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. Acetylcholinesterase Inhibitor and N-Methyl D-Aspartate (NMDA) Receptor Antagonist Drug Class Review

P&T Comments

A. Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of all the FDA-approved acetycholinesterase inhibitors and NMDA receptor antagonists available in the U.S. for the treatment of Alzheimer's disease. The Alzheimer's disease therapeutic class was defined as the acetylcholinesterase inhibitors: donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne) and tacrine (Cognex); and the NMDA receptor antagonist memantine (Namenda). 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 C.F.R. 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.

During a twelve month period ending July 31, 2005, 69,940 Military Health System (MHS) patients were prescribed an acetylcholinesterase inhibitor or NMDA receptor antagonist. This class is now ranked 29th in MHS drug class expenditures at a cost of $65 million annually.

1.) *Efficacy:* All acetylcholinesterase inhibitors have FDA approved indications for the treatment of mild to moderate Alzheimer's disease. The NMDA receptor antagonist memantine is FDA approved for moderate to severe Alzheimer's disease. As there are no well-designed head-to head trials comparing the four

acetylcholinesterase inhibitors or memantine, the available placebo controlled trials and meta-analyses were reviewed.

Endpoints: Outcome measures used to assess the beneficial effects of the medications used in the treatment of Alzheimer's disease measure functioning in four categories which include cognitive function, global assessment, activities of daily living and behavioral disturbance. The two most consistent outcome measures used in randomized controlled trials evaluate cognitive function (Alzheimer's Disease Assessment Scale, ADAS-Cog) and global assessment (Clinician's Interview Based Assessment of Change-Plus, CIBIC-Plus). The ADAS is an 11-item scale with scores ranging from 0 (no impairment) to 70 (very severe impairment). On average, untreated patients with moderate AD decline 7 to 11 points per year while treated patients with mild or severe disease decline 0 to 5 points per year. Generally an improvement of 4 or more points is considered to be clinically meaningful, roughly equivalent to a six-month delay in cognitive decline. In clinical trials, improvement is characterized by a slowing of deterioration as opposed to improvement above baseline.

Mild to moderate Alzheimer's disease: The acetylcholinesterase inhibitors have been studied in mild to moderate Alzheimer's disease. Outcome measures included the ADAS-Cog and the CIBIC-plus. In well-designed randomized controlled trials involving donepezil vs. placebo, rivastigmine vs. placebo, galantamine vs. placebo and tacrine vs. placebo, all of the achetylcholinesterase inhibitors showed statistically significant differences in the primary outcome measures compared to placebo. Systematic reviews by Cochrane, the British National Institute for Clinical Excellence (NICE), the Canadian Coordinating Office of Health Technology Assessment (CCOHTA) and others have found that treatment with these drugs conferred a small clinical benefit when compared to placebo.

Moderate to severe Alzheimer's disease: Memantine is FDA approved for treatment of moderate to severe Alzheimer's disease. Clinical trials comparing memantine to placebo used the ADAS-Cog and the Severe Impairment Battery (SIB) for primary outcome measures. In all of the trials, memantine showed a statistically and clinically significant improvement over placebo in the primary outcome measures.

Efficacy conclusion: All of the drugs used for Alzheimer's disease show statistically significant changes in cognition rating scores compared to baseline. Whether these results are clinically significant is debatable. There are no direct comparative trials available, but there is no evidence to suggest that any one Alzheimer's disease drug is more efficacious than another, when used according to FDA indications.

2.) *Safety/Tolerability:*

Serious effects – hepatotoxicity: Tacrine has been shown to cause elevated liver function tests (LFTs) in over 50% of patients, with 7% of patients experiencing LFT elevations greater than 10 times the upper limits of normal (ULN). In a

major clinical trial, these LFT elevations led to an overall 72% discontinuation rate at the higher dosage range. The FDA requires a black box warning for the possibility of severe liver failure and death, and frequent monitoring of LFTs is mandated for patients using tacrine.

Side effects: Rivastigmine and galantamine are associated with a higher incidence of GI side-effects and consequently require more complex titration than the other cholinesterase inhibitors or memantine. A complex titration schedule possibly affects the likelihood that patients will adhere to these regimens. In clinical trials of memantine, the rate of patients discontinuing due to side effects was not statistically different from placebo.

Drug interactions: Donepezil and galantamine are metabolized by the CYP 450 enzyme system and thus may be prone to more drug interactions than other agents. However, it should be noted that interactions that increase levels of the Alzheimer's drugs are not generally considered to be clinically significant.

Safety/tolerability conclusion: The P&T Committee agreed that among the acetylcholinesterase inhibitors, tacrine differed significantly in terms of safety due to its potential to cause hepatic injury. While minor differences exist among the other acetylcholinesterase inhibitors and memantine, none were considered significantly different with respect to major contraindications, drug interactions, and adverse drug reactions.

3.) Other Factors:

Titration and dosing frequency: A difference in ease of dosing and dose titration schedules exists among these agents. Donepezil and galantamine extended release are dosed once daily, the other agents are dosed twice daily (galantamine immediate release, rivastigmine and memantine) or four times daily (tacrine). There are no well-designed randomized controlled trials that demonstrate improved outcomes with once daily dosing of these agents, however once daily products have the theoretical advantage of yielding a lower burden on caregivers.

DoD Provider Preferences: In a PEC survey of DOD providers (neurologists, geriatricians, internists, and family practitioners) the majority of respondents favored products with once daily dosing. Most respondents relayed that they avoided tacrine because of hepatotoxicity; all expressed a preference for donepezil based on ease of titration and familiarity; most said that they add or switch to memantine when acetylcholinesterase inhibitors failed to provide expected benefit; and most felt that these medications should not be discontinued once they stopped arresting cognitive decline since patients decline precipitously once these medications were stopped.

Other Factors Conclusion: There is no evidence to suggest clinical superiority of any one Alzheimer's agent based on differences in dosing and titration schedules or DoD provider opinion.

COMMITTEE ACTION: The P&T Committee voted that for the purposes of the Uniform Formulary clinical review, that tacrine possessed a safety disadvantage relative to other available acetylcholinesterase inhibitors, but that all were similar in terms of effectiveness and clinical outcome; and that memantine has a place in therapy due to its indication for treatment of dementia in moderate to severe Alzheimer's disease.

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

The first step in determining the relative cost-effectiveness of the selected agents in this class was to conduct a cost-analysis to calculate the total weighted average cost per day of treatment for each agent. The second step was to conduct the appropriate pharmacoeconomic analysis taking into account the conclusions of the clinical review. Because the clinical review concluded, with the exception of tacrine, that all of the agents within the Alzheimer's drug class had similar relative clinical effectiveness (efficacy, safety and tolerability), a cost-minimization analysis (CMA) was selected. To adjust for the safety issues associated with the use of tacrine, the cost of monitoring liver function tests was added to the drug cost of tacrine in the CMA.

The cost analysis only considered drug costs. The results showed tacrine to be the acetylcholinesterase inhibitor with the lowest total weighted average cost per day of treatment across all points of service (MTF, Retail, Mail). The CMA, which considered lab costs for monitoring tacrine, showed that donepezil was the most cost-effective agent when the additional requirement of multiple liver function tests was taken into account.

The results of the above analyses were then incorporated into a Budget Impact Analysis (BIA), which accounted for other factors and costs associated with a potential decision regarding formulary status of Alzheimer's drugs within the UF. These factors included: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and switch costs. The results of the budget impact analysis further confirmed the results of the CMA. Donepezil was found to be the most cost-effective Alzheimer's drug overall.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to recommend non-formulary status for tacrine, with donepezil, rivastigmine, galantamine, and memantine maintaining formulary status on the Uniform Formulary at the formulary cost share.

C. Implementation Plan: Because of the low number of beneficiaries that would be affected by this formulary action (five patients known to be taking tacrine across the MHS), the P&T Committee recommended an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

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

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

III. Acetylcholinesterase Inhibitor and N-Methyl D-Aspartate (NMDA) Receptor Antagonist Drug Class Review (cont.)

BAP Comments

A. Relative Clinical Effectiveness*:* The P&T Committee concluded that tacrine has less clinical utility than the other acetylcholinesterase inhibitors used in the treatment of the cognitive symptoms of Alzheimer's disease. Furthermore the safety concerns regarding the use of tacrine outweighed any cost benefit that might be obtained by keeping it on the Uniform Formulary. The P&T Committee further concluded that safety considerations for tacrine would support a Prior Authorization; however, due to the extremely low number of unique utilizers (single digits) any potential problem was felt to be self-limiting. The P&T Committee concluded that all the remaining acetylcholinesterase inhibitors have similar relative clinical effectiveness for treating mild to moderate dementia associated with Alzheimer's disease. The P&T Committee agreed that memantine has a place in therapy for the treatment of moderate to severe dementia associated with Alzheimer's disease. With regard to safety and tolerability, memantine has an adverse event rate similar to placebo.

B. Relative Cost Effectiveness: The P&T Committee agreed with the relative cost-effectiveness analysis of the Alzheimer's drugs presented. The P&T Committee concluded that the safety concerns regarding the use of tacrine outweighed any cost benefit that might be obtained by keeping it on the Uniform Formulary.

C. Uniform Formulary Recommendation: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the Alzheimer's drugs, the P&T Committee recommended that

the status of tacrine be changed from formulary to non-formulary on the Uniform Formulary, with donepezil, rivastigmine, galantamine, and memantine maintaining formulary status on the Uniform Formulary with the formulary cost share. To address the safety concerns of tacrine, a Prior Authorization (PA) for tacrine was initially considered. However, due to the extremely low number of unique utilizers (single digits) currently being treated with tacrine across the MHS, the P&T Committee felt the medical community was adequately aware of

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

the risks associated with tacrine use, and safety concerns were already being appropriately addressed.

D. Implementation Plan: The Committee voted to recommend an implementation period of 90 days.

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

IV. Nasal Corticosteroids Drug Class Review

P&T Comments

***A.* Relative Clinical Effectiveness:** The Committee evaluated the relative clinical effectiveness of the six nasal corticosteroids marketed in the US: beclomethasone dipropionate (Beconase AQ, Vancenase AQ and Vancenase AQ DS), budesonide (Rhinocort AQ), flunisolide (Nasarel), fluticasone propionate (Flonase), mometasone furoate (Nasonex), and triamcinolone acetonide (Nasacort AQ). Information regarding the safety, effectiveness, and clinical outcome 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.

1) *Efficacy*: All of the nasal corticosteroids are FDA-approved for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). Endpoints used in clinical trials included patient scoring on the total nasal symptom score (nasal blockage, rhinorrhea, sneezing and nasal itching) or total symptom score (itchy/burning eyes, tearing, redness). Two clinical reviews of seventeen randomized controlled trials evaluating various nasal corticosteroids determined

equal efficacy amongst the nasal corticosteroids. Twenty placebo-controlled/head-to-head trials also concluded that nasal corticosteroids were equally effective at equipotent doses at relieving allergic rhinitis symptoms. Possible differences may lie in individual physician/patient preferences and population specific safety concerns.

Efficacy Conclusion: Multiple clinical reviews over the past two decades suggest comparable efficacy between the nasal corticosteroids at relieving allergic rhinitis symptoms when used in equipotent doses.

2) *Safety and Tolerability*:

   a. Local effects:

      i. Transient local reactions, such as nasal irritation and stinging, sneezing, dryness, headaches, and occasional sore throat, are the common side effects seen with nasal corticosteroids. All of the aqueous nasal corticosteroid sprays can cause epistaxis, but in clinical trials, the placebo spray also had an appreciable rate of epistaxis. Other, rarely reported local adverse events include nasal septum ulceration and septal perforation. There is no evidence to suggest that one nasal corticosteroid is more likely to cause local adverse effects than another. According to package insert data, approximately 2-3% of patients discontinue a nasal corticosteroid treatment due to adverse events.

   b Systemic Adverse Events:

      i. *Hypothalmic adrenal axis (HPA) suppression:* HPA-axis suppression is a concern with all corticosteroids (oral, inhaled, and nasal) as it can progress to acute adrenal crisis in all ages. Two separate review articles, one evaluating 19 randomized clinical trials and the other 7 additional randomized clinical trials, found no significant differences between the nasal corticosteroids in suppression of the HPA-axis. The true clinical relevance of nasal corticosteroid use and any resultant significant adrenal gland suppression/adrenal crisis is difficult to ascertain as the trials report changes in surrogate markers (e.g. urinary cortisol excretion, serum cortisol or adrenocorticotropin hormone (ACTH) concentration) and are not consistent across testing methods. Placebo-controlled trials show similar HPA-axis suppression between placebo and nasal corticosteroids, as evidenced by reductions in lab values; comparisons with oral prednisone showed greater suppression than nasal corticosteroids. It is unlikely that the risks of HPA-axis suppression differ among nasal corticosteroids, although theoretically fluticasone propionate and mometasone furoate may confer lower risk due to lower bioavailability than the others.

      ii. *Growth retardation:* All inhaled and nasal corticosteroids are required by the FDA to have a warning label in their package inserts regarding the potential risk of growth suppression. Regular monitoring is especially necessary for children receiving multiple corticosteroid therapies, as

excessive corticosteroid doses can lead to proven growth suppression. Head to head trials and placebo-controlled trials have shown conflicting results among the nasal corticosteroids in outcomes measuring lower leg growth velocity and standing height. Inconsistency across trials in growth measurement and study methodology make it difficult to interpret actual growth suppression and to determine the possible effects of nasal corticosteroids when predicting future pediatric growth velocity. In general, nasal corticosteroids should be used with care in children by titrating to the lowest effective dose so to keep growth suppression to a minimum.

iii. *Cataracts:* A large retrospective evaluation from the UK compared the use of nasal corticosteroids in over 280,000 patients with and without diagnosed cataracts. Over 70% of the patients were solely receiving beclomethasone dipropionate. No increased association was found between nasal steroid use and cataract formation, however patients receiving chronic oral corticosteroid therapy were found to have an increased frequency of cataract formation. Excessive doses of nasal corticosteroids can lead to rare effects of cataracts. There is insufficient evidence to predict whether one nasal corticosteroid is more likely to cause cataracts than the other.

Overall safety conclusion: Nasal irritation, epistaxis, and rhinorrhea are the most common local adverse events, and are equally likely to occur with any of the nasal corticosteroids. For systemic effects (HPA-axis suppression, growth suppression, and cataract formation), there is no definitive evidence that one nasal corticosteroid is more likely to cause these effects than another. Depending on the severity of allergic rhinitis symptoms, the benefits of nasal corticosteroids may outweigh the risks of systemic adverse effects. According to the package inserts, the risk of systemic effects is increased when higher than normal amounts of nasal corticosteroids are used.

3) *Other Factors:*

a. *Dosing frequency*: Most of the nasal corticosteroid products are marketed for once daily administration. Budesonide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide are dosed once a day, while beclomethasone dipropionate and flunisolide require at least twice to three times daily dosing. Dosing may contribute to patient adherence or patient preference for an individual product. Theoretically once daily dosing may result in improved patient compliance vs. products requiring multiple daily dosing.

b. *Kinetics/dynamics*: Molecular weight, lipophilicity, and thixotropy are types of pharmacokinetic measures used to differentiate potency between the nasal corticosteroids. When evaluating potency, varying results have been reported between nasal corticosteroids, as experimental set-ups in the laboratory setting do not conclusively correlate with what providers may witness in their

patients. There is no evidence that differences in these kinetic/dynamic parameters are linked to differences in clinical outcomes.

c. *Formulation*: The nasal aerosol formulations of Beconase (beclomethasone dipropionate), Vancenase (beclomethasone dipropionate), and Rhinocort (budesonide) have declined in popularity as physicians and patients have chosen the ease and convenience of use with the newer aqueous nasal formulations (Beconase AQ, Vancenase AQ, Vancenase AQ DS, Rhinocort AQ, Flonase, Nasonex, Nasacort AQ).

d. *Pediatric Populations:* All the nasal corticosteroids are indicated for use in children 6 years of age or older, but fluticasone propionate is indicated for children down to the age of four years and mometasone furoate is indicated for use in children as young as two years old.

e. *Pregnancy:* The only nasal corticosteroid with a FDA Category B (low risk in humans) rating is budesonide. This indication was given primarily due to a retrospective epidemiological study reviewing data from three Swedish registries and a pregnancy outcome study (Steroid Treatment and Regular Therapy [START] study) of over 6,000 infants. All the other nasal corticosteroids are rated Category C (risk cannot be ruled out). There is one placebo-controlled human study that focused specifically on the safety and efficacy of maternal nasal corticosteroid (fluticasone propionate) use during pregnancy. There were no differences found between the treatment and placebo groups in pregnancy outcomes. Pregnant patients are still recommended to discuss benefit versus risk ratios of nasal corticosteroid use with their OB/GYN provider.

f. *Patient preference/tolerability*: Patient's attitudes toward features such as taste, odor, irritation, and moistness may attribute to adherence of certain nasal corticosteroids. Patient preference may play a role in differentiating between the nasal corticosteroids, but the available clinical data is poor, and no one nasal corticosteroid has proven superior to the others in patient preference trials. More well-designed head-to-head randomized controlled trials are needed to support that one nasal corticosteroid is superior to another in tolerability or compliance.

Conclusion for Other Factors: Minor differences exist among the agents in terms of frequency of dosing, kinetic/dynamic parameters, pediatric labeling, and use in pregnancy.

COMMITTEE ACTION: The P&T Committee voted that for the purposes of the Uniform Formulary clinical review that none of the nasal corticosteroids have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other nasal corticosteroids.

Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the agents considering possible differences in safety, tolerability and effectiveness in accordance with 32 CFR 199.21 (e)(2).

Two separate economic evaluations were performed, a pharmacoeconomic analysis and a budget impact analysis. From the proceeding relative clinical effectiveness evaluation, the P&T Committee determined that nasal corticosteroids have similar relative clinical efficacy, but some small differences in terms of dosing frequency, use in pregnancy, use in pediatric populations and DoD provider preferences. The agents within the nasal corticosteroid therapeutic class were thus shown to differ slightly in relative clinical effectiveness.

The above stated differences in the nasal corticosteroids have not been evaluated in clinical trials for their effect on treatment outcomes. The PEC surveyed DoD medical providers to evaluate their opinion on these difference. The PEC conducted two cost analyses, one analysis with no effectiveness measure and the second analysis incorporating the results of the survey as an effectiveness measure.

In the first cost analysis of the cost per day of therapy across DoD alone, the results showed that flunisolide was the most effective; budesonide, fluticasone propionate, mometasone furoate and triamcinolone acetonide (not in rank order) were less cost effective and beclomethasone was not cost effective.

In the second cost analysis of the cost per day of therapy across DoD incorporating the effectiveness measure, the results showed that (all in alphabetical order) flunisolide, fluticasone propionate & mometasone furoate were the most cost effective and beclomethasone dipropionate, budesonide and triamcinolone acetonide were not cost effective.

Both cost analyses were incorporated into a budget impact analysis, to analyze the cost to the DoD under various formulary status configurations and estimating the cost of formulary changes to the DoD. The results of the budget impact analysis revealed that the best combination of agents to meet DoD's clinical and fiscal goals is the group of formulary agents that included flunisolide, fluticasone propionate and mometasone furoate. These results matched the results from our cost analysis incorporating the effectiveness measure derived from the survey of DoD providers.

COMMITTEE ACTION: The P&T Committee, based on its collective professional judgment, voted to recommend formulary status for flunisolide, fluticasone propionate and mometasone furoate; and non-formulary status for beclomethasone dipropionate, budesonide and triamcinolone acetonide under the UF.

C. **Implementation Plan*:*** Due to the relatively low number of patients that will be affected by this formulary action, the P&T Committee recommended an effective date no later than the first Wednesday following a 90-day implementation period.

COMMITTEE ACTION: The Committee voted to recommend an implementation period of 90 days.

V. Nasal Corticosteroids Drug Class (cont.)

BAP Comments

A. **Relative Clinical Effectiveness***:* The DoD P&T Committee concluded that 1) in equipotent doses, the nasal corticosteroids are equally effective at relieving symptoms of allergic rhinitis; 2) in equipotent doses the nasal corticosteroids have similar local side effect profiles; 3) there is a lower risk of systemic adverse effects (HPA-axis suppression, growth retardation, cataract formation) when nasal corticosteroids are used according to labeled dosing instructions, however, there is no evidence that systemic effects are likely to occur more with one agent versus another; 4) products that are dosed once daily may have advantages in terms of patient preference over products requiring multiple daily dosing; 5) minor differences in pharmacokinetic/dynamic factors (thixotropy, molecular weight, lipophilicity) have not translated into differences in clinical outcomes; 6) mometasone furoate is indicated for use in pediatric patients as young as 2 years of age; 7) budesonide is rated pregnancy category B, while fluticasone propionate has evidence from one trial that pregnancy outcomes were not adversely affected with use during pregnancy; and 8) there is no clear difference between the nasal corticosteroids in terms of patient preference and tolerability.

B. Relative Cost Effectiveness: The P&T Committee, based on its collective professional judgment, voted to accept the nasal corticosteroid cost effectiveness analysis presented by the PEC. The P&T Committee concluded that flunisolide, fluticasone propionate and mometasone furoate had similar cost effectiveness and that they had greater cost effectiveness than beclomethasone dipropionate, budesonide and triamcinolone acetonide.

C. Uniform Formulary Recommendation: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness evaluations, and other relevant factors, the P&T Committee recommended that beclomethasone dipropionate, budesonide, and triamcinolone acetonide be classified as non-formulary under the UF, and that flunisolide, fluticasone propionate and mometasone furoate be classified as formulary on the UF.

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

D. Implementation Plan*:* The Committee voted to recommend an implementation period of 90 days.

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

VI. Antidepressants (AD1) Drug Class Review

P&T Comments

***A.* Relative Clinical Effectiveness:** The Committee evaluated the relative clinical effectiveness of antidepressant medications. The drug class reviewed includes all U.S marketed antidepressants except monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), which will be reviewed separately. Individual medications are outlined in the table below. Although the receptor-binding characteristics and pharmacological classification of these medications vary, the Committee agreed that there is sufficient overlap in their clinical use to review them as a single class of medications.

The Committee considered information concerning the safety, tolerability, efficacy, and clinical outcome of the AD1s. Like many medications, the AD1s have multiple potential uses in addition to the treatment of depression. The Committee's review focused most heavily on the use of these agents for depression, but also considered the clinical effectiveness of individual agents in the treatment of other psychiatric and non-psychiatric conditions. FDA-approved indications for the AD1s are outlined in the table below. The clinical review included, but was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21.

1) *Safety and Tolerability:* The Committee assessed the comparative safety and tolerability of the AD1s, including common adverse effects, rare but serious adverse effects, potential for drug interactions, safety of use in special populations, the risk of adverse effects when discontinuing use (discontinuation syndrome), and safety/tolerability issues with special formulations of paroxetine, fluoxetine, and bupropion.

   a. Common Adverse Effects

      i. Adverse effect profiles of the AD1s are known to differ. A particular agent made be chosen to either avoid a know side effect or to take advantage of a known side effect clinically (e.g., selecting an antidepressant likely to cause sedation for an elderly patient who is having difficulty sleeping).

      ii. Differences in clinical trials designs, patient populations, and methods of collecting adverse effect information make direct comparison of adverse effects difficult. Head-to-head trials comparing two or more AD1s are typically not powered to find significant differences in discontinuation rates due to adverse effects. Discontinuation rates in clinical trials are typically

lower than in actual practice. In addition, many adverse effects tend to resolve with continued treatment and may or may not affect adherence to therapy or clinical outcomes. There are few long-term, prospective head-to-head trials under "real-world" conditions.

iii. Overall, bupropion, fluoxetine, and paroxetine appear to be most associated with agitation/activation; nefazodone, trazodone, and mirtazapine appear most likely to cause sedation. Anticholinergic effects have been reported with paroxetine and fluvoxamine. Gastrointestinal symptoms (e.g., nausea) are commonly reported with SSRIs, may be more common with venlafaxine, and may be less common with nefazodone, trazodone, bupropion, or mirtazapine. Diarrhea may occur more commonly with sertraline compared to bupropion SR, paroxetine, and mirtazapine.

iv. Sexual dysfunction appears less likely to occur with bupropion, mirtazapine, trazodone, and nefazodone than with the SSRIs or SNRIs. There have been multiple trials supporting a lower risk of sexual dysfunction with bupropion compared to SSRIs.

v. Elevations in blood pressure have been reported with the SNRIs (venlafaxine and duloxetine). This may be more frequent with venlafaxine than with duloxetine, although comparative data is lacking. There have also been reports of increases in blood pressure with bupropion and fluoxetine. Clinically relevant and statistically significant increases in cholesterol have been reported in a small percentage of patients treated with venlafaxine.

vi. Most serotonergic antidepressants are associated with adverse effects when abruptly discontinued. This discontinuation syndrome appears to be related to elimination half-life, with symptoms occurring more frequently with medications with shorter half-lives (Propensity for syndrome among SSRIs)): fluvoxamine > paroxetine > sertraline >escitalopram > citalopram > fluoxetine (half-life 6 days). Venlafaxine, which has a short half-life, may be associated with more discontinuation symptoms than the SSRIs. Comparative information with duloxetine is unavailable, but discontinuation symptoms have been reported. Little information is available concerning discontinuation symptoms with trazodone; there have been only anecdotal reports with nefazodone and mirtazapine. Discontinuation symptoms from abrupt discontinuation of bupropion, which has little effect on the serotonergic system, appear uncommon.

b. Rare but Serious Adverse Effects / Use in Special Populations

i. Abnormal bleeding, movement disorders, and hyponatremia have been rarely reported with SSRIs; there is insufficient data to determine if any one SSRI is associated with higher risk.

ii. The manufacturer of duloxetine issued a "Dear Doctor" letter in Oct 2005 expanding existing recommendations to avoid use of duloxetine in patients with substantial alcohol use to include patients with preexisting liver disease, following reports of hepatic injury in patients receiving duloxetine.

Duloxetine is not recommended in patients with any degree of hepatic insufficiency due to substantially reduced clearance. Duloxetine is contraindicated in patients with uncontrolled narrow-angle glaucoma because it can cause mydriasis, and should be used in caution in patients receiving medications or having medical conditions that slow gastric emptying.

iii. Bupropion is contraindicated in patients with seizure disorder or conditions predisposing to seizure disorder or at increased seizure risk due to abrupt discontinuation of alcohol or sedatives. The risk of seizure in patients without predisposing factors appears low (0.1-0.4% at doses of 300-450 mg/d), but increases sharply at higher doses. Bupropion should be used with caution in hepatic impairment and extreme caution in severe hepatic cirrhosis.

iv. Nefazodone has a black box warning stating that it should not be used in patients with active liver disease or preexisting transaminase elevation.

v. Trazodone should be used with caution in patients with cardiac disease. Priapism has been rarely reported with trazodone.

vi. Agranulocytosis has been rarely reported with mirtazapine.

vii. All AD1s are Pregnancy Category C except bupropion, which is Pregnancy Category B. Non-teratogenic adverse effects (e.g., respiratory distress) have been reported with serotonergic antidepressants when given in the third trimester. A recent epidemiological study cited in new labeling for paroxetine reported a greater than two fold increase in risk for birth defects in the first trimester with paroxetine compared to other SSRIs.

viii. A recent FDA analysis showed a higher risk of suicidal ideation or suicidality during the first few months of treatment with antidepressants in children and adolescents (4% vs. 2% with placebo). The FDA has issued a Public Health Advisory urging particular caution in watching for signs of worsening depression or suicidal thoughts at the beginning of antidepressant therapy or whenever the dose is changed, and this information has been added to antidepressant labeling in general. Despite a number of meta-analyses and observational studies addressing the risk of suicidality with antidepressants, no one antidepressant appears to be consistently associated with a higher risk of suicidality. The FDA continues to analyze data; adult results are expected in 2006.

c. Potential for drug interactions

i. Unlike fluoxetine, paroxetine, and fluvoxamine, which are metabolized by the cytochrome P450 system [fluoxetine and paroxetine inhibit P450 2D6 and fluvoxamine inhibits multiple P450 isoenzymes], sertraline, citalopram, and escitalopram are considered the least likely to result in significant drug interactions.

ii. Of the SNRIs, venlafaxine is primarily eliminated renally and has minimal effect on P450 isoenzymes; clinically meaningful drug interactions appear unlikely. Duloxetine has a moderate inhibitory effect on P450 2D6, is metabolized by 2D6 and 1A2, and may have increased hepatotoxicity in patients with substantial alcohol use. In addition it has a potential interaction with drugs affecting gastric acidity.

iii. Nefazodone, which inhibits 3A4, may interact with multiple medications. Information with trazodone is unclear. Bupropion does not appear to have substantial drug interactions, although it should not be used with drugs that lower the seizure threshold. Mirtazapine appears unlikely to cause substantial drug interactions, since it is metabolized by multiple pathways and does not appear to be a potent inhibitor of 2D6, 1A2, or 3A4.

d. Special Formulations

i. *Paroxetine controlled release* - The controlled release formulation of paroxetine (Paxil CR) is designed to release its contents over 4-5 hours after the medication reaches the small intestine; the intent is to reduce the incidence of nausea and related GI symptoms compared to the immediate release (IR) product. Both products are given once daily.

Based on pooled data from two 12-week double-blind randomized placebo-controlled MDD trials comparing paroxetine CR and IR at similar doses [Golden et al. *J Clin Psychiatry* 2002; 63:577-84], patients receiving paroxetine CR showed significantly lower rates of nausea in the first week compared to paroxetine IR (14% vs. 23%, $p \leq 0.05$). Nausea rates began to decline in both groups starting in week 2, with no significant differences after week 1, and no numerical advantage for the CR formulation after week 3. Discontinuations due to adverse effects occurred in 6% of patients in the placebo group, 10% of patients in the paroxetine CR group ($p=0.14$ vs. placebo), and 16% of patients in the paroxetine IR group ($p=0.0008$ vs. placebo). There was no statistically significant difference between the CR and IR group. Discontinuations due specifically to nausea occurred in 3% of patients in the CR group, 4% in the IR group, and 0.5% in the placebo group.

There are no head-to-head trials comparing paroxetine CR to other SSRIs and thus no direct evidence comparing rates of nausea or discontinuation due to adverse effects.

ii. *Fluoxetine 90-mg delayed release capsules (Prozac Weekly)* - Fluoxetine has a much longer half-life than other SSRIs, a fact that is exploited by the 90-mg weekly formulation. Fluoxetine weekly has an enteric coating that delays the onset of absorption by 1 to 2 hours relative to IR formulations, but does not otherwise extend the release of fluoxetine. It is FDA-approved only for maintenance of response in patients with MDD, not for initial therapy. The advantage of fluoxetine weekly is patient convenience and potentially increased adherence to treatment. This point has not been well

established, although one study reported greater compliance with the once-weekly regimen compared to 20 mg daily during a 3-month continuation phase [Claxton et al. *J Clin Psychiatry* 2000; 61:928-32]. Since compliance during a clinical trial may be very different from compliance in practice, it is unclear whether this represents a real advantage for fluoxetine weekly. It is not clear whether fluoxetine 90 mg weekly is equivalent to fluoxetine 20 mg/d in maintaining response.

iii. *Fluoxetine in special packaging for PMDD (Sarafem)* – Fluoxetine 10 and 20 mg capsules are available in special packaging and with special labeling for the treatment of premenstrual dysphoric disorder (PMDD), under the name of Sarafem. Usual dosing is 20 mg/day; the product does not appear to differ from the other branded fluoxetine product (Prozac), except for differences in the color of the capsules. When Sarafem was first introduced, the manufacturer stated the intent was to allow patients with PMDD to avoid the stigma associated with use of antidepressants.

iv. Bupropion extended release (Wellbutrin XL) – The main advantage offered by the extended release bupropion product (Wellbutrin XL) compared to sustained release bupropion is once-daily vs. twice-daily administration. This is not regarded as an overwhelming advantage for medications in most disease states, although there is some evidence that patients have poorer adherence to twice daily versus once daily regimens and that patients with depression have worse adherence to medication than non-depressed patients. In the case of bupropion sustained release, package labeling advises separating doses by 8 hours. Since patients are usually advised not to take bupropion late in the day due to its activating properties, bupropion sustained release is likely to be dosed in the morning and early afternoon, which may present more logistical problems than typical twice-daily regimens. Bupropion extended release may be taken as a single dose in the morning.

Safety /Tolerability Conclusion: The Committee concluded that adverse effect profiles differ across AD1s, but there is little data to support any substantial difference among AD1s with respect to tolerability. One possible exception is the SNRI venlafaxine, which appears to be associated with more adverse effects than the SSRIs. It is not clear whether duloxetine will prove to be better tolerated than venlafaxine. Bupropion, mirtazapine, nefazodone, and trazodone appear to have a lower risk of sexual dysfunction compared with SSRIs and SNRIs. The Committee agreed that fluvoxamine, fluoxetine, paroxetine and duloxetine have a generally higher potential for drug interactions than citalopram, escitalopram, sertraline, and venlafaxine. Available evidence addressing the likelihood of discontinuation syndrome with SSRIs tends to correlate with a rank-order of risk based on half-life (greatest to least risk): fluvoxamine > paroxetine > sertraline >escitalopram > citalopram > fluoxetine. Venlafaxine has a short half-life and may be associated with more discontinuation symptoms than SSRIs; duloxetine may be similar based on half-life. Discontinuation symptoms appear uncommon with bupropion; data are limited with trazodone, nefazodone, and mirtazapine. Rare but serious adverse

effects appear to be associated with duloxetine (recent case reports of hepatotoxicity), bupropion (seizure), nefazodone (hepatotoxicity), mirtazapine (agranulocytosis), and trazodone (priapism). Drugs with issues of particular concern in specific patient populations include duloxetine (avoid in hepatic insufficiency, substantial alcohol use, liver disease, narrow angle glaucoma), paroxetine (recent epidemiological evidence of increased risk in pregnancy), and bupropion (avoid in patients with increased seizure risk).

2) *Efficacy/Clinical Outcomes*

a. *Major Depressive Disorder (MDD)*

i. *SSRIs vs. SSRIs* - Of 23 head-to-head trials comparing SSRIs to other SSRIs, very few reported any significant differences between SSRIs. These trials were mostly of short duration, with many lasting only 6-8 weeks; they typically assessed changes on the two most commonly used depression scales, the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery Asberg Depression Rating Scale (MADRS). Most of these trials reported response rates (≥ 50% decrease on the HAM-D or MADRS), with a few reporting remission rates (percent of patients achieving a certain HAM-D or MADRS score). A 9-month "real-world" effectiveness trial comparing paroxetine, sertraline, and fluoxetine in primary care patients with depression as determined by the primary care provider [Kroenke et al. *JAMA* 2001; 286:2947-55] found no significant differences in efficacy among these three SSRIs. Two meta-analyses of response rates performed by Oregon reviewers showed no differences between paroxetine and fluoxetine and a very slight and probably clinically insignificant difference (RR 1.10, 95% CI 1.01-1.22) favoring sertraline over fluoxetine. Only two trials reported statistically significant differences in efficacy [Lepola et al. *Int Clin Psychopharmacol* 2003; 18(4):211-7; Moore et al. *Int Clin Psychopharmacol* 2005; 20(3):131-7]. Both of these trials reported greater efficacy with escitalopram compared to citalopram; a third trial comparing citalopram and escitalopram showed no significant differences [Burke et al. *J Clin Psychiatry* 2002; 53:331-6]. Results of an unpublished trial comparing escitalopram to sertraline supplied by the manufacturer of escitalopram showed no significant differences between these two SSRIs. There is no published data supporting greater efficacy for paroxetine CR or fluoxetine weekly, compared to the original formulations or to other SSRIs.

ii. *Venlafaxine vs. SSRIs* - There are a number of head-to-head trials and meta-analyses comparing venlafaxine and various SSRIs, including paroxetine, fluoxetine, sertraline, and escitalopram. Overall, few of these trials reported significant differences between SSRIs and venlafaxine. Two meta-analyses comparing venlafaxine to fluoxetine showed a modest efficacy advantage for venlafaxine [Smith et al. *Br J Psychiatry* 2002; 180:364-404; Oregon reviewers], although venlafaxine was associated with more adverse effects. Two 8-week randomized controlled trials comparing venlafaxine XR to escitalopram showed no differences in efficacy

[Montgomery et al. *Neuropsychobiol* 2004; 50(1):57-64; Bielski et al. *J Clin Psychiatry* 2004; 65(9):1190-6].

iii. *Duloxetine vs. SSRIs* - There are no published head-to-head trials designed to compare duloxetine with other AD1s, although limited comparative data are available from six 8-week duloxetine trials that included active control arms (fluoxetine or paroxetine). However, these trials were not powered to directly compare active treatments; fluoxetine or paroxetine doses were limited to 20 mg/d while duloxetine was dosed from 40 to 120 mg/d. Duloxetine 60 mg/d appeared generally comparable to escitalopram 10 mg/d based on results of an unpublished randomized placebo-controlled trial supplied by the manufacturer of duloxetine.

Based on *in vitro* data, duloxetine appears to bind more equally to serotonin and norepinephrine reuptake transporters than does venlafaxine. This "more balanced" inhibition is theorized to have favorable effects on pain, since inhibitory modulation of pain signals in neural pathways occurs via release of both serotonin and norepinephrine. A complementary argument is that duloxetine may be a better treatment than other antidepressants for depressed patients presenting with "painful symptoms of depression." Support for this argument is limited. Patients with depression commonly present with physical (somatic) symptoms, including pain, which resolve along with mood symptoms following antidepressant treatment. Brannan et al [*J Psychiatric Res* 2005; 39:43-53] reported results of a randomized placebo-controlled trial assessing the effects of duloxetine on pain in depressed patients with painful symptoms at baseline. The mean difference in Brief Pain Index (BPI) average pain scores (0=no pain; 10 = as bad as you can imagine) was consistently a little less than a point lower with duloxetine vs. placebo, starting at week 1. The difference reached statistical significance at weeks 1, 2, and 5, but was not significantly different at endpoint (p=0.066). Whether these results translate into a real advantage for duloxetine compared to other antidepressants in depressed patients presenting with somatic symptoms of pain is unclear.

iv. *Venlafaxine vs. duloxetine* –There are no published head-to-head trials comparing venlafaxine and duloxetine for the treatment of depression. A 2005 meta-analysis [Vis et al. *Ann Pharmacother* 2005; 39:1789-807] comparing placebo-controlled trials with venlafaxine and duloxetine did not show a statistically significant difference between duloxetine and venlafaxine XR, although remission and response rates tended to favor venlafaxine XR. A summary of pooled results of two unpublished double-blind MDD RCTs comparing duloxetine and venlafaxine supplied by the manufacturer of duloxetine showed no significant differences between venlafaxine and duloxetine based on Global Benefit-Risk (GBR) assessment (a statistical method that weighs both efficacy and adverse effects), remission rate, or change from baseline in HAM-D total score.

v. *Bupropion* – Based on six head-to-head trials and one meta-analysis, bupropion appears similar in efficacy to SSRIs (fluoxetine, paroxetine, sertraline). There is no published data supporting greater efficacy for bupropion extended release, compared to the immediate or sustained release formulations of bupropion or to other SSRIs.

vi. *Mirtazapine* – Based on five head-to-head trials, mirtazapine appears similar in efficacy to SSRIs (fluoxetine, paroxetine, sertraline).

vii. *Nefazodone* – Based on three head-to-head trials, nefazodone appeared similar in efficacy to SSRIs (fluoxetine, paroxetine, and sertraline). One of these studies included pooled data from three trials with identical protocols focusing primarily on effects of nefazodone or fluoxetine on sleep quality; nefazodone appeared to significantly improve sleep quality compared to fluoxetine.

viii. *Trazodone* – Based on five 6-week trials, trazodone appeared similar in efficacy to fluoxetine, bupropion, and possibly less efficacious than venlafaxine, although insufficient evidence exists to draw any real conclusion. At present, the major role of trazodone in depressed patients appears to be as an adjunctive medication for the treatment of insomnia.

ix. *Treatment of depression in children and adolescents* – Fluoxetine is the only antidepressant FDA-approved for MDD in children and is used in most pediatric MDD trials. The FDA has concluded that only fluoxetine has been shown to have a favorable risk-benefit profile in pediatric patients, based on the fact that it is the only antidepressant that has demonstrated efficacy in a pediatric population.

b. *Other Psychiatric Conditions*:

i. *Generalized Anxiety Disorder (GAD)*: Venlafaxine, paroxetine, and escitalopram are FDA-approved for treatment of GAD. Sertraline appears to be efficacious for the treatment of GAD based on results of a large published placebo-controlled trial [Allgulander et al. *Am J Psychiatry* 2004; 161:1642-9]. Two head-to-head trials, one comparing paroxetine and sertraline and the other comparing paroxetine and escitalopram, reported no difference between active treatments based on reductions in anxiety (HAM-A) scores [Ball et al. *J Clin Psychiatry* 2005; 66:94-9; Bielski et al. *Ann Clin Psychiatry* 2005; 17:65-9].

ii. *Obsessive Compulsive Disorder (OCD)*: Fluoxetine, fluvoxamine, paroxetine, and sertraline are FDA-approved for the treatment of OCD; fluoxetine, sertraline, and fluvoxamine are approved for use in children and adolescents. At least four separately conducted meta-analyses, one focusing on trials in pediatric patients, showed no significant difference between included SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline). Two head-to-head trials, one comparing sertraline and fluoxetine, and the other comparing paroxetine and venlafaxine XR, showed no difference in efficacy between active treatments [Bergeron et al. *J Clin*

Psychopharmacol 2002; 22(2):148-54; Denys et al. *J Clin Psychopharmacol* 2003; 23(6):568-75]. Citalopram appears to be effective for the treatment of OCD based on results of a long-term (> 6 month) trial [Montgomery et al. *Int Clin Psychopharmacol* 2001; 16:75-86].

iii. *Panic Disorder (PD)*: Fluoxetine, paroxetine, and sertraline are FDA-approved for panic disorder. A head-to-head trial comparing sertraline and paroxetine showed no significant differences in efficacy [Bandelow et al. *J Clin Psychiatry* 2004; 65:405-13]. Fluvoxamine and venlafaxine XR appear efficacious based on short-term placebo-controlled trials. Citalopram appears to be efficacious for panic disorder based on results of a placebo-controlled trial with a 1-year extension [Wade et al. *Br J Psychiatry* 1997; 170:549-53; Lepola et al. *J Clin Psychiatry* 1998; 59:528-34]. A 10-week trial comparing both citalopram and escitalopram to placebo reported significant improvement with both active treatments on many measures, including quality of life, although only escitalopram significantly reduced the frequency of panic attacks compared to placebo [Stahl et al. *J Clin Psychiatry* 2003; 64:1322-7]. This trial was not designed to compare active medications.

iv. *Premenstrual Dysphoric Disorder (PMDD)*: Fluoxetine (as Sarafem), paroxetine, and sertraline are FDA-approved for the treatment of PMDD. Evidence supporting efficacy is also available for citalopram, fluvoxamine, and venlafaxine [Wyatt et al. *Cochrane Database Syst Rev* 2002; 4:CD001396; Freeman et al. *Obstet Gynecol* 2001; 98(5 Pt 1):737-44]. There are no head-to-head trials.

v. *Post-Traumatic Stress Disorder (PTSD)*: Sertraline and paroxetine are FDA-approved for PTSD. Mirtazapine may be efficacious in PTSD based on a 6-week head-to-head open-label trial with sertraline which showed a higher percentage of responders with mirtazapine [Chung et al. *Human Psychopharmacol* 2004; 19:489-94]. Published data supporting efficacy of fluoxetine for PTSD includes two small placebo-controlled trials, one of which showed a significant effect on prevention of relapse over a 6-month period [Connor et al. *Br J Psychiatry* 1999; 175:17-22; Davidson et al. *J Clin Psychopharmacol* 2005; 25:166-9].

vi. *Social Anxiety Disorder (SAD)*: Paroxetine, sertraline and venlafaxine are FDA-approved for the treatment of SAD. Two placebo-controlled trials comparing venlafaxine XR and paroxetine showed no differences in efficacy between active treatments, although venlafaxine XR appeared to be associated with a faster onset of action in one trial [Liebowitz et al. *Arch Gen Psychiatry* 2005; 62:190-8; Allgulander et al. *Human Psychopharmacol* 2004; 19:387-96]. Escitalopram appears efficacious for SAD based on results of a placebo- and paroxetine-controlled trial [Lader et al. *Depress Anxiety* 2004; 19:234-40] and an additional 12-week placebo-controlled trial [Kaspar et al. *Br J Psychiatry* 2005; 186:222-6]. A small trial

with fluvoxamine showed significant improvement in efficacy compared to placebo [Stein et al. *Am J Psychiatry* 1999; 156:756-60].

vii. *Bulimia*: Fluoxetine is the only AD1 that is FDA-approved for treatment of bulimia. The majority of data (and all the larger trials) supporting efficacy of SSRIs for bulimia/binge eating disorder were done with fluoxetine. Although there are small trials with other AD1s, data is insufficient to draw conclusions about the efficacy of other AD1s for bulimia.

c. *Non-psychiatric conditions*

i. Diabetic peripheral neuropathic pain (DPNP)

A recent Cochrane systematic review [Saarto et al, *Cochrane Database System Rev.* 2005; (3):CD005454] addressed the use of antidepressants for the treatment of neuropathic pain in adult patients. The review included 50 trials of 29 antidepressants (total n=2515). The overall conclusion supported efficacy of TCAs for neuropathic pain, with amitriptyline having a number-needed-to-treat (NNT) of 2 (95% CI 1.7-2.5) and a relative risk (RR) of 4.1 (95% CI 2.9-5.9) for obtaining at least moderate relief of pain. Researchers found limited evidence for the efficacy of SSRIs, and insufficient evidence for other antidepressants, including venlafaxine.

In addition to antidepressants, a number of anticonvulsants are used to treat DPNP. After excluding non-diabetic etiologies and stabilizing glycemic control, the American Diabetes Association (ADA) advises starting treatment of DPNP with a TCA, (e.g., amitriptyline 25-150 mg at bedtime), or an anticonvulsant (e.g., gabapentin 1800 mg daily) [Boulton et al. *Diabetes Care* 2005; 28:956].

Duloxetine is FDA-approved for the treatment of diabetic peripheral neuropathic pain (DPNP). Safety and efficacy of duloxetine for the treatment of DPNP were established in two 12-week randomized controlled studies (total n=1074), one of which is published [Goldstein et al. *Pain* 2005; 116(1-2):109-18.]. Based on the published trial, the percent of patients achieving a ≥ 50% reduction in 24h Average Pain Score was 49% for patients receiving duloxetine 60 mg/d and 52% with 120 mg/d, compared to 26% of patients receiving placebo. The 60 mg/d dose of duloxetine was better tolerated.

Venlafaxine also appears to be efficacious and safe in DPNP. Rowbotham et al [*Pain* 2004; 110:697-706] evaluated low dose (75mg) and high dose venlafaxine (150-225 mg) versus placebo in patients with painful diabetic neuropathy. The multicenter, double blind, randomized, placebo-controlled study included 244 adult outpatients with stable type 1 or 2 diabetes. At week 6 the percentage of patients achieving a 50% reduction in Visual Analog Pain Intensity score from baseline was 27% for placebo, 32% for 75mg, and 50% for 150-225mg, $p<0.001$ v. placebo.

Overall, there is insufficient evidence to determine the relative effectiveness of TCAs, SNRIs, or anticonvulsants for the treatment of DPNP or non-

diabetic neuropathic pain. The AD1s and the newly introduced anticonvulsant pregabalin are not yet represented in clinical practice guidelines for DPNP and comparative evidence versus more established therapies is largely unavailable.

ii. Other Non-Psychiatric Conditions

The Committee did not attempt to review all non-psychiatric conditions in which one or more of the AD1s may have a beneficial effect. Some of these apply only to very limited populations (e.g., neurocardiogenic syncope/recurrent idiopathic dizziness), to predictably exploit side effects of the medications (e.g., treatment of premature ejaculation with SSRIs), or to be only an additional option among multiple possible options (e.g., migraine prophylaxis). The Committee noted the following:

- Duloxetine is approved for the treatment of stress urinary incontinence in Europe, under the name of Yentreve. The manufacturer of duloxetine has rescinded their new drug application (NDA) for U.S. approval for stress urinary incontinence. It is unclear whether clinical evidence was felt to be insufficient or whether the FDA is further investigating reports of suicide attempts and suicidal ideation occurring during clinical trials of duloxetine for SUI. The FDA's information sheet on duloxetine currently suggests that physicians consider the data on suicidality before prescribing duloxetine for SUI. Increases in suicidality have not been reported in trials of duloxetine for depression or DPNP.
- There are several clinical trials assessing use of AD1s for the treatment of hot flashes, of particular interest because of the scarcity of effective options for women unwilling or unable to take estrogens. Short-term trials with several AD1s, including venlafaxine, paroxetine, and fluoxetine, have shown efficacy; however, a 9-month placebo-controlled trial with citalopram and fluoxetine failed to show a significant decrease in hot flashes with either medication, compared with placebo. There is insufficient data to support greater efficacy for any one AD1.
- Duloxetine was shown to be efficacious for the treatment of fibromyalgia in female patients with or without MDD in a 10-week randomized, double-blind, placebo-controlled trial [Arnold et al, *Am J Med* 2002; 112:191-7], based on significantly greater improvement with duloxetine on the Fibromyalgia Impact Questionnaire (FIQ) total score (mean difference -5.5 points; score range 0-80, 0 = no impact). Response rates, based on patients achieving a ≥ 50% reduction in FIQ pain score (score range 0-10, 0 = no impact), were 28% for duloxetine vs. 17% for placebo (p=0.06).

Efficacy / Clinical Outcome Conclusion: The Committee concluded that the AD1s offer similar efficacy in treating MDD with the exception of data supporting slightly greater efficacy with venlafaxine compared to the SSRIs and with escitalopram compared to citalopram. Fluoxetine has a unique advantage for the treatment of MDD in children.

The Committee noted that efficacy in other psychiatric conditions (GAD, OCD, PD, PMDD, PTSD, SAD, and bulimia) contributes to the overall usefulness of the AD1s. The Committee agreed that the existence of published clinical evidence supporting efficacy in these disease states should be taken into account in addition to FDA-approved indications. By this measure, paroxetine and sertraline appear to be the most broadly useful SSRIs. Bupropion, mirtazapine, trazodone, and nefazodone are indicated only for MDD. With regard to the SNRIs, venlafaxine has FDA-approved indications for GAD and SAD in addition to MDD.

Duloxetine is the only AD1 with an FDA-approved indication for a non-psychiatric condition, DPNP. It is not clear whether duloxetine offers advantages over other agents used for the treatment of DPNP.

3) *Provider Opinion*

The Committee reviewed results of a survey sent to the Army, Navy, and Air Force specialty consultants and distributed by them to MTF internal medicine, family practice, and psychiatry providers. The survey was also posted on the PEC's webforum, RxNet, to facilitate discussion. Providers were asked to identify clinical situations and differences in safety and tolerability among agents that would lead them to favor one antidepressant over another and which antidepressants they rarely prescribed and could theoretically live without.

Of 42 responses, 21 were from psychiatrists and 21 from general practitioners. Overall, providers agreed that SSRIs as a class were more useful than SNRIs, followed by bupropion, trazodone, and mirtazapine.

Providers found sertraline to be most useful, followed by escitalopram, fluoxetine, citalopram, paroxetine, and fluvoxamine. About half of the responders perceived escitalopram to offer an efficacy or tolerability advantage over citalopram; the other half saw little or no difference. Provider comments indicated definite niches in therapy for sertraline (many indications; lower risk of adverse effects and drug interactions); fluoxetine (can be used in children, activating); venlafaxine (may be more effective than SSRIs but also has more adverse effects); bupropion (low risk of sexual adverse effects, can be used to treat sexual adverse effects from SSRIs; may be useful in smokers and ADHD patients); trazodone (treatment of sleep symptoms); and mirtazapine (sedating; may be useful to stimulate weight gain in elderly or oncology patients or in HIV wasting).

COMMITTEE ACTION: The Committee voted to accept the clinical effectiveness conclusion as stated in VIIa.

B.* Relative Cost Effectiveness*: The P&T Committee evaluated the relative cost-effectiveness of the AD1s in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e) (2).

To determine the relative cost effectiveness of the AD1s, two separate economic analyses were performed, a pharmacoeconomic analysis and budget impact analysis (BIA). From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that AD1s differed in regards to efficacy, safety, and tolerability in the treatment of Major Depressive Disorder (MDD) and other psychiatric illness. To account for the difference in relative clinical effectiveness in this therapeutic class, two cost-effectiveness analyses (CEAs) were performed, a CEA based on the results obtained via a Multi-attribute Utility Theory Analysis (MAUT) and a CEA based on the findings reported in Drug Class Review on Second Generation Antidepressants by the Oregon Health & Science University Drug Effectiveness Review Project (OHSU-DERP). In a CEA, the agents within a therapeutic class are competed on two dimensions, cost and effect (outcomes). In both CEAs, the drug cost used in the analysis was the point of service adjusted total weighted average cost per day of treatment (for all three points of service).

The CEA-MAUT was presented first. For this analysis, the effectiveness measure used for each agent was the composite score derived from the MAUT analysis that ranked the agents based on clinical outcome evidence. The MAUT accounted for the differences in clinical outcome evidence, FDA indication supporting an agent's use for psychiatric and non-psychiatric conditions other than Major Depressive Disorder, such as Generalized Anxiety Disorder, Post Traumatic Stress Disorder, Diabetic Peripheral Neuropathic Pain, etc.; evidence supporting efficacy and safety in the pediatric population; differences in safety (e.g., drug interactions, use in pregnancy, contraindications, potential for cardiovascular adverse events, and potential for rare but serious adverse events); and differences in tolerability (e.g., sexual dysfunction).

Overall, the results of the CEA-MAUT were as follows:

- Trazodone was determined to be the most cost-effective agent
- Fluoxetine and sertraline were determined to be more effective and more costly compared to trazodone
- Other agents were shown to be less effective and more costly, compared to trazodone, fluoxetine, and sertraline

With respect to the SSRIs:

- Fluoxetine was most-effective, followed by citalopram, paroxetine IR, escitalopram, and paroxetine CR, in that order

With respect to the SNRIs:

- Venlafaxine was shown to be more cost-effective compared to duloxetine.

With respect to the other AD1s:

- Trazodone was the most cost effective agent followed by mirtazapine, nefazodone, bupropion SR, and bupropion XL, in that order

- (Note: Although trazodone was determined to be the most cost-effective agent and nefazodone was shown to be more cost-effective compared to bupropion SR and bupropion XL, neither trazodone nor nefazodone was considered a viable first-line monotherapy treatment alternative for MDD).

The second cost-effectiveness analysis (CEA-Response) was based on the OHSU-DERP report for major depressive disorder. This report examined 49 head-to-head randomized controlled clinical trials and one systematic review. The overall conclusion of the report was that "effectiveness and efficacy were similar and the majority of trials did not identify substantial differences among drugs. Studies were often small and relatively underpowered to detect significant differences in efficacy." However, both the OHSU-DERP and PEC clinical review did acknowledge that there was some evidence to suggest that: escitalopram is more effective compared to citalopram; venlafaxine has a modest but statistically significant additional treatment effect compared to fluoxetine; and that escitalopram and venlafaxine are equally effective, however one of two studies reported significantly greater discontinuations due to adverse effects in the venlafaxine group than in the escitalopram group. To account for these potential differences in clinical outcomes, a CEA-Response model was constructed. This model examined the costs and outcomes of treatment for MDD during the acute phase of treatment (8-weeks). In addition to drug costs, other direct medical costs included provider costs and costs associated with the treatment of adverse events. The effectiveness measure was reported response rate at 8-weeks.

Overall, the results from the CEA-Response analysis revealed that:

- Fluoxetine was the most cost-effective agent
- Escitalopram was more effective and more costly
- Venlafaxine was equivalent in effectiveness compared to escitalopram, but was significantly more costly
- Other agents were equivalent in effectiveness compared to fluoxetine but were more costly

A summary analysis was then conducted based on the CEA-MAUT and CEA-Response results. The summary analysis focused on comparisons either between the most cost-effective agent and the more costly agents within a sub-class or between a generic agent and its branded product extension (e.g., paroxetine IR and paroxetine CR). This analysis focused on the:

- SSRIs – fluoxetine in special packaging for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly), sertraline, escitalopram, and paroxetine CR
- SNRIs – venlafaxine versus duloxetine
- Bupropion XL versus Bupropion SR

The results of the summary analysis showed:

For the SSRIs:

- Fluoxetine branded product extensions - Sarafem and Prozac Weekly were > 7-fold more costly and had similar relative clinical effectiveness compared to generic fluoxetine
- Sertraline had equal (CEA-Response) or slightly greater (CEA-MAUT) relative clinical effectiveness but was significantly more costly compared to fluoxetine
    - (note: sertraline is projected to go generic in June 2006)
- Escitalopram was shown to have lower overall relative clinical effectiveness (CEA-MAUT) compared to fluoxetine but potentially greater relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to citalopram, however at a significantly greater cost
- The CEA-MAUT and CEA-Response both showed the paroxetine IR and paroxetine CR had similar relative clinical effectiveness, but paroxetine CR was significantly more costly compared to paroxetine IR.

For the SNRIs:

- Venlafaxine was shown to have greater overall relative clinical effectiveness (CEA-MAUT) and greater relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to duloxetine for a similar cost.
- Bupropion XL was shown to have greater overall relative clinical effectiveness (CEA-MAUT) but similar relative clinical effectiveness in the treatment of MDD (CEA-Response) compared to bupropion SR at a significantly greater cost.

The results of the CEAs were subsequently incorporated into a budget impact analysis (BIA). A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of AD1s best meets the clinical needs of the DoD population at the lowest cost to the MHS. Based on the BIA results and other clinical considerations (e.g., the need to make a broad array of antidepressants available to meet the clinical coverage needs), the Committee agreed that a group of AD1s that included: bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine IR, sertraline, trazodone, and venlafaxine best achieved this goal when compared to other combination groups of AD1s, and thus were determined to be more cost-effective relative to other combination groups.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to recommend that fluoxetine in special packaging

for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly) escitalopram, and paroxetine CR, duloxetine, and bupropion XL be classified as non-formulary under the UF, with bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine remaining on the UF. In addition, the P&T Committee recommended that existing quantity limits for fluoxetine 90-mg delayed release capsules (Prozac Weekly) of 4 capsules per 30 days, 12 capsules per 90 days be continued.

C. **Implementation Plan:** Because a substantial number of patients are currently receiving non-formulary AD1s and the need to carefully assess and monitor patients taking this class of medication, the P&T Committee recommended an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA

COMMITTEE ACTION: The P&T Committee recommended an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

VII. Antidepressants (AD1) Drug Class Review (cont.)

BAP Comments

A. **Relative Clinical Effectiveness:** The Committee concluded that the AD1s offer similar efficacy in treating MDD with the exception of data supporting slightly greater efficacy with venlafaxine compared to the SSRIs and with escitalopram compared to citalopram. Fluoxetine has a unique advantage for the treatment of MDD in children. With respect to other psychiatric conditions, paroxetine and sertraline appear to be the most broadly useful AD1s based on FDA-approved indications and published clinical evidence. Duloxetine is the only AD1 with an FDA-approved indication for a non-psychiatric condition, DPNP; it is not clear whether duloxetine offers advantages over other agents used for the treatment of DPNP.

The Committee concluded that adverse effects differ across AD1s, but there is little data to support any substantial difference among AD1s with respect to tolerability. One possible exception is the SNRI venlafaxine, which appears to be associated with more adverse effects than the SSRIs. It is not clear whether duloxetine will prove to be better tolerated than venlafaxine. The difference in adverse effects between agents may affect the choice of agent in individual patients, creates specific niches in which adverse effects become useful therapeutic effects (e.g., mirtazapine), and increases the number of AD1s necessary to provide adequate clinical coverage.

Bupropion, mirtazapine, nefazodone, and trazodone appear to have a lower risk of sexual dysfunction compared with SSRIs and SNRIs. Fluvoxamine, fluoxetine, paroxetine and duloxetine have a generally higher potential for drug interactions

than citalopram, escitalopram, sertraline, and venlafaxine. The likelihood of discontinuation syndrome with the SSRIs appears to correlate with half-life. Venlafaxine may be associated with more discontinuation symptoms than SSRIs; duloxetine may be similar, although data are lacking. Discontinuation symptoms appear to be rare with bupropion, which has little serotonergic effect.

Rare but serious adverse effects include recent case reports of hepatotoxicity with duloxetine, increased seizure risk with bupropion, hepatotoxicity with nefazodone, agranulocytosis with mirtazapine, and priapism with trazodone. Drugs with issues of particular concern in specific patient populations include duloxetine (avoid in hepatic insufficiency, substantial alcohol use, liver disease, narrow angle glaucoma), paroxetine (recent epidemiological evidence of increased risk in pregnancy), and bupropion (avoid in patients with increased seizure risk). All AD1s are Pregnancy Category C except for bupropion, which is Pregnancy Category B.

B. Relative Cost Effectiveness: The P&T Committee, based upon its collective professional judgment, voted to accept the AD1 cost-analysis presented by the PEC. The P&T Committee concluded that: fluoxetine in special packaging for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly), escitalopram, and paroxetine CR were not cost-effective relative to the other agents within the SSRI sub-class; duloxetine was not cost-effective compared to venlafaxine; bupropion XL was not cost-effective compared to bupropion. Ultimately, the P&T committee did not value escitalopram's potentially greater relative clinical effectiveness in the treatment of MDD (based on clinical trial evidence supporting a clinical efficacy advantage over citalopram) or bupropion XL's greater overall relative clinical effectiveness (based on its once-daily dosing regimen) enough to overcome the agents' significantly higher cost. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the AD1s, and other relevant factors, the P&T Committee recommended that fluoxetine in special packaging for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly) escitalopram, and paroxetine CR, duloxetine, and bupropion XL be classified as non-formulary under the UF and that bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine (HCl and mesylate formulations), sertraline, trazodone, and venlafaxine be classified as formulary on the UF. The P&T Committee recommended that existing quantity limits for fluoxetine 90-mg delayed release capsules (Prozac Weekly) of 4 capsules per 30 days, 12 capsules per 90 days be continued, since there is little new information to support the safety and efficacy of weekly doses exceeding 90 mg.

C. Uniform Formulary Recommendation: The P&T Committee, based upon its collective professional judgment, voted) to recommend that fluoxetine in special packaging for PMDD (Sarafem), fluoxetine weekly (Prozac Weekly) escitalopram, and paroxetine CR, duloxetine, and bupropion XL be classified as non-formulary under the UF, with bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine remaining on the UF. In addition, the P&T Committee recommended that existing

quantity limits for fluoxetine 90-mg delayed release capsules (Prozac Weekly) of 4 capsules per 30 days, 12 capsules per 90 days be continued.

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

D. Implementation Plan: The P&T Committee recommended an effective date no later than the first Wednesday following a 180-day

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

VIII. Oral Ketolide/Marcrolide Drug Class Review

P&T Comments

A. Relative Clinical Effectiveness: The DoD P&T Committee evaluated the relative clinical effectiveness of the macrolides: [azithromycin (Zithromax), azithromycin 2 gram extended release suspension (Zmax), clarithromycin immediate release (IR) (Biaxin and various generics), clarithromycin extended release (ER) (Biaxin XL), all erythromycin salts and esters as well as erythromycin/sulfisoxazole combination suspension (various generics)], and the ketolide, telithromycin (Ketek). Information regarding the safety, effectiveness, and clinical outcomes for the treatment of various infections was considered. The clinical review included, but was not limited to the requirements stated in the UF Rule, 32 CFR 199.21.

1) Spectrum of Activity/Resistance: Increasing use of macrolides has resulted in increased rates of macrolide resistant *S. pneumoniae.* Macrolide resistance to *S. pneumoniae* appears to be a class effect. *In-vitro*, telithromycin remains active against macrolide and penicillin resistant *Streptococcus,* and is the only agent in the class with an FDA indication for multi-drug resistant *S. pneumoniae* (MDRSP). However, telithromycin's ability to overcome MDRSP has not resulted in higher cure rates. Erythromycin is commonly resistant to *H. influenzae*, whereas azithromycin, clarithromycin and telithromycin are active against *H. influenzae*

2) Efficacy

a) Endpoints: Endpoints in the clinical trials included clinical cure rate, bacteriologic eradication, and antibiotic failure rates. Any applicable trials evaluating clinical outcomes, such as mortality, hospital admission rates, or length of hospitalization, were also evaluated.

b) Efficacy for Community Acquired Pneumonia (CAP)

Place in Therapy: The American Thoracic Society (ATS), The Infectious Diseases Society of America (IDSA), and The Canadian Infectious Diseases Society/Canadian Thoracic Society (CIDS/CTS) guidelines do not give a preference for azithromycin or clarithromycin for treating CAP, but state that erythromycin is not preferred due to poor tolerability and limited spectrum of activity. There are no specific recommendations yet for telithromycin, although an update in ATS/IDSA guidelines are expected soon.

Efficacy of Macrolides/Ketolide: The Committee reviewed 17 head-to-head trials comparing one macrolide/telithromycin to another macrolide/telithromycin, or one macrolide/telithromycin versus another antimicrobial agent. Sixteen trials showed similar cure rates and/or bacteriological eradication rates. One poor quality trial comparing azithromycin to clarithromycin found a significant decrease in length of hospitalization and mortality with azithromycin. Another trial examined healthcare utilization from two pooled trials comparing clarithromycin IR to telithromycin. Despite equivalent cure rates in the individual trials, telithromycin was associated with significantly fewer CAP-related hospitalizations than clarithromycin IR in the pooled analysis. The original studies in the pooled analysis were not designed to analyze healthcare utilization; therefore, results were interpreted with caution.

CAP Conclusion: The Committee concluded there was no evidence of a difference in clinical cure rates/bacterial eradication rates between azithromycin, Zmax, clarithromycin IR/ER, erythromycin, and telithromycin when treating CAP. Erythromycin may have limited clinical utility in treating CAP caused by *H. influenzae,* due to its inactivity against the microorganism.

c) Efficacy for Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB):

Place in Therapy: Guidelines from the American College of Physicians (ACP), American Society of Internal Medicine (ASIM), and American College of Chest Physicians (ACCP) do not give specific recommendations for the treatment of ABECB. Other recommendations from noted infectious disease physicians state azithromycin and clarithromycin are recommended in patients with uncomplicated ABECB (< 65 years of age; < 4 exacerbation per year, no co-morbidities, and minimal or no impairment in pulmonary function). Erythromycin was not recommended due to limited activity against *H. influenzae.* No guidelines or recommendations have addressed the use of telithromycin for ABECB.

Efficacy of Macrolides/Ketolide: The Committee reviewed 6 double-blind head-to-head trials comparing one macrolide/telithromycin to another macrolide, or another antimicrobial agent. All 6 trials showed similar cure rates and/or bacteriological eradication rates for the treatment of ABECB. One trial evaluated healthcare utilization and found telithromycin was associated with significantly fewer respiratory-related hospitalizations, all-

cause hospitalizations and emergency room visits than clarithromycin IR, despite similar clinical cure rates. Healthcare utilization was a secondary endpoint to this study and results should be interpreted with caution.

ABECB Conclusions: The Committee concluded there is no evidence of a difference in clinical cure rates/bacterial eradication rates between azithromycin, Zmax, clarithromycin IR/ER, erythromycin, and telithromycin when treating ABECB. Erythromycin may have limited clinical utility in treating ABECB caused by *H. influenzae,* due to its inactivity against the microorganism

d) Efficacy for Acute Bacterial Sinusitis (ABS):

Place in Therapy: Treatment guidelines from the American Academy of Pediatrics (AAP) and the Sinus and Allergy Health Partnership (SAHP) recommend clarithromycin and azithromycin in patients with mild uncomplicated ABS who have a type I hypersensitivity to penicillin. The AAP guidelines no longer recommend erythromycin for ABS due to the increasing resistance. However the SAHP guidelines do not give preference to any macrolide, and include telithromycin in the same treatment category as the other macrolides for ABS.

Efficacy of Macrolides/Ketolides: Six double-blind head-to-head trials comparing a macrolide/telithromycin to another macrolide or another antimicrobial showed similar cure rates and/or bacteriological eradication rates for the treatment of ABS. A retrospective cohort study of 29,102 patients with ABS concluded that newer broad spectrum antibiotics (azithromycin clarithromycin and amoxicillin-clavulanate) were no better than amoxicillin, trimethoprim-sulfamethoxazole, or erythromycin.

Acute Bacterial Sinusitis Conclusions: The Committee agreed that all the macrolides (azithromycin, Zmax, clarithromycin IR/ER, and erythromycin) and telithromycin have shown efficacy for the treatment of ABS, and there is no evidence of a difference in clinical cure rates/bacterial eradication rates between the products when treating ABS.

e) Efficacy for Acute Pharyngitis:

Place in Therapy: The IDSA guidelines and a position paper by the ACP/ASIM for the treatment of group A β-hemolytic streptococcus pharyngitis (GABHS) recommend erythromycin only in patients with a history of a penicillin allergy. Erythromycin is recommended due to its narrow spectrum of activity compared to azithromycin and clarithromycin. Azithromycin, clarithromycin, or telithromycin are recommended in patients who cannot tolerate erythromycin.

Efficacy of Macrolides/Ketolide: Three trials comparing clarithromycin IR to azithromycin or telithromycin, as well as one trial comparing azithromycin to erythromycin showed similar clinical cure rates. Six trials comparing all the products, (except Zmax, which has not been studied) have shown similar cure

rates to penicillin, the gold standard for the initial treatment of acute pharyngitis.

Acute Pharyngitis Conclusions: The Committee agreed that azithromycin, clarithromycin IR/ER, erythromycin, and telithromycin have shown efficacy for the treatment of pharyngitis, and there is no evidence of a difference in clinical cure rates/bacterial eradication rates between the products. Currently there are no published trials evaluating Zmax for the treatment of acute pharyngitis

f) Efficacy for Acute Otitis Media (AOM):

Place in Therapy: The AAP and the American Academy of Family Physicians (AAFP) guidelines recommended macrolides as third-line agents, with use reserved for patients with a history of a type I reaction to penicillins and cephalosporins. The guidelines state that azithromycin, clarithromycin, and erythromycin/sulfisoxazole are all considered preferred macrolides. Erythromycin alone is not recommended due to its lack or activity against *H. influenzae*.

Efficacy of Macrolides: Two head-to-head trials comparing azithromycin to clarithromycin showed similar clinical cure rates. In addition, trials comparing azithromycin, clarithromycin IR, erythromycin-sulfisoxazole and erythromycin to either standard dose amoxicillin or amoxicillin-clavulanate showed similar cure rates. There were no clinical trials found evaluating clarithromycin ER, Zmax and telithromycin for the treatment of AOM, and these agents do not have an FDA indication for the treatment of AOM.

AOM Conclusions: The Committee agreed that azithromycin, clarithromycin IR, erythromycin-sulfisoxazole and erythromycin have shown efficacy against AOM vs. amoxicillin or amoxicillin-clavulanate, and there is no evidence of a difference in clinical cure rates/bacterial eradication rates between the products. Erythromycin alone may not be as effective for AOM compared to the other macrolides due to its inactivity against *H. influenzae*. There were no clinical trials found evaluating clarithromycin ER, Zmax and telithromycin for the treatment of AOM.

g) Efficacy for H. pylori infections and Mycobacterium avium complex(MAC):

Macrolides/ketolides are also used to treat infections cause by mycobacterium avium complex in the immunocompromised population and *H. pylori*-associated peptic ulcer disease. These infections occur with less frequency in DoD than respiratory infections, thus the Committee briefly reviewed the data and concluded the following: For *H. pylori* eradication, clarithromycin-based regimens appear to be superior to azithromycin-based regimens; other macrolide/ketolides have not been adequately evaluated. For the prevention of MAC, either azithromycin or clarithromycin IR are recommended; there is insufficient data from the other macrolides/ketolides to recommend their use. For treatment of MAC, clarithromycin IR may be

superior to azithromycin at clearing MAC from the blood, but trials have shown no mortality difference between the two drugs.

3) Safety and Tolerability:

Rare but Serious Adverse Drug Reactions (ADRs): All the macrolides/ketolides have the propensity, based on case reports and clinical trials, to cause pseudomembranous colitis, hepatotoxicity, and to prolong the QTc interval. Erythromycin and telithromycin may cause exacerbation of myasthenia gravis, and should be used with caution in these patients.

Other ADRs: All the macrolide/ketolide products can cause taste perversion/abnormal taste, dizziness, rash, and headache, and transient hearing loss. Cases of visual disturbances have been reported with telithromycin.

Gastrointestinal (GI) ADRs: Erythromycin has the highest incidence of GI adverse effects (abdominal pain, diarrhea, nausea/vomiting) compared to the other products. Package insert data suggests that Zmax and telithromycin cause more GI related adverse effects than clarithromycin IR/ER or azithromycin.

Special Populations: Pregnancy and Pediatric: Azithromycin and erythromycin are rated pregnancy category B rating whereas clarithromycin and telithromycin are rated pregnancy category C. Azithromycin, clarithromycin IR and erythromycin are the only agents that have been evaluated in pediatric patients.

Drug Interactions: Azithromycin and Zmax are not metabolized via hepatic cytochrome P450 3A4 mechanisms, and are associated with fewer drug interactions than clarithromycin IR/ER, erythromycin, or telithromycin.

Overall Safety and Tolerability Conclusion: The Committee concluded that azithromycin and Zmax have the most favorable safety/tolerability profile, followed by clarithromycin and telithromycin, with erythromycin having the least favorable safety/tolerability profile.

4) Other Factors:

Pharmacokinetics: Erythromycin stearate and base need to be given on an empty stomach, whereas erythromycin ethylsuccinate and estolate can be given without regards to meals. Zmax bioavailability increases greater than two fold when administered with food, but should be given on an empty stomach due the possibility of increasing the risk of adverse effects. Azithromycin, clarithromycin and telithromycin can be given without regard to meals. Azithromycin and Zmax are not interchangeable, due to differences in absorption and the time to reach peak serum concentration. Both clarithromycin and telithromycin require dosage adjustment for renal dysfunction; telithromycin requires dosage adjustment for liver dysfunction with concomitant renal dysfunction.

Dosing: The following agents can be given daily: azithromycin, clarithromycin ER, and telithromycin. Clarithromycin IR is dosed twice daily, whereas erythromycin can be dosed between two to four times daily. Zmax is the only agent that is administered as a one time dose.

Palatability of Oral Suspensions: Clinical studies evaluating taste preferences of antibiotic suspensions showed that pediatric patients preferred the taste of azithromycin over clarithromycin or erythromycin/sulfisoxazole.

Provider Opinion: A survey of DoD providers revealed that MDRSP was not considered a problem when treating CAP in the outpatient setting; there was not an advantage of Zmax's one time dosing vs other azithromycin products; azithromycin was preferred over the other agents in the class; and telithromycin and Zmax were thought to confer no additional benefit over the other members in the drug class.

Conclusions for Other Factors: There are minor differences in the pharmacokinetic profiles, dosing frequency, and palatability of the macrolides/ketolides that can affect individual patient preferences. Provider opinion favored azithromycin.

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

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

The macrolide cost-effectiveness review was conducted as two discreet analyses: The first analysis considered only the erythromycin salts and base, while the second analysis compared the newer macrolides [azithromycin, Zmax (brand), clarithromycin and telithromycin]. The first step for each evaluation utilized a cost-analysis to calculate the total weighted average cost per course of therapy for each agent. The second step was to conduct the appropriate pharmacoeconomic analysis taking into account the conclusions of the clinical review. Because the clinical review suggested minimal differences in clinical effectiveness (efficacy, safety and tolerability) between the erythromycin salts and base, the appropriate pharmacoeconomic analysis for these agents was determined to be cost-minimization. However, a cost-effectiveness analysis (CEA) was used to evaluate Zmax, azithromycin, clarithromycin and telithromycin because the clinical review suggested differences in clinical effectiveness (efficacy, safety and tolerability) between these agents. Effectiveness differences between the agents were quantified through the use of a Multi-Attribute Utility Table (MAUT).

Although the results of the erythromycin cost analysis (salts and base) determined erythromycin base to have the lowest total weighted average cost per course of

therapy across all points of service (MTF, Retail, Mail), the cost-effectiveness profiles for all the erythromycin agents were considered favorable.

The cost-analysis evaluation between azithromycin, Zmax, clarithromycin and telithromycin determined azithromycin to have the lowest total weighted average cost per course of therapy across all points of service, followed by Zmax, clarithromycin and telithromycin. The CEA produced results with the same rank order: azithromycin being the most cost-effective followed by Zmax, clarithromycin and telithromycin.

The results of the above analyses were then incorporated into a Budget Impact Analysis (BIA), which accounted for other factors and costs associated with a potential decision regarding formulary status of macrolide antibiotics within the UF. These factors included: market share migration (due to changing provider prescribing practices), cost reduction associated with non-formulary status, and medical necessity processing fees. Switch costs were not included because the macrolides were assumed to be used acutely rather than on a chronic basis. The results of the budget impact analysis confirmed the results of the preliminary analyses. Erythromycin and azithromycin (other than the Z-max formulation) were found to be the most cost-effective macrolide antibiotics overall. A sensitivity analysis conducted around the uncertainty of azithromycin prices due to its generic availability suggested: 1) as the price of generic azithromycin falls, azithromycin becomes even more cost effective compared to other second generation macrolides; and 2) as the price of generic azithromycin falls, scenarios placing the branded Z-max formulation into the non-formulary tier become increasingly more cost beneficial to DoD.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to recommend non-formulary status on the Uniform Formulary for telithromycin and the Zmax formulation of azithromycin, with erythromycin salts and base, all forms of clarithromycin and non-Zmax formulations of azithromycin maintaining formulary status on the Uniform Formulary at the formulary cost share.

B. Uniform Formulary Recommendation. See above COMMITTEE ACTION.

C. Implementation Plan: Because of the low utilization of Zmax and telithromycin at the military treatment facilities (MTFs), and the fact that these agents, for the most part, are not used chronically, the Committee recommended an effective date no later than the first Wednesday following a 60-day implementation

COMMITTEE ACTION: The DoD P&T Committee voted to recommend an implementation period of 60 days

IX. Oral Ketolide/Marcrolide Drug Class Review (cont.)

BAP Comments

A. Relative Clinical Effectiveness: The Committee concluded that (1) telithromycin *in vitro* shows activity against MDRSP, but this has not translated into superior clinical cure/improvement/bacteriological eradication rates in clinical trials; (2) erythromycin may have a limited role in treating many common types of upper and lower respiratory tract infections due to inactivity against *H. influenzae*; (3) clinical cure rates/bacterial eradication rates are similar between the macrolides/ketolides when used for treating CAP, ABECB, ABS, and acute pharyngitis; (4) for AOM, there is no clinical trial experience with clarithromycin ER or Zmax; clinical cure rates are similar with the other products; (5) clarithromycin IR has the best evidence for the treatment of *H. pylori* infections; (6) either azithromycin or clarithromycin can be used for prevention of MAC infection and clarithromycin IR is preferred over azithromycin for the treatment of MAC infections (7) azithromycin is preferred relative to other macrolides and telithromycin in terms of safety and tolerability; (8) there are minor differences amongst the agents in terms of other factors. Overall the Committee concluded that azithromycin has increased overall clinical effectiveness relative to Zmax, clarithromycin IR/ER, erythromycin, and telithromycin.

B. Relative Cost Effectiveness: The P&T Committee agreed with the relative-cost effectiveness analyses presented for the macrolide antibiotics. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the macrolide antibiotics, the P&T Committee recommended that the status of telithromycin and the Zmax formulation of azithromycin be changed from formulary to non-formulary on the Uniform Formulary, with erythromycin (base and salts), clarithromycin immediate and extended release and non-Zmax formulations of azithromycin maintaining formulary status on the Uniform Formulary with the formulary cost share.

C. Uniform Formulary Recommendation: The P&T Committee, based upon its collective professional judgment, voted to recommend non-formulary status on the Uniform Formulary for telithromycin and the Zmax formulation of azithromycin, with erythromycin salts and base, all forms of clarithromycin and non-Zmax formulations of azithromycin maintaining formulary status on the Uniform Formulary at the formulary cost share.

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

D. Implementation Plan: The DoD P&T Committee voted to recommend an implementation period of 60 days

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

X. Prior Authorization Requirement for Mecasermin (Increlex) Injection

Mecasermin, used for the long-term treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion that have developed neutralizing antibodies to GH. Severe Primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment. Mecasermin presents some unique concerns regarding appropriate patient selection, dosing, administration, potential for misuse, and monitoring for possible low blood glucose levels (hypoglycemia) because it has insulin-like hypoglycemic effects. Labeling for mecasermin includes specific recommendations for patient selection. Mecasermin should only be used by patients who have the clinical diagnosis of severe Primary IGFD and following up with their providers (e.g. pediatric endocrinologist/nephrologist) on a regular basis. Patients using mecasermin must understand how to adjust mecasermin and be able to recognize hypoglycemia. Mecasermin is not indicated for use in patients with closed epiphyses (bone growth plates).

Mecasermin, used for the long-term treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion that have developed neutralizing antibodies to GH. Severe Primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment. Mecasermin presents some unique concerns regarding appropriate patient selection, dosing, administration, potential for misuse, and monitoring for possible low blood glucose levels (hypoglycemia) because it has insulin-like hypoglycemic effects. Labeling for mecasermin includes specific recommendations for patient selection. Mecasermin should only be used by patients who have the clinical diagnosis of severe Primary IGFD and following up with their providers (e.g. pediatric endocrinologist/nephrologist) on a regular basis. Patients using mecasermin must understand how to adjust mecasermin and be able to recognize hypoglycemia. Mecasermin is not indicated for use in patients with closed epiphyses (bone growth plates).

COMMITTEE ACTION: Based on the need for careful patient selection to ensure safety and effectiveness, the P&T Committee recommended that a PA be

required for mecasermin. The Committee recommended that the PA should have an effective date no later than the first Wednesday following a 30-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

XI. Prior Authorization Requirement for Mecasermin (Increlex) Injection (cont.)

BAP Comments

A. PA Criteria

Coverage is provided for the use of mecasermin as treatment in severe Primary IGFD and in patients who meet all of the following criteria:

- Height standard deviation score $\leq$ -3 and
- Basal IGF-1 standard deviation score $\leq$ -3 and
- Normal or elevated growth hormone (GH)
- Are receiving ongoing care under the guidance of a health care provider skilled in the diagnosis and management of patients with growth disorders.
- Thyroid and nutritional deficiencies corrected before initiating mecasermin treatment.
- Have been educated on monitoring and management of hypoglycemia.

Coverage is not provided for patients who:

- Have closed epiphyses (bone growth plates are closed).
- Have active or suspected neoplasia (therapy should be discontinued if evidence of neoplasia develops).
- Have other cases of growth failure (secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids).

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