enbrel did not appear to be efficacious in Crohn's disease, for which Humira is indicated. Humira lacks published evidence in JRA and has limited published evidence in psoriasis; however, the manufacturer has unpublished data suggesting efficacy in both disease states and both are under consideration by the FDA. For disease states in which both are indicated, there is little evidence to suggest any clinically relevant difference in treatment effect.
- f) Amevive and Raptiva FDA-indicated only for psoriasis; they appear to compare favorably to Enbrel in terms of treatment effect. Their place in therapy relative to Enbrel and Remicade (and potentially Humira) in the treatment of psoriasis is probably dependent on factors such as IM administration of Amevive, recommended lab monitoring with both agents, and greater familiarity of providers with the TNF inhibitors.
- g) Overall, TIBs were well-tolerated during clinical trials; the most common and consistently reported AEs are injection site or infusion reactions (depending on route). Kineret may cause more injection reactions than Humira and Enbrel based on the mean crude incidence of injection reactions calculated by DERP reviewers from clinical trials included in that review: 17.5% for Humira (95% CI 7.1-27.9); 22.4% for Enbrel (95% CI 8.5-36.3); but 67.2% for Kineret (95% CI 38.7-95.7). In addition, Kineret is given once daily, as opposed to weekly or every other week dosing for Humira and Enbrel.
- h) The primary safety concerns with TIBs are related to the potential for increased risk of serious AEs (e.g., infections, malignancies, autoimmune disorders, etc), most of which are associated with the drugs' effects on the immune system. These effects are rare and cannot be assessed reliably during clinical trials, although the overall incidence of serious AEs tends to be higher with TIBs compared to placebo, and trends in large RCTs approach statistical significance. There is insufficient evidence to draw conclusions about comparative risk of any of these serious AEs.
- i) There is fair evidence of an increased risk of serious infections (including TB) for TIBs compared to placebo.

- ii) Observational evidence indicates a higher risk of lymphoma for patients treated with Remicade or Enbrel. Results of studies addressing other malignancies are mixed.
- iii) Evidence concerning the safety of TIBs in patients with chronic HF and the effects of TIBs on the development of chronic HF is mixed. Data from Enbrel and Remicade RCTs evaluating these TIBs for the *treatment* of chronic HF suggested higher rates of mortality compared to placebo. However, observational studies have reported *lower* rates of cardiovascular events in RA patients on TNF inhibitors compared to those on conventional therapy.
- iv) All TNF inhibitors appear to cause the development of autoantibodies to some extent. Cases of drug-induced lupus, lupus-like syndromes and other autoimmune disorders have been reported with Enbrel, Humira, and Remicade.
- v) Humira, Enbrel, and Remicade may be associated with demyelination. Hepatotoxicity has been reported with Remicade and Amevive.
- vi) Laboratory monitoring is required or recommended for Kineret (neutrophil counts), Amevive (CD4+ T lymphocyte counts), and Raptiva (platelet counts) due to reports of hematologic abnormalities.
- i) There is little substantive information concerning potential drug interactions with the TIBs, which are in general considered safe for use with the large number of drugs used concomitantly in clinical trials. Based on two combination trials (one with Kineret plus Enbrel and one with Orencia plus Enbrel), additive effects on the immune system appear to preclude concomitant treatment with more than one TIB.
- j) Overall, TIBs do not appear to have major differences in terms of efficacy or safety/tolerability in specific subsets of patients (e.g., based on age, gender, race, or comorbid conditions), with the exception of a reported higher risk of mortality among chronic HF patients treated with Enbrel or Remicade. Potential differences include varying pregnancy categories (B vs. C) across drugs (Amevive, Orencia, and Rituxan are Category C); the need for dose reduction of Kineret in patients with impaired renal function; and availability of data in pediatric patients (Enbrel for JRA; Remicade for pediatric Crohn's disease).

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

## **B. TIBs – Relative Cost Effectiveness**

The P&T Committee evaluated the relative cost effectiveness of the TIBs in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents

in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

The TIBs were grouped into sub-groups according to the number of indications for treatment that each agent possessed. The multi-indication agents included Enbrel and Humira, and the single-indication agents consisted of Kineret, Raptiva, and Amevive. The cost effectiveness review compared the estimated cost of treatment by disease state for RA and plaque psoriasis. For RA, the analysis compared Enbrel, Humira, Kineret, and Remicade, while the analysis of plaque psoriasis compared Raptiva, Enbrel, and Amevive. Although Remicade is not part of the pharmacy benefit (it is covered under the TRICARE medical benefit), it was included in the analysis because it has indications for treatment that are similar to the products evaluated for the TIBs cost effectiveness review.

The relative clinical effectiveness evaluation concluded that the TIBs are effective for the treatment of RA and plaque psoriasis. Moreover, there was insufficient evidence to suggest that the TIBs' treatment effectiveness differed for RA and plaque psoriasis with one exception: Kineret appeared to be less effective for the treatment of RA than the multi-indication TIBs, based on the available evidence.

With this information, a cost analysis for RA was conducted to compare the expected cost per year of treatment for each drug product by indication across all three points of service. Results from the analysis showed that Humira was the most cost effective TIB for treatment of RA. Enbrel was more costly than Humira with similar clinical effectiveness, while Kineret was the most costly agent evaluated and was less effective than the multi-indication TIBs. The results showed that neither Enbrel nor Kineret were cost effective when compared to Humira for the treatment of RA, and the conclusions were robust to assumptions about dose escalation with Humira. In the analysis of plaque psoriasis, all three products evaluated had comparable cost effectiveness profiles.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of various formulary scenarios was conducted to estimate the influence of other factors associated with a UF decision (i.e., condition sets, market share migration, switch costs, non-formulary cost shares). The goal of the BIA was to aid the Committee in determining which group of multi-indication TIBs best met the majority of the clinical needs of the DOD population at the lowest expected cost to the MHS. The results showed that the scenario where Humira was the sole multi-indication TIB on the UF was the most cost-effective scenario evaluated in the BIA.

***Cost Effectiveness Conclusion*** – The P&T Committee concluded that:

- 1) For RA, the clinical effectiveness evaluation concluded that Kineret appears to be less effective for the treatment of RA than the multi-indication TIBs. A cost effectiveness analysis comparing the expected cost per year of treatment across all three points of service for Enbrel, Humira, and Kineret showed that Humira was the most cost effective TIB for treatment of RA. Enbrel was more costly than

Humira with similar effectiveness, while Kineret was both more costly and less effective.

- 2) For psoriasis, there was insufficient evidence to definitely conclude that treatment effectiveness differed among agents. A cost analysis comparing the expected cost per year of treatment across all three points of service for Raptiva, Enbrel, and Amevive showed similar cost effectiveness profiles for all three agents.
- 3) The UF scenario that placed Humira as the sole multi-indication TIB on the UF was the most cost effective scenario.

**COMMITTEE ACTION:** The DOD P&T Committee voted to accept the TIB relative cost effectiveness analysis as presented by the PEC. The Committee concluded that the UF scenario that placed Humira as the sole multi-indication TIB on the UF was the most cost effective UF scenario.

### **C. TIBs - Uniform Formulary Recommendation:**

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the TIBs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that Humira, Raptiva, and Amevive be maintained as formulary on the UF and that Enbrel and Kineret be classified as non-formulary under the UF.

### **D. TIBs – UF Implementation Period**

The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

### **E. TIBs – PA Requirements, Criteria, and Implementation Period**

The P&T Committee recommended that no changes be made to PA criteria for Enbrel, Humira, Kineret, and Raptiva; 2) that a PA be required for Amevive under the PA criteria outlined above; and 3) that the effective date for the Amevive PA be timed to coincide with that established for the UF decision in this class.

## **VII. TIBs (cont.)**

### ***BAP Comments***

#### **A. Uniform Formulary Recommendation:**

The P&T Committee, based upon its collective professional judgment, voted to recommend that Humira, Raptiva, and Amevive be maintained as formulary on the UF and that Enbrel and Kineret be classified as non-formulary under the UF.

The P&T Committee recommended that no changes be made to PA criteria for Enbrel, Humira, Kineret, and Raptiva; 2) that a PA be required for Amevive under the PA criteria outlined above; and 3) that the effective date for the Amevive PA be timed to coincide with that established for the UF decision in this class.

*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 at the TMOP and TRRx, and at the MTFs no later than 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:

## VIII. RECENTLY APPROVED AGENTS - Valsartan/Amlodipine (Exforge)

### A. Relative Clinical Effectiveness

The proprietary product Exforge contains the combination of valsartan (Diovan) with amlodipine (Norvasc). It is the first fixed-dose combination product containing an angiotensin receptor blocker (ARB) with a dihydropyridine calcium channel blocker (DHP CCB). Generic formulations of amlodipine are now commercially available.

The DoD P&T Committee previously reviewed several subclasses of the Renin Angiotensin Antihypertensive (RAA) drug class, including the angiotensin converting enzyme (ACE) inhibitors and ACE/diuretic combinations in August 2005, the ACE/CCB combinations in February 2006, the ARBs and ARB/diuretic combinations in February 2005 and May 2007, and the direct renin inhibitor aliskiren (Tekturna) in August 2007.

Fixed-dose combination RAA agents designated as UF are benazepril/amlodipine (Lotrel, generics), telmisartan/ hydrochlorothiazide (HCTZ) (Micardis HCT), candesartan/HCTZ (Atacand HCT), losartan/HCTZ (Hyzaar), lisinopril/HCTZ (Prinzide, Zestoretic, generics), captopril/HCTZ (Capozide, generics), benazepril/HCTZ (Lotensin HCT, generics), enalapril/HCTZ (Vaseretic, generics), and fosinopril/HCTZ (Monopril HCT, generics).

Exforge is approved for treating hypertension in patients whose blood pressure (BP) is not adequately controlled with an ARB or DHP CCB administered as monotherapy. Although Exforge is not approved for the initial treatment of



hypertension, there is no evidence to suggest that it would not be effective when used in that manner clinically.

With regard to efficacy, combining an ARB with a DHP CCB provides two differing mechanisms to reduce BP. Two randomized controlled trials in over 2,000 patients showed superior BP reduction and control with Exforge compared to valsartan and amlodipine administered as monotherapy, and compared to placebo. A trial in 130 patients with Stage 2 hypertension (>160/>100 mm Hg) found similar BP reductions when Exforge was compared to the fixed dose combination of lisinopril/HCTZ (Zestoretic, Prinzide, generics).

There are no clinical trials with Exforge that have evaluated clinical outcomes of reducing mortality, stroke, heart failure (HF) hospitalization, or need for renal dialysis/transplantation. However, valsartan and amlodipine individually have shown benefits in these areas, and there is no evidence to suggest that Exforge would not be beneficial here.

With regard to safety, the package labeling for Exforge reflects that of the individual components for adverse events, drug interactions, and black box warnings (e.g., teratogenicity concerns with ARBs). In clinical trials, the incidence of peripheral edema with Exforge was lower than that observed with amlodipine monotherapy.

Although not specifically evaluated in a controlled clinical trial with Exforge, potential benefits to fixed dose combination drugs include reduced tablet burden, simplified drug regimens, increased patient convenience, and improved adherence to therapy.

***Relative Clinical Effectiveness Conclusion*** – The P&T Committee concluded that, while Exforge offers a slight convenience to the patient in terms of decreased tablet burden and simplified medication regimen, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other antihypertensive agents included on the UF.

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

## **B. Relative Cost Effectiveness**

The P&T Committee evaluated the relative cost-effectiveness of valsartan/amlodipine (Exforge) in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly the ARBs. Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2).

A cost minimization analysis (CMA) was employed to evaluate the cost effectiveness of Exforge. The cost-effectiveness of Exforge was evaluated relative to the following combinations of single agents: telmisartan (Micardis)/amlodipine (the most cost-effective UF ARB), candesartan

(Atacand)/amlodipine (chronic HF indication UF ARB), and valsartan (Diovan)/amlodipine (single agents of Exforge).

The results of the CMA showed that the projected weighted average daily cost of Exforge was significantly higher than the weighted average daily cost of the combinations of UF ARBs with amlodipine.

**Cost Effectiveness Conclusion** – The P&T Committee concluded that Exforge is not cost effective relative to the other agents in the RAA class. The weighted average cost of combined individual agents (UF ARBs and generic amlodipine) is more cost-effective relative to Exforge.

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

### C. Uniform Formulary Recommendations

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of Exforge, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that Exforge be designated as non-formulary on the UF.

### D. Uniform Formulary Implementation Period

The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRICARE Retail Pharmacy Network (TRRx), and at the Military Treatment Facilities (MTFs) no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

## IX. RECENTLY APPROVED AGENTS - Valsartan/Amlodipine (Exforge)

### BAP Comments

**A. Uniform Formulary Recommendations.** P&T Committee, based upon its collective professional judgment, voted to recommend that Exforge be designated as non-formulary on the UF.

|                     |   |
|---------------------|---|
| <b>BAP Comment:</b> | <input type="checkbox"/> Concur <input type="checkbox"/> Non-concur |
|                     | Additional Comments and Dissentions:                                |

**B. Implementation Plan:** The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the

TRICARE Mail Order Pharmacy (TMOP) program and TRICARE Retail Pharmacy Network (TRRx), and at the Military Treatment Facilities (MTFs) no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

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| <i>BAP Comment:</i> | <input type="checkbox"/> Concur <input type="checkbox"/> Non-concur |
|                     | Additional Comments and Dissentions:                                |

**X. RECENTLY APPROVED AGENTS - Lisdexamfetamine dimesylate (Vyvanse)**

**A. Relative Clinical Effectiveness** – Lisdexamfetamine (Vyvanse) is a new stimulant drug approved for treating attention deficit/hyperactivity disorder (ADHD) in children 6 to 12 years of age. In contrast to methylphenidate extended release (Concerta), mixed amphetamine salts extended release (Adderall XR), and atomoxetine (Strattera), lisdexamfetamine is not currently indicated for treating adolescents and adults. Vyvanse and Adderall XR are manufactured by the same company; generic formulations of Adderall XR are anticipated in 2009.

The ADHD and narcolepsy drugs were evaluated at the November 2006 DoD P&T Committee meeting. The UF designated ADHD drugs include the non-stimulant atomoxetine (Strattera), and the stimulants dextroamphetamine (Dexedrine, generics), methamphetamine (Desoxyn), mixed amphetamines salts (Adderall, and generics; Adderall XR), and all oral formulations of methylphenidate (Concerta, all Metadate products, all Methylin products, all Ritalin products, and generics). Methylphenidate transdermal system (Daytrana) and dexmethylphenidate (Focalin and Focalin XR) were classified as non-formulary.

With regard to efficacy, there is insufficient evidence to suggest that clinically relevant differences exist between lisdexamfetamine and other ADHD stimulant products. One randomized published trial in 290 children showed significant improvements in ADHD rating scales with lisdexamfetamine compared to placebo. A double-blind, placebo-controlled crossover study available only in abstract form showed significant reductions in observer ratings of ADHD behaviors (e.g., improved ADHD control) with either lisdexamfetamine or mixed amphetamine salts (Adderall XR) in 52 children compared to placebo; outcomes with Vyvanse were not directly compared to Adderall XR.

With regard to safety, there is no evidence to suggest that the adverse event profile of lisdexamfetamine differs clinically from other amphetamine formulations, although no comparative trials are available. Up to 33% of patients

report appetite suppression. The package labeling for lisdexamfetamine carries the same black box warning as the other stimulants for tolerance, dependence, abuse potential and sudden cardiac death in children with pre-existing structural cardiovascular abnormalities. The drug interaction profile is the same as other ADHD stimulants, and lisdexamfetamine should not be used concurrently with monoamine oxidase inhibitors, due to the risk of hypertensive crisis.

With regard to abuse potential, lisdexamfetamine is a Schedule II controlled substance, as are the other ADHD stimulants (e.g., methylphenidate and amphetamines). Lisdexamfetamine is a pro-drug that is hydrolyzed in the GI tract to dextroamphetamine and the amino acid l-lysine, and was thus designed to have less potential for abuse, diversion and overdose toxicity than amphetamine. Two unpublished studies reported the preference of lisdexamfetamine in a total of 50 drug abusers. At lisdexamfetamine doses less than 100 mg “likeability” scores on a Drug Rating Questionnaire scale were similar to placebo, while doses exceeding 100 mg showed similar likeability as with dextroamphetamine (the maximum recommended lisdexamfetamine dose currently marketed is 70 mg).

***Relative Clinical Effectiveness Conclusion*** – The P&T Committee concluded that lisdexamfetamine (Vyvanse) does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other ADHD agents included on the UF.

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

**B. Relative Cost Effectiveness** – The P&T Committee evaluated the relative cost-effectiveness of Lisdexamfetamine (Vyvanse) in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly the other once-daily ADHD stimulant medications. Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2).

The ADHD stimulants include methylphenidate immediate release and extended release and various immediate and extended release formulations of amphetamines (dextroamphetamine, methamphetamine, mixed salts of amphetamine, and lisdexamfetamine). The comparators for the cost effectiveness analysis of Vyvanse included the UF once daily formulations ADHD stimulants: methylphenidate (Concerta, Metadate CD, Ritalin LA), and mixed salts of amphetamine extended release (Adderall XR).

The relative clinical effectiveness evaluation concluded that there is insufficient evidence of a clinically meaningful difference between once daily stimulants for the treatment of ADHD. As a result, a cost minimization analysis (CMA) was employed to determine the cost effectiveness of Vyvanse relative to the UF once daily ADHD stimulants.

Results from the CMA revealed that the weighted average cost per day of therapy for Vyvanse was similar to the other UF once daily ADHD stimulants.

**Cost Effectiveness Conclusion** – The P&T Committee concluded that lisdexamfetamine (Vyvanse) had similar relative cost-effectiveness compared to the other UF once daily ADHD stimulants.

**COMMITTEE ACTION:** The P&T Committee voted to accept the cost effectiveness conclusion stated above

**C. UF Recommendation**

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of Lisdexamfetamine (Vyvanse), and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that lisdexamfetamine (Vyvanse) be designated as non-formulary on the UF. This recommendation was primarily based upon the determination that lisdexamfetamine (Vyvanse) offers no clinically meaningful therapeutic advantage over other once daily ADHD stimulants.

**D. Implementation period.**

The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRICARE Retail Pharmacy Network (TRRx), and at the Military Treatment Facilities (MTFs) no later than a 60-day implementation period.

**XI. RECENTLY APPROVED AGENTS - Lisdexamfetamine dimesylate (Vyvanse)**

**BAP Comments**

**A. Uniform Formulary Recommendations.** Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of Lisdexamfetamine (Vyvanse), and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that lisdexamfetamine (Vyvanse) be designated as non-formulary on the UF. This recommendation was primarily based upon the determination that lisdexamfetamine (Vyvanse) offers no clinically meaningful therapeutic advantage over other once daily ADHD stimulants

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| Additional Comments and Dissentions: |                                 |                                     |

**B. Implmentatoin Period.** The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRICARE Retail Pharmacy Network (TRRx), and at the Military Treatment Facilities (MTFs) no later than a 60-day implementation period.

*BAP Comment:*

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Additional Comments and Dissentions:

## **XII. RECENTLY APPROVED AGENTS - Ethinyl estradiol 20 mcg/levonorgestrel 0.09 mg (Lybrel)**

- 1) **A. Relative Clinical Effectiveness** – The contraceptive drug class was reviewed in May 2006. Lybrel is a new contraceptive marketed in July 2007 that contains 20 mcg of ethinyl estradiol (EE) and 90 mcg of levonorgestrel. It is the first FDA-approved contraceptive formulation specifically packaged for continuous use. Active tablets are taken 365 days a year, with the intent of eliminating cyclical bleeding periods.

Contraceptives containing 20 mcg of EE with 100 mcg of levonorgestrel (Lutera, Levlite or equivalent) are included on the BCF. The Lybrel product cannot be exactly duplicated by using conventional packages of Lutera or its equivalents, due to the 10 mcg difference in the levonorgestrel component; however this difference in the progestin content is of questionable clinical relevance.

Contraceptives are traditionally available in conventional 28-day packaging containing 21 days of active tablets followed by 7 days of placebo tablets, which leads to 13 cycles of withdrawal bleeding yearly. Some recently introduced oral contraceptives reduce the number of placebo tablets to 4 (Yaz, Loestrin-24 Fe), thus shorting the bleeding period, or extend the number of active tablets to 84, resulting in only 4 withdrawal bleeding periods per year (e.g., Seasonique, Seasonale). Continuous use of oral contraceptives may be beneficial in women with symptoms related to fluctuations in hormone levels (e.g., endometriosis or menstrual migraines) and in women desiring cessation of cyclical bleeding. Conventionally packaged contraceptives are commonly used on a continuous or extended cycle basis: four conventional contraceptive packs are dispensed every 90 days, and the patient is instructed to discard the unneeded placebo tablets. This practice also provides access to the full array of oral contraceptive products, with varying estrogen levels and types of progestins.

With respect to efficacy, there is no evidence to suggest that Lybrel would differ from other similar contraceptives. One head-to-head, open-label trial in 641 women that compared Lybrel with a traditional regimen of 20 mcg EE/100 mg levonorgestrel (Lutera, Levlite or equivalents) reported no difference in pregnancy rates after one year (zero vs. three, respectively). A non-comparative trial in over 2,000 women reported 23 pregnancies after one year (a rate of 1.55

per 100 user years), which is similar to pregnancy rates reported with other contraceptives containing 20 mcg EE.

With respect to safety, breakthrough bleeding/spotting is common with all extended-cycle or continuous regimens, particularly in the first few months of use. In the non-comparative trial, 18.6% of women discontinued therapy because of uterine bleeding. However, this decreased over time (48% incidence of breakthrough bleeding at pack 3 vs. 21% at pack 13), and approximately 60% of women achieved amenorrhea after one year. In the head-to-head trial mentioned previously, the incidence of common adverse effects (dysmenorrhea, nausea, and headache) was similar between Lybrel and the comparator (Lutera, Levlite or equivalents). The safety profile of Lybrel has not been evaluated for longer than two years.

**Relative Clinical Effectiveness Conclusion:** The Committee concluded that Lybrel did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness or clinical outcome over other oral contraceptives included on the UF.

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

- 2) **B. Relative Cost Effectiveness** – The P&T Committee evaluated the relative cost-effectiveness of ethinyl estradiol 20/levonorgestrel 0.09 (Lybrel) in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly other monophasic ethinyl estradiol 20 mcg (M 20 EE) contraceptives. Information considered by the P&T Committee included, but was not limited to sources of information listed in 32 CFR 199.21 (e)(2).

The relative clinical effectiveness evaluation concluded that Lybrel does not show compelling clinical superiority over currently available contraceptives on the UF in the M20 EE subclass. As a result, a cost minimization analysis (CMA) was employed to determine the cost effectiveness of Lybrel relative to other UF M20 EE agents (Sronyx, Lutera, Levlite-28, Aviane, and Lessina-28) used on a continuous cycle basis.

The results from the CMA revealed that the weighted average cost per day for treatment for Lybrel is significantly higher than other UF M20 EE agents used on a continuous cycle basis.

**Cost Effectiveness Conclusion:** The P&T Committee concluded that: Lybrel is not cost-effective relative to other UF M20 EE agents used on a continuous cycle basis.

**COMMITTEE ACTION:** The P&T Committee voted to accept the cost effectiveness conclusion stated above

### **C. UF Recommendation**

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the M20 EE contraceptive agents, and other relevant factors, the P&T Committee, based upon its collective professional

judgment, voted to recommend that: Lybrel (Ethinyl Estradiol 20/levonorgestrel 0.09) be designated non-formulary on the UF.

**D. Implementation period.**

The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRICARE Retail Pharmacy Network (TRRx), and at the Military Treatment Facilities (MTFs) no later than a 60-day implementation period.

**XIII. RECENTLY APPROVED AGENTS - Ethinyl estradiol 20 mcg/levonorgestrel 0.09 mg (Lybrel)**

**BAP Comments**

**A. Uniform Formulary Recommendations.** Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the M20 EE contraceptive agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that: Lybrel (Ethinyl Estradiol 20/levonorgestrel 0.09) be designated non-formulary on the UF.

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**B. Implmentation Period.** The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRICARE Retail Pharmacy Network (TRRx), and at the Military Treatment Facilities (MTFs) no later than a 60-day implementation period.

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**XIV. RE-EVALUATION OF AMLODIPINE’S UNIFORM FORMULARY STATUS**

On an ongoing basis, the DoD PEC monitors changes in the clinical information, current costs, and utilization trends to evaluate whether the UF status of agents designated as non-formulary needs to be readdressed. At this meeting, the UF status of amlodipine



(Norvasc, generics) was re-evaluated due to a significant decrease in cost across all three points of service.

In early 2007, the FDA approved Mylan Pharmaceutical's first-time generic for Norvasc. Until recently, the price for amlodipine, even though available generically, was similar to the price for brand name Norvasc and did not support a change in its UF status.

At the August 2005 P&T Committee meeting, the Committee concluded that in general, amlodipine (Norvasc, generics) had similar clinical effectiveness relative to other DHP CCBs in regards to efficacy, safety, and tolerability. In consideration of the Committee's previous relative clinical effectiveness conclusion, a CMA was performed to determine the cost-effectiveness of amlodipine relative to the other DHP CCBs included on the UF. The results of the CMA showed amlodipine to be the most-cost effective DHP CCB.

**Cost Effectiveness Conclusion** – The P&T Committee accepted the conclusions from the cost effectiveness analyses stated above.

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

**B. UF Recommendation**

In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the DHP CCB, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that amlodipine (Norvasc, generics) be reclassified as formulary on the UF.

**D. Implementation period**

The P&T Committee recommends an effective date as the date the Director, TMA signs the minutes.

**XV. RE-EVALUATION OF AMLODIPINE'S UNIFORM FORMULARY STATUS**

**BAP Comments**

**A. Uniform Formulary Recommendations.** In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the DHP CCB, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that amlodipine (Norvasc, generics) be reclassified as formulary on the UF.

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**B. Implmentation Period.** The P&T Committee recommends an effective date as the date the Director, TMA signs the minutes.

*BAP Comment:*

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Additional Comments and Dissentions: