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. NEWER ANTIHISTAMINES (NAs)

P&T Comments

A. Relative Clinical Effectiveness:

1) *Efficacy*

The relative clinical effectiveness evaluation was based upon an evidence based review of the clinical literature found in PubMed, Cochrane Library, National Guidelines Clearinghouse and reference lists of systematic review articles published through June 07. In particular, this evaluation relied heavily upon the following sources: the Allergic Rhinitis and Its Impact on Asthma (ARIA) 2001 Guidelines and the draft 2007 update; the Agency for Healthcare Research and Quality (AHRQ) 2002 Evidence and Technology Report/WHO: Rhinitis; the European Dermatology Forum (EDF) 2004 Consensus Statement: Urticaria; and the Oregon Drug Effectiveness Review Project (DERP) 2004 and 2006 Drug Class Review.

a) Seasonal Allergic Rhinitis

Adults

The committee concluded that for the treatment of seasonal allergic rhinitis (SAR) in adults that there was insufficient evidence to suggest clinically significant differences in efficacy between fexofenadine (Allegra, generics), loratadine (Claritin, generics) and cetirizine (Zyrtec) or desloratadine (Clarinex) and fexofenadine (Allegra, generics). There is insufficient evidence to compare acrivastine/pseudoephedrine (Semprex-D) to the other agents in the treatment of SAR.

Five head-to-head comparative trials assessed the efficacy of various newer antihistamines in the treatment of SAR in adults. The trials varied in country, season, and baseline characteristics of patients. These trials demonstrated no statistically significant difference between agents in total symptom score

(TSS) change from baseline between cetirizine (Zyrtec) versus loratadine (Claritin, generics), cetirizine (Zyrtec) versus fexofenadine (Allegra, generics), or loratadine (Claritin, generics) versus fexofenadine (Allegra, generics). The trials were too heterogeneous for meta-analysis. A recent head-to-head trial [Berger 2006] compared the efficacy of desloratadine (Clarinex) and fexofenadine (Allegra, generics) to placebo in patients with SAR. Results showed that both agents provided comparable efficacy, and were more effective than placebo. In the trial, subjects were randomized to desloratadine (Clarinex) 5 mg, fexofenadine (Allegra, generics) 180 mg once daily, or placebo. Mean daytime instantaneous TSS was significantly reduced from baseline by 28% with desloratadine (Clarinex), $p = 0.006$ and by 27% with fexofenadine (Allegra, generics), $p = 0.024$ versus placebo. The between agent mean TSS reduction was not statistically different ($p = 0.491$).

Children

There is insufficient evidence to suggest any clinical significant differences in efficacy in the treatment of SAR in children ≤ 12 years. There were no head-to-head comparative trials identified for children with SAR. Placebo and active controlled trials demonstrated that cetirizine (Zyrtec), fexofenadine (Allegra, generics), and loratadine (Claritin, generics) were more effective than placebo.

b) Perennial Allergic Rhinitis

Adults

The committee concluded that for the treatment of perennial allergic rhinitis (PAR) in adults there is insufficient evidence to suggest clinically significant differences between the agents. Desloratadine has shown efficacy in the treatment of PAR in adults in a placebo-controlled trial, while loratadine has shown efficacy compared to placebo in an active-controlled trial that also included the older antihistamine clemastine. There were no head-to-head trials of sufficient quality identified for adults with PAR.

Children

There is insufficient evidence to suggest any clinically significant differences in efficacy in the treatment of PAR in children ≤ 12 years. There was one head-to-head comparative trial for loratadine (Claritin, generics) versus cetirizine (Zyrtec). The parent assessment results of this 4-week trial in 80 children, ages 2 to 6, showed cetirizine (Zyrtec) to be more effective than loratadine ($p < 0.001$) in relieving nasal symptoms associated with PAR. However, the global evaluation score by investigator showed no statistically significant difference. Placebo- and active-controlled trials for cetirizine (Zyrtec) and a placebo-controlled trial for loratadine (Claritin, generics) showed the agents to be more effective than placebo in the treatment of PAR.

c) Chronic Idiopathic Urticaria

Adults

For chronic idiopathic urticaria (CIU), the P&T Committee concluded that limited evidence suggests loratadine (Claritin, generics) may be more effective than cetirizine (Zyrtec) and that cetirizine (Zyrtec) may be more effective than fexofenadine (Allegra, generics) in adults.

Two fair quality head-to-head trials in adults with CIU were identified. One trial reported that loratadine (Claritin, generics) 10 mg qd was more effective ($p<0.01$) in reducing TSS than cetirizine (Zyrtec) 10 mg qd or placebo [loratadine -81%, cetirizine -69%, placebo -55%]. There was no statistically significant difference in response rate between the two active agents [loratadine 63% vs. cetirizine 45%, placebo 13%]. The other comparative trial reported that cetirizine (Zyrtec) 10 mg qd was more effective (p-value not reported) than fexofenadine (Allegra, generics) 180 mg qd in symptom-free patients [cetirizine 51.9% vs. fexofenadine 4.4%].

Children

Only cetirizine (Zyrtec) has evidence of efficacy for the treatment of CIU in children, based on both an active- and placebo-controlled trial.

2) *Safety / Tolerability*

As a class, the newer antihistamines are safe and well tolerated. There are few drug-drug interactions and clinical trial withdrawal rates are low (2 to 3%). The drugs can be used extensively in special populations.

Adverse Effects – While adverse effects with NAs occurred at a rate between 21 to 51% in clinical trials included in the 2006 DERP review, they tended to be minor, similar to placebo, and associated with a low discontinuation rate (2 to 3%). Minor adverse effects included stomach pain, lightheadedness, headache, and nausea.

Sedation – The newer antihistamines generally cause less drowsiness and sedation than older antihistamines. Cetirizine (Zyrtec) has been shown to cause more sedation than fexofenadine (Allegra, generics) and loratadine (Claritin, generics). Loratadine (Claritin, generics) and desloratadine (Clarinex), while causing minimal sedation at recommended dosages, have shown to cause significant sedation at higher doses. Fexofenadine (Allegra, generics) has not shown sedation even in doses as high as 360 mg.

Cardiac arrhythmias – Cardiac toxicity has been a concern with NAs in the past, but does not appear to be a major issue with currently marketed products. Astemizole (Hismanal) and terfenadine (Seldane), two of the first newer antihistamines, were removed from the market because of their potential to cause prolonged QTc and torsade de pointes. However, newer second generation antihistamines have undergone extensive testing regarding their propensity to cause cardiac arrhythmias. Juniper et al (2005) reviewed these studies and concluded that cetirizine (Zyrtec), fexofenadine (Allegra, generics) and loratadine (Claritin, generics) appear to have little potential to cause arrhythmias.

Pseudoephedrine-Containing Products – Combination products with pseudoephedrine can cause CNS stimulation, dizziness, weakness and insomnia. Pseudoephedrine has also been noted to cause palpitations as well as anxiety. Combination products containing pseudoephedrine are contraindicated in patients with narrow angle glaucoma, urinary retention, and with monoamine oxidase inhibitors (MAOIs). They should be used with *caution* in patients with hypertension, diabetes mellitus, ischemic heart disease, increased in ocular pressure, hyperthyroidism, renal impairment, and prostatic hypertrophy, and with *extreme* caution in patients with severe hypertension and/or severe coronary artery disease.

Use in Special Populations

- *Renal Failure* – All the NAs except acrivastine/pseudoephedrine (Semprex-D) have alternative dosing recommendations for patients with moderate to severe renal failure. Acrivastine/pseudoephedrine (Semprex-D) is not recommended in patients with a creatinine clearance less than or equal to 48 mL per minute.
- *Hepatic Failure* – Cetirizine (Zyrtec), desloratadine (Clarinex), and loratadine (Claritin, generics) have alternative dosing recommendations for patients with hepatic failure. Because fexofenadine (Allegra, generics) is metabolized to a very small extent, dosing changes in patients with hepatic failure is not necessary. The manufacturers of acrivastine/pseudoephedrine (Semprex-D) have not made recommendations for alternative dosing of patients with hepatic failure.
- *Geriatrics* – There is insufficient data for manufacturers to make recommendations in populations greater than 70 years of age.
- *Pediatrics* – All the drugs, except acrivastine/pseudoephedrine (Semprex-D) and pseudoephedrine combination products, have indications for pediatric patients. Cetirizine (Zyrtec), fexofenadine (Allegra, generics), and desloratadine (Clarinex) have dosing recommendations for patients down to age 6 months. Loratadine (Claritin, generics) has indications for patients to age 2 years and older.
- *Pregnancy and Lactation* – Acrivastine/pseudoephedrine (Semprex-D), cetirizine (Zyrtec) and loratadine (Claritin, generics) are FDA pregnancy category B. Although evidence from a randomized, controlled trial is not available, a cohort study of Israeli women showed no increase in major abnormalities of children born to women exposed to loratadine (Claritin, generics) (RR 0.77; 95% CI 0.27 to 2.19) when compared to a no treatment control group. Secondary measures, including rate of still births, preterm deliveries and median birth weight, were similar between cohort groups. Desloratadine (Clarinex), fexofenadine (Allegra, generics) and the combination products containing pseudoephedrine are FDA pregnancy category C.

The manufacturer states that loratadine (Claritin, generics) is compatible with breast-feeding. The manufacturers of other agents state that infant risk cannot be ruled out.

Drug Interactions

Drug interactions with ketoconazole and/or erythromycin have been reported with loratadine, desloratadine, and fexofenadine. However, despite the increased blood levels, there were no changes in QT interval, clinical condition, lab tests, or reported adverse events; dosage changes are not considered to be necessary. Antacids appear to reduce the AUC of fexofenadine (Allegra, generics) by ~43%. Acrivastine/pseudoephedrine (Semprex-D) and pseudoephedrine combination products can interact with antihypertensive drugs and reduce their antihypertensive effect. They should not be given within 14 days of a MAOI.

3) *Other Factors*

The NAs do not appear to differ significantly with regard to the availability of additional formulations, with the exception of acrivastine/pseudoephedrine (Semprex-D). All the single agent products have multiple alternate dosage formulations (oral dissolving tablets, rapid dissolving tablets, solutions or suspensions) and combination products containing pseudoephedrine.

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

a) Based on randomized placebo-controlled trials, cetirizine (Zyrtec), desloratadine (Clarinex) and loratadine (Claritin, generics) are more efficacious than placebo for the symptomatic relief of SAR, PAR and CIU. Fexofenadine (Allegra, generics) is more efficacious than placebo for the symptomatic relief of SAR, and CIU. Acrivastine/pseudoephedrine (Semprex-D) is more efficacious than placebo for the symptomatic relief of SAR.

b) Based on six comparative trials in adults with SAR, there is insufficient evidence to suggest that there are clinically significant differences between cetirizine (Zyrtec), fexofenadine (Allegra, generics), and loratadine, or desloratadine (Clarinex) and fexofenadine (Allegra, generics). There is insufficient evidence to compare any of the agents in children less than 12 years old with this condition.

c) For the treatment of PAR in adults, there is insufficient evidence to suggest clinically significant differences between the agents. In children 2 to 6 years old, limited evidence based on one fair – poor quality comparative trial suggests that cetirizine (Zyrtec) may be more efficacious than loratadine (Claritin, generics) with PAR.

d) For the treatment of CIU in adults, limited evidence based on two poor quality comparative trial suggests suggest that loratadine (Claritin, generics) may be more efficacious than cetirizine (Zyrtec) for total symptom score reductions (but not response time), and cetirizine (Zyrtec) may be more efficacious than fexofenadine (Allegra, generics). In children, only cetirizine (Zyrtec) has

evidence of efficacy for the treatment of CIU in children, based on both an active- and placebo-controlled trial.

e) The NAs appear to have similar adverse effect profiles and to result in similar low rates of discontinuation due to adverse events in clinical trials. There do not appear to be any major disadvantages for any one agent with respect to drug-drug interactions.

f) No NA appears preferable in hepatic impaired, renal impaired and pediatric patients. Loratadine (Claritin, generics), cetirizine (Zyrtec) and acrivastine/pseudoephedrine (Semprex-D) are FDA pregnancy category B, while desloratadine (Clarinex), fexofenadine (Allegra, generics) and the combination products containing pseudoephedrine are FDA pregnancy category C.

g) All the parent products have multiple dosage forms and a pseudoephedrine-containing combination product.

h) It is likely that at least one NA is needed for adequate clinical coverage, based on provider responses regarding prescribing practices and likely patient response.

i) Loratadine (Claritin, generics) has been identified as a candidate drug for the DoD OTC Pilot Program.

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

B. NAs – Relative Cost Effectiveness

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the NAs differed in regards to efficacy, safety, tolerability, or clinical outcomes data. As a result, cost minimization analysis (CMAs) were performed to compare the relative cost effectiveness of the single agent NAs and the pseudoephedrine combinations. The CMAs compared the weighted average cost per day of treatment for each drug product across all three points of service.

Results from the NA CMAs showed that desloratadine (Clarinex) and desloratadine/pseudoephedrine (Clarinex D) were not cost effective relative to the other agents in the newer antihistamine class. All other medications in the class were determined to be cost-effective relative to their comparators.

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

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

1) Desloratadine (Clarinex) and desloratadine/pseudoephedrine (Clarinex D) were not cost effective relative to other comparable agents in the newer antihistamine class.

2) The UF scenario that designated desloratadine (Clarinex) and desloratadine/ pseudoephedrine (Clarinex D) as non-formulary under the UF was the most cost effective scenario.

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

C. Uniform Formulary Recommendation

In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the NAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that:

1) Fexofenadine (Allegra, generics), fexofenadine/pseudoephedrine (Allegra D), cetirizine (Zyrtec), cetirizine/pseudoephedrine (Zyrtec D), and acrivastine/pseudoephedrine (Semprex-D) should be maintained as formulary on the UF.

2) Desloratadine (Clarinex) and desloratadine/pseudoephedrine (Clarinex D) should be classified as non-formulary.

3) Loratadine (Claritin, generics) and loratadine/pseudoephedrine (Claritin D) should be added to the UF for purposes of the TRICARE OTC Pilot Program.

4) At such time as cetirizine (Zyrtec) and cetirizine/pseudoephedrine (Zyrtec D) are made available over-the-counter, both products should be maintained on the UF for purposes of the TRICARE OTC Pilot Program.

Desloratadine -/+ pseudoephedrine (Clarinex and Clarinex D) should be reclassified as formulary on the UF when the generic products are available and cost effective relative to similar agents in the newer antihistamine class.

D. Implementation Plan:

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

III. NEWER ANTIHISTAMINES (NAs) (cont.)

BAP Comments

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

1) Fexofenadine (Allegra, generics), fexofenadine/pseudoephedrine (Allegra D), cetirizine (Zyrtec), cetirizine/pseudoephedrine (Zyrtec D), and acrivastine/pseudoephedrine (Semprex-D) should be maintained as formulary on the UF.

2) Desloratadine (Clarinex) and desloratadine/pseudoephedrine (Clarinex D) should be classified as non-formulary.

3) Loratadine (Claritin, generics) and loratadine/pseudoephedrine (Claritin D) should be added to the UF for purposes of the TRICARE OTC Pilot Program.

4) At such time as cetirizine (Zyrtec) and cetirizine/pseudoephedrine (Zyrtec D) are made available over-the-counter, both products should be maintained on the UF for purposes of the TRICARE OTC Pilot Program.

Desloratadine -/+ pseudoephedrine (Clarinex and Clarinex D) should be reclassified as formulary on the UF when the generic products are available and cost effective relative to similar agents in the newer antihistamine class.

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

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

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

IV. Leukotrience Modifiers (LMs)

P&T Comments

A. **Relative Clinical Effectiveness*:***

FDA-approved indications

a) Asthma

Montelukast (Singulair), zafirlukast (Accolate) and zileuton (Zyflo) are all indicated for the treatment of asthma in adults and children. Montelukast is approved in children as young as one year of age, zafirlukast is indicated in children down to age of six years, and zileuton is approved for use in children aged 12 years and older. The LMs are most often used as adjunctive therapy to first-line asthma therapies including inhaled corticosteroids and long-acting beta agonists (LABA).

b) SAR and PAR

Montelukast is the only LM with indications other than asthma; it is FDA-approved for treating allergic rhinitis in adults and children. For SAR, montelukast is approved down to the age of two years, and for PAR down to the age of six months.

c) Exercise-Induced Bronchoconstriction (EIB)

In Apr 07, montelukast received approval for use in exercise-induced bronchoconstriction (EIB) in patients older than 15 years of age.

2) Efficacy

a) Asthma

i) National guidelines – The National Heart, Lung and Blood Institute's (NHLBI) National Asthma Education Prevention Program (NAEPP) guidelines state that LMs are not first-line therapy. For all age groups, inhaled corticosteroids (ICS) are considered first-line. In adolescents older than 12 years and adults, LABAs are preferred over LMs for adjunctive therapy; in this age group zileuton is an alternative, but not preferred therapy due to limited efficacy data and requirements for liver function test (LFT) monitoring. For younger children, LMs are an alternative based on the convenience of delivery device (oral administration vs. nebulizer or oral inhaler) and safety data, rather than efficacy data.

ii) Meta-Analyses and Systematic Reviews – Three meta-analyses evaluated efficacy of the LMs compared with other asthma controller therapies.

- Sin et al (JAMA 2004) found that LMs were less effective than ICS in reducing asthma exacerbations and improving forced expiratory volume in 1 sec (FEV1) (RR 1.72; 95% CI 1.28-2.31).
- ICS were also preferred in a Cochrane review (Ducharme, DiSilva) where patients taking LMs versus those taking inhaled corticosteroids were approximately 60%-70% more likely to have an asthma exacerbation (RR 1.65; 95% CI 1.36-2.0). Other endpoints such as FEV1 improvements, withdrawal rates from therapy due to poor symptom control, and asthma symptoms scores were consistently more favorable with inhaled corticosteroids.
- A second Cochrane review (Ducharme, Kakauma) that compared the combination of LMs to ICS versus ICS alone demonstrated minimal

differences in combination therapy versus monotherapy (e.g., decreased need for albuterol by only one puff per week and no change in steroid dose vs. using the ICS alone). The combination of LABA plus ICS was superior in preventing asthma exacerbations requiring oral steroids than the combination of LM plus ICS.

iii) Clinical Trials – There are no head–to-head clinical trials evaluating the LMs for asthma. Results of placebo controlled trials or trials using ICS as an active comparator show that all three LMs produced statistically significant changes in FEV1, peak expiratory flow, and asthma symptoms score, compared to placebo. Indirect comparisons of placebo-controlled trials with similar study design using montelukast and zafirlukast suggest similar effects on asthma control, based on increases in FEV1 and as-needed beta agonist use. Fewer studies are available with zileuton.

iv) Steroid-Sparing Effects –Whether the LMs allow a reduction in ICS dose is controversial. The product labeling for montelukast states that a lower dose of ICS than previously used was able to control asthma symptoms when the LM was added on to ICS in one study in 226 patients. The Ducharme / Kakauma Cochrane analysis found no effect on steroid dose when a LM was added on to ICS. There is insufficient evidence to determine the steroid sparing effects of zafirlukast and zileuton. NHLBI/NAEPP guidelines caution that the steroid sparing effects of the LMs are inconclusive, and that patients cannot be entirely weaned from the ICS.

b) EIB

i) National Guidelines – NHLBI/NAEPP guidelines for EIB consider albuterol as the drug of choice, as albuterol prevents EIB in more than 80% of patients and is backed by good quality (Level A) evidence. Similar efficacy rates are seen with the LABAs (also considered Level A evidence); however, caution is required as tolerance develops with chronic use. In contrast, montelukast attenuates EIB in 50% of patients and is supported by Level B evidence. The guidelines stress that EIB is frequently a marker of inadequate asthma management, and that prevention and improved asthma control are recommended.

ii) Clinical Trials – Montelukast received FDA approval for EIB in patients older than 15 years in Apr 07 based on a placebo controlled trial showing a statistically significant benefit 2 hours after dosing. Montelukast has an onset of action of 1-2 hours, and a duration of action lasting up to 24 hours. There are no head-to-head trials comparing montelukast with albuterol. Two comparative trials with montelukast and salmeterol (Serevent) showed similar efficacy at preventing EIB within one hour prior to exercise. One study has evaluated efficacy of zileuton for EIB, but it is not approved by the FDA for this use.

c) Allergic Rhinitis (AR)

i) *Efficacy Measures* - Meta-analyses and clinical trials evaluating treatment for allergic rhinitis most frequently used two efficacy measures; variations of the rhinitis symptom score where the severity of nasal symptoms of congestion, itching, rhinorrhea are assessed, and the rhinoconjunctivitis-specific quality of life (RQLQ).

ii) *National Guidelines* – A preview of the updated Allergic Rhinitis in Asthma (ARIA) guidelines from the World Health Organization lists NA or NCS as first-line therapy for mild AR; the combination of a NA and NCS for moderate AR; and the combination of NA and NCS plus a LM for severe AR.

iii) *Meta-Analyses and Systematic Reviews* - Two meta-analyses have evaluated efficacy of the LMs vs. nasal corticosteroids (NCS) and newer antihistamines (NAs) for SAR; one by Wilson et al (2004) and the other by Rodrigo et al (2006).

- *LM vs. placebo* – The Wilson meta-analysis included eight randomized controlled trials (one with zafirlukast; 7 with montelukast; over 3,900 patients) comparing a LM either alone or in combination with NAs or NCS vs. placebo or other treatments. The LMs significantly improved the nasal symptom score 5% more than placebo (95% CI 3-7%). This was of questionable clinical significance, as the authors used a 10% change as designating a minimally important result. There is no one recognized minimally important change in nasal score.

  The four studies where RQLQ was evaluated found that the LM significantly improved RQLQ by 0.3 units compared with placebo (95% CI 0.24 to 0.36). A minimally important change in RQLQ is accepted to be a change of at least 0.57 units.

- *LM vs. NAs* – The treatment efficacy of LMs vs. NAs was compared in both the Wilson (4 RCTs) and Rodrigo (5 RCTs) meta-analyses. The trials included all compared montelukast with loratadine (Claritin, generics). In the Wilson analysis, loratadine improved nasal symptom score 2% more than montelukast, but the results were not statistically significant (95% CI 0% to 4%). Treatment with loratadine significantly improved RQLQ by 0.11 units more than montelukast (95% CI 0.04 to 0.18 units). The Rodrigo meta-analysis found no statistically significant difference between montelukast and loratadine in nasal symptom score or RQLQ; additionally, when individual eye symptoms were scored, there was no significant difference between montelukast and loratadine.

- *LM vs. NCS* – In the Wilson meta-analysis, montelukast was compared with fluticasone (3 RCTs), mometasone (1 RCT), budesonide (1 RCT), and zafirlukast was compared with beclomethasone (1 RCT). NCS improved nasal symptom score 12% more than the LM (95% CI 5% to 18%); RQLQ was not assessed.
- *LM plus NA vs. NCS* – The Rodrigo meta-analysis evaluated the combination of LM with a NA vs. NCS. Overall there were only minimal differences noted, although there was a trend toward superiority of the NCS.

iv) PAR – There are no meta-analyses evaluating LM efficacy for PAR. Montelukast is the only LM approved for PAR, which was supported by one placebo-controlled trial in over 1,900 patients that showed statistically significant improvements in daytime and nighttime symptom scores, RQLQ scores, and provider and patient global assessment.

In the pediatric population, montelukast is approved for use in SAR in children age two years and older, and for PAR in age 6 months and older. However, published clinical trial data is limited in the pediatric population, and is primarily based on safety. In two studies in children with PAR, montelukast was less efficacious than cetirizine (Zyrtec) in most of the endpoints studied.

v) Pediatric Issues

- *FDA Labeling* – Although montelukast is approved for patients as young as 6 months with PAR, and as young as 2 years with SAR, the product labeling states that efficacy data is extrapolated from studies with adolescents older than 15 years with AR.
- *Clinical Trials* – Two small placebo controlled studies evaluated montelukast with cetirizine (Zyrtec) in Taiwanese children ranging in age from 2-6 years and 6-12 years with PAR. Cetirizine (Zyrtec) was statistically significantly superior to montelukast in improving total nasal symptoms and the individual symptom of nasal congestion.
- *National Guidelines* – The ARIA guidelines for children recommend following the same principles as adults. They acknowledge that NCS are the most effective treatment of pediatric AR, but recognize that long-term safety remains controversial for growth suppression and hypothalamic-pituitary axis suppression.
- *Other Treatments* – Other treatments for AR are approved for use in children as young as 6 months [cetirizine (Zyrtec), fexofenadine (Allegra, generics), and desloratadine (Clarinex)], two years [loratadine (Claritin, generics) and mometasone (Nasonex)], and 4 years [fluticasone propionate (Flonase, generics).

d) Off-Label Uses

The Committee reviewed several off-label uses for the LMs; most of these lack sufficient data to prove safe and efficacious use at this time. Treatment of nasal polyps and treatment of reactive airways disease after acute respiratory syncytial virus (RSV) illness in children appear to have sufficient published evidence to prove safe and clinically effective.

3) *Safety and Tolerability*

a) Serious Adverse Effects

i) Churg-Strauss Syndrome – Case reports of montelukast (Singulair) and zafirlukast (Accolate) causing systemic eosinophilic vasculitis in patients with asthma and AR are available. However, it is uncertain whether this is a direct effect of the LM or due to concomitant withdrawal of corticosteroids. There is insufficient evidence to determine whether one LM is more likely than another to cause this syndrome.

ii) Hepatotoxicity

- *Montelukast* – The product labeling states there are rare reports of hepatic injury without increases in LFTs. The incidence of in aspartate aminotransferase (AST) elevations is 1.7% with montelukast vs. 1.2% with placebo.
- *Zafirlukast* – Product labeling describes rare reports of hepatic failure, with resolution of symptoms and LFT elevations upon drug discontinuation; there is no requirement in labeling for LFT monitoring. According to the manufacturer, there have been 8 published cases linking zafirlukast with hepatic failure, two of which required transplant. A Freedom of Information Act (FOIA) request from the FDA revealed 66 cases of hepatitis or liver failure and 23 deaths between 1997 and 2002. These cases were spontaneous reports, and a direct causality with zafirlukast has not been assessed.
- *Zileuton* – Use is contraindicated in patients with active hepatic disease of LFT elevations greater than 3 the upper limit of normal (ULN). In clinical trials of over 5,000 patients, the incidence of AST elevations more than 3 times the ULN was 4.6% with zileuton. LFT monitoring is required at baseline, monthly for the initial three months of treatment, and every 2-3 months thereafter.

b) Minor Adverse Effects – Overall the LMs have a low incidence of minor adverse effects, with headache and GI complaints reported most commonly. Pooled data from the product labeling suggests that there is no relevant difference between the LMs in minor adverse effects.

c) *Drug-Drug Interactions* – Montelukast has not been associated with clinically significant drug interactions. Zafirlukast and zileuton both can increase the prothrombin time when administered with warfarin (Coumadin). Zileuton can decrease theophylline metabolism, leading to increased theophylline concentrations; theophylline dosage reductions of 50% are required with concomitant use.

d) *Special Populations* – Montelukast is rated pregnancy category B, while both zafirlukast and zileuton are rated pregnancy category C. Dosage adjustments in renal impairment are not necessary with the LMs. Zileuton is contraindicated for use in patients with active liver disease.

4) *Other Factors*

Montelukast is available in several dosage formulations (tablets, chewable tablet, and granules), and is dosed once daily. Zafirlukast requires BID dosing, while zileuton requires QID dosing.

5) *Therapeutic Interchangeability*

There is a low degree of therapeutic interchangeability between the three LMs. Montelukast has advantages in terms of multiple indications, multiple formulations, a more favorable safety profile, and FDA-approval in the pediatric population.

6) *Clinical Coverage*

To meet the needs of MHS patients, one LM is required; however, it must have a favorable safety profile. For EIB, availability of montelukast, the only LM approved for this indication, is less urgent, due to efficacy and acceptance of albuterol and LABA.

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

a) For the treatment of asthma, NHLBI/NAEPP guidelines include LMs as alternative, but not preferred therapy. LMs are more effective than placebo in controlling asthma symptoms, but are less effective than ICS, and are less effective when added on to LABA vs. use of a LABA with ICS. Addition of a LM to ICS provides modest benefit over use of the ICS as monotherapy.

b) In placebo controlled trials for asthma, the three LMs montelukast, zafirlukast, and zileuton demonstrate clinical effectiveness in endpoints such as reduction in exacerbations, improvements in FEV1, asthma symptoms scores and short acting beta-agonist use. There is insufficient evidence to determine whether one LM is more efficacious at controlling asthma symptoms than another.

c) Limited evidence suggests that LMs may permit a reduced inhaled steroid dose, or could be used in patients resistant or unable to tolerate inhaled steroids. The extent or clinical significance of this "steroid sparing" effect is uncertain.

d) Montelukast is the only LM that is FDA approved for the treatment of allergic rhinitis, and is specifically approved for both SAR and PAR. There are a few small clinical trials that evaluate zafirlukast in the treatment of allergic rhinitis, but they fail to consistently show efficacy. There is no data to support the use of zileuton in allergic rhinitis.

e) For allergic rhinitis, meta-analyses show that LMs are superior to placebo in clinically relevant allergic rhinitis endpoints such as rhinitis symptoms scores and rhinoconjunctivitis quality of life scores; however, the treatment effect is modest. When compared to antihistamines, the LMs show relatively similar efficacy. Nasal corticosteroids are clinically superior to montelukast in all clinical endpoints studied. Combinations of an LM with an antihistamine is modestly more effective than either agent alone, but not superior to NCS in improving nasal symptoms of AR.

j) In the pediatric population, montelukast is approved for use in SAR in children age two years and older, and for PAR in age 6 months and older. However, published clinical trial data is limited in the pediatric population, and is primarily based on safety. In two studies in children with PAR, montelukast was less efficacious than cetirizine (Zyrtec) in most of the endpoints studied.

k) In regard to safety and tolerability, zileuton has been associated with hepatotoxicity, requires LFT monitoring, and is contraindicated in patients with active liver disease. Zafirlukast has also been associated with hepatotoxicity including liver failure and death; however, this data is from spontaneously reported adverse events reports and must be interpreted cautiously. Zafirlukast and zileuton are associated with more clinically significant drug interactions than montelukast.

l) In regard to other factors, montelukast has the advantage of a greater number of FDA approved indications, pediatric indications, less frequent dosing (once daily versus twice and four-times daily for zafirlukast and zileuton), and availability of alternative dosage formulations.

m) Overall, based on clinical issues alone, montelukast is preferred over zafirlukast, which in turn is preferred over zileuton.

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

B. Relative Cost Effectiveness: The relative clinical effectiveness evaluation determined that there was enough evidence to show that the LM medications differed in regards to efficacy and safety in the treatment of asthma, allergic rhinitis, and exercised induced bronchospasm. Moreover, the clinical review concluded that the LMs have a role in the management of asthma and are gaining acceptance in the treatment of exercised induced bronchospasm. However, the use of LMs in allergic rhinitis remains controversial. As a result, the pharmacoeconomic analysis first compared the LMs in a cost-minimization analysis (CMAs) to gauge the cost effectiveness of the agents within the LM class. Once complete, the analysis then

considered the cost-effectiveness of LMs as compared to newer antihistamines and nasal corticosteroids in the treatment of allergic rhinitis. Each analysis compared the weighted average cost per day of treatment across all three points of service.

Results from the LM CMA showed that zafirlukast (Accolate) was the least costly agent in the class. In comparison, montelukast (Singulair) was more costly per day of treatment but also provided additional indications, a better adverse event profile, multiple dosage forms, and more evidence in pediatrics than the other agents in the class. The least cost-effective product was zileuton (Zyflo).

In the treatment of allergic rhinitis, the cost-effectiveness analysis showed that newer antihistamines and nasal corticosteroids were the most cost effective options for the treatment of allergic rhinitis. The LMs were less effective than the nasal steroids and provided comparable efficacy to the newer antihistamines. However, the LMs were significantly more costly per day of treatment than either the newer antihistamines or the nasal steroids. Hence, pervasive use of LMs as first-line therapy in allergic rhinitis should be discouraged to optimize treatment of allergic rhinitis in the Military Health System.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a budget impact analysis (BIA) of a Uniform Formulary scenario that required prior authorization for use of LMs in allergic rhinitis (with no prior authorization for other indications) was compared to a scenario with no prior authorization required for use of LMs in any indication. The analysis was conducted to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost shares). The goal of the BIA was to estimate the impact of enacting a prior authorization policy for allergic rhinitis in the LM class and to aid the Committee in determining which group of LMs best met the clinical needs of the majority of the DOD population at the lowest expected cost to the MHS.

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

1) Zafirlukast (Accolate) was the least costly agent in the class; montelukast (Singulair) was more costly relative to Zafirlukast (Accolate) but provided additional indications, a better adverse event profile, multiple dosage forms, and more evidence in pediatrics than the other agents in the class; zileuton (Zyflo) was not cost-effective relative to the other products.
2) LMs are not cost-effective in the treatment of allergic rhinitis relative to antihistamines and nasal corticosteroids and should not be considered as first-line therapy in the treatment of allergic rhinitis.
3) The Committee concluded that the Uniform Formulary scenario that placed zafirlukast (Accolate) and montelukast (Singulair) on formulary with a prior authorization required for use in allergic rhinitis was the scenario that resulted in the lowest expected expenditures in the LM class.

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

C. Uniform Formulary Recommendation: In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the LMs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that zafirlukast (Accolate) and montelukast (Singulair) be maintained as formulary on the UF and that zileuton (Zyflo) be classified as non-formulary.

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

V. LMs (cont.)

BAP Comments

A. **Uniform Formulary Recommendation:** In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the LMs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that zafirlukast (Accolate) and montelukast (Singulair) be maintained as formulary on the UF and that zileuton (Zyflo) be classified as non-formulary.

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

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

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

VI. GROWTH STIMULATING AGENTS (GSAs)

A. Relative Clinical Effectiveness:

Table 1: Growth Stimulating Agents Available in the U.S.

Subclass	Generic Name	Brand Name	FDA Indication
Growth Hormone	Somatropin	Genotropin (Pfizer) Genotropin Miniquick	GHD, PWS, TS, SGA
		Humatrope (Eli Lilly)	GHD, TS, ISS, SHOX
		Nutropin (Genentech) Nutropin AQ	GHD, TS, CRI, ISS
		Norditropin (Novo Nordisk) Norditropin Nordiflex	GHD, Noonan's Syndrome
		Omnitrope (Sandoz)	GHD
		Saizen (Serono)	GHD
		Serostim (Serono)	AIDS/HIV wasting
		Tev-Tropin (Teva/Gate)	GHD (pediatric patients only)
		Zorbtive (Serono)	SBS
Insulin-like growth factor (IGF-1)	Mecasermin	Increlex (Tercica)*	IGFD

*A second mecasermin product, mecasermin rinfabate (Iplex; Insmed) has been withdrawn from the market due to patent litigation settlement; the manufacturer continues to develop the product for the treatment of non-growth related conditions.

GHD = Growth Hormone Deficiency; IGF-1 = Insulin-like Growth Factor Deficiency; PWS = Prader-Willi Syndrome; CRI = Chronic Renal Insufficiency; SGA = Small for Gestational Age; ISS = Idiopathic Short Stature; SHOX = Short stature Homeobox gene; SBS = Short Bowel Syndrome; TS = Turner Syndrome

1) Background

a) Growth stimulant agents

i) Products

This class of drugs includes only two molecular entities, somatropin and mecasermin. There are multiple competing somatropin products. The majority of these are indicated for the treatment of growth hormone deficiency (GHD), which is the most common use, although manufacturers are constantly researching additional FDA indications. Mecasermin is an orphan drug approved by the FDA in 2005 to treat severe primary insulin-like growth factor deficiency (IGFD), which affects a very small number of patients (about 6,000 in the United States).

ii) FDA Approval process

At present, the FDA has no mechanism for approving "generic" versions of biologic drugs (large-molecule or complex proteins that are synthetic or recombinant versions of natural biological substances), which are regulated under Section 351 of the Public Health Service Act. The lack of a mechanism for approval of generic biologic products produces a unique situation in this class, with multiple competitive branded products available.

iii) Off-Label Uses

Growth hormone has the potential for substantial off-label use. It has been proposed as an anti-aging medication based on its effect on growth and metabolism. However, a systematic review found little evidence that growth hormone is clinically beneficial in healthy elderly patients and substantial evidence suggesting high adverse event rates. The data did not support improvements in bone mineral density, lipid levels, or fasting glucose and insulin levels.

2) Efficacy

a) Efficacy Measures

The following measures are used as efficacy trial endpoints for both somatropin and mecasermin in growth-related condition:

- *Height expressed in centimeter (cm) or inches (in):* Absolute or change from baseline
- *Standard Deviation Score (SDS):* Actual height minus mean height for age divided by the standard deviation of height for age. The normal population mean is zero; a normal SD score will lie between -2 SD and +2SD.
- *Final height:* Stipulates that the individual has stopped growing based on 1) the growth rate has slowed to less than 1-2 cm/year or 2) epiphyseal closure has occurred as confirmed by radiography
- *Near final height:* Based on height velocity less than a certain value, chronological age greater than 15-17 years, or skeletal age greater than 14-16 years
- *Height velocity:* Growth per period of time
- *Mid-parental height:* For boys, add 2.5 in or 6.5 cm to the mean of the parents' heights. For girls, subtract 2.5 in or 6.5 cm from the mean of the parents' heights. This sex-adjusted mid-parental height represents the statistically most probable adult height for the child, based on parental contribution.
- Predicted Adult Height (assuming no intervention): Predicted based on current height, age, and a set of tables known as the Bayley-Pinneau tables, which use radiographic bone age to determine growth potential.

b) Somatropin Efficacy

i) Introduction

Growth hormone (somatropin) treatment is indicated for treatment of a variety of conditions that largely affect linear growth. FDA indications overlap to some degree (see Table 1). All products except Zorbtive and Serostim are indicated to treat GHD, but only three are indicated for treatment of short stature associated with Turner syndrome, and only one

is indicated for treatment of Prader-Willi syndrome. However, treatment endpoints are similar across all growth-related conditions, and treatment goals are achieved by physiologic replacement or supplementation of growth hormone.

Of prescriptions filled by the Air Force High Dollar Program in July 2007, 62% were for pediatric GHD, another 16% were for adult GHD, 8% were for panhypopituitarism, 6% were for Turner's Syndrome, and the rest were split out across various miscellaneous indications. While these data are limited, usage of the growth hormones products by age across the MHS confirms that the great majority of use is for pediatric indications (usage peaks in the 5-14 year age group), with some use in adults (45 years and older).

ii) Somatropin Clinical Efficacy

All marketed somatropin products contain recombinant human growth hormone that is bioequivalent and equally biopotent, and are therefore unlikely to differ in efficacy for the treatment of growth related disorders. There are no studies that compare two or more somatropin products for any indication.

- *Treatment of Childhood Growth Disorders* – Published evidence supports clinical efficacy of somatropin in achieving growth-related clinical endpoints in these conditions, including growth hormone deficiency, Turner Syndrome, Prader-Willi Syndrome, growth restriction related to chronic kidney disease, and small for gestational age. Clinical endpoints evaluated in published clinical trials comparing growth hormone to untreated controls have included: total gains in height, increases in growth velocity, and final or near final adult height vs. mid-parental height or normal population means.
- *Treatment of Adult GHD* – published evidence supports the clinical efficacy of somatropin treatment in achieving various clinical endpoints, including improvements in body composition (reduction of fat mass, increases in lean body mass); modest reductions in cardiovascular risk factors such as blood pressure, total and LDL cholesterol, and triglycerides; and reduction of C-reactive protein. Modest improvements in bone mineral density (4-10% via DEXA) have also been shown. The data do not support clinically and statistically meaningful improvements in adults without GHD.
- *HIV/AIDS related wasting / cachexia and short bowel syndrome (SBS) in adults* – Growth hormone has been demonstrated to be efficacious in these conditions. The use of somatropin in AIDS wasting results in increased lean body mass and improved muscular strength and endurance, compared to untreated controls. No mortality benefit has been demonstrated. Treatment of SBS with somatropin is based on evidence that somatropin accelerates the process of bowel adaptation.

This process involves morphologic changes of the remaining bowel allowing it to have greater absorption of nutrients and fluids and lessen the need for parenteral nutrition. Data are limited, but suggest that up to four weeks of GH treatment has been beneficial in reducing the need for parenteral nutrition in SBS patients.

- *Noonan Syndrome and SHOX deficiency* – The FDA recently approved somatropin for use in two additional pediatric growth disorders: Noonan Syndrome and SHOX deficiency. Both of these conditions are genetic disorders associated with severely restricted growth. Published clinical trials have demonstrated significant improvements in growth-related endpoints in both conditions, compared to untreated control patients.
- *Idiopathic Short Stature (ISS)* – Idiopathic short stature—or non-growth hormone deficient short stature—refers to individuals who are at least 2.25 standard deviations shorter than the mean height for sex and age (the shortest 1.2% of the population). These individuals have no identified physiologic abnormality affecting growth and appear to be healthy otherwise. Growth velocity and final height gains are modest even with somatropin treatment; individuals usually remain shorter than average regardless of treatment. There are no data showing that the gains in height following growth hormone treatment are associated with improvements in quality of life or psychosocial functioning. Treatment of ISS is not considered medically necessary and is therefore not a covered benefit under TRICARE.

iii) Mecasermin Clinical Efficacy

FDA approval of mecasermin was based on the results of five clinical trials, which are unpublished but summarized in product labeling. These trials enrolled a total of 71 children (mean age 7 years) with symptoms of primary IGFD (slow growth rates, low IGF-1 serum concentrations, and normal growth hormone secretion) and extreme short stature (height almost 7 SD below normal). For years 1 through 6, pooled results showed a significant increase in height velocity in mecasermin-treated patients, compared to baseline. Although statistical interpretation was complicated by the uncontrolled, longitudinal nature of the data and the varying lengths of exposure to mecasermin treatment (range <1 to 11.5 years), children appeared to gain, on average, an additional one inch per year for each year on therapy, compared to pretreatment growth patterns.

Bone age, relative to chronological age, was assessed in 49 subjects, since a disproportional acceleration of bone age (specifically epiphyseal closure) could lessen the eventual height reached even if the drug was otherwise effective at accelerating growth. Radiographically-assessed bone age advanced only marginally above chronologic age (4.9 $\pm$ 3.4 years mean $\pm$ SD change in chronological age vs. a 5.3 + 33.4 years change in bone

age). Subjects felt to be close to adult height all exceeded the mean height of untreated subjects, suggesting a positive net effect.

iv) GSA Efficacy Conclusion

Somatropin appears to be efficacious for the treatment of a number of growth-related disorders, including GHD, Prader Willi syndrome, Turner syndrome, chronic renal insufficiency, children who are small for gestational age, SHOX deficiency, and Noonan's syndrome, as well as non-growth related disorders, including adult GHD, AIDS/HIV wasting, and SBS. There are no studies that compare any somatropin product to another for any given indication. Given that all of the products contain the same concentration (3 IU rhGH/mg) of bioidentical recombinant human growth hormone, they are unlikely to differ in efficacy for the treatment of growth-related or other disorders.

Mecasermin increased height in children with severe IGFD, especially in the first year of administration, but not enough to bring these children close to the normal range. It is unlikely to be as effective as GH treatment for children who can respond to GH.

3) *Safety and Tolerability*

a) Somatropin

Mortality in children with GHD is due almost entirely to other pituitary hormone deficiencies. These children have an increased relative risk of death in adulthood from cardiovascular causes resulting from altered body composition and dyslipidemia. Adverse effects of somatropin appear to be dose-related. Initial somatropin studies used higher doses associated with many adverse effects; lower dosages are currently used.

i) Serious Adverse Effects

- *Pseudotumor cerebri or benign intracranial hypertension* – This is more common in children than adults; the FDA has received at least 23 reports in children, 1 in an adult. In all cases, symptoms of intracranial hypertension (headaches) resolved after discontinuation of GH therapy. Only a few patients experienced recurrent headaches and papilledema upon resuming therapy.
- *Slipped capital femoral epiphysis* – This condition is attributed to GH therapy, but may be linked to the result of diathesis induced by GHD and intensified by rapid growth. Children on GH therapy complaining of hip or knee pain should be carefully examined for slipped capital femoral epiphysis.
- *Patients with acute catabolism* – Use of somatropin products is contraindicated in this patient population, including preoperative and post-operative patients, critically ill patients, and burn patients. In a phase III prospective, randomized, placebo-controlled trial in Europe conducted in critically ill patients in an intensive-care unit facility,

patients were given 5.3 mg or 8 mg per day (weight-dependant) of GH therapy for 21 days. A significantly higher mortality (41.7% vs. 18.2%) was seen in the GH-treated group compared to placebo.

- *Retinopathy* is a rare complication of GH treatment. Three case reports (1 adult; 2 children) reported development of retinopathy following GH treatment, although one trial involving 85 children showed no retinopathy after 6.4 ± 2.9 years. A baseline funduscopic evaluation is recommended before starting GH treatment.
- *Malignancies* – Concern has surfaced about the association of GH treatment with tumor recurrence or development of malignancies. This has not been reported in adult GHD patients. An increase in leukemia was reported in Japanese pediatric GHD patients, although this was not confirmed by subsequent studies. Studies in the United States did not confirm an increase in frequency and have shown some differences in incidence related to other risk factors, for example, patients who previously received radiation therapy. This question remains unanswered.

ii) More Common Adverse Effects reported with somatropin include injection site *reactions*, hypothyroidism, transient gynecomastia, headaches, agitation, fatigue, seizures, and nausea/vomiting. Fluid retention and edema of the extremities, as well as arthralgia, myalgia, carpal tunnel syndrome, and blood pressure increases, are reported primarily in adults. GH may also be associated with insulin resistance and glucose intolerance. Some adverse effects appear to be dose-related.

Reported rates of adverse effects do vary from product to product, although this is potentially due to a number of factors, including differences in dosing regimens for specific indications, patient populations studied, or methods of collecting adverse effects. All products contain the same molecular entity (somatropin).

- *Fluid retention, edema, arthralgia, myalgia, and carpal tunnel syndrome* – Adult starting doses for GH were initially higher than those currently recommended. These higher doses were associated with fluid retention in conjunction with edema of the extremities, resulting in arthralgias, myalgias, and carpal tunnel syndrome. These adverse effects are more frequent in adults but do occur occasionally in GH-treated pediatric patients. In a study of 115 adult patients with GHD given GH therapy for 6 months, 37.4% developed edema, 19.1% developed arthralgia, 15.7% myalgia, 7.8% paresthesias, and 1.7% carpal tunnel syndrome. Most adverse effects occurred at the beginning of treatment and resolved within 1 to 2 months with continued treatment. Fluid retention can also cause increases in blood pressure.

- *Effects on blood glucose* – High doses of GH have been associated with hypoglycemia followed by hyperglycemia, since GH induces transient resistance to the actions of insulin. In patients with limited insulin reserve, glucose intolerance may result. Insulin resistance and type 2 diabetes were reported in a few patients in early large clinical trials. A placebo-controlled GH trial reported that a higher number of patients receiving GH had worsening glucose tolerance compared to those receiving placebo, with impaired glucose tolerance seen in 13% and diabetes in 4% of GH patients.

iii) Contraindications – Somatropin is contraindicated in patients with active neoplasms or intracranial lesions and treatment should be stopped if evidence of tumor growth develops. Treatment should not be initiated in patients with proliferative or preproliferative diabetic retinopathy; Prader Willi Syndrome patients who are severely obese or have severe respiratory impairment; acute critically ill patients; and patients with growth-related disorders whose epiphyses have closed. Somatropin products containing the preservative benzyl alcohol are not suitable for use in newborns.

iv) Drug-Drug Interactions – Limited published data suggest that somatropin treatment increases cytochrome P450 (CYP450) mediated antipyrine clearance in man. Somatropin may therefore alter the clearance of compounds known to be metabolized by CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, or cyclosporine). Careful monitoring is *advisable* when somatropin is administered in combination with other drugs known to be metabolized by CYP450 liver enzymes. Formal drug interaction studies have not been conducted.

v) Tolerability – There is insufficient evidence to conclude that any one somatropin product is more tolerable or leads to better compliance than any other somatropin product. Any such differences are likely to be based on factors such as formulation / preservative differences and packaging.

vi) Other Considerations – Since marketed somatropin products appear to be similar in efficacy and safety, the primary differences between products is based on educational materials; drug formulations / preservatives; delivery devices (pen or vial/syringe); and storage requirements (refrigeration vs. room temperature). Table 2 outlines differences between somatropin products with regard to many of these issues.

Table 2: Somatropin Products – Other Consideration

Drugs	Preservative-free	Delivery Device			Storage		1-800 number
		Vial	Pen Device	Dose calculation to use pen	Ready to use	Room Temperature Storage	
Genotropin	yes		yes	Not required	Miniquick syringe only (single-dose)	Before initial use: Miniquick syringe	yes
Humatrope		yes	yes	Not required			yes
Norditropin			yes	Not required	yes	After initial use: (21 days for Nordiflex 5 & 10 mg pens)	yes
Nutropin & Nutropin AQ		yes	yes	Required	yes		yes
Omnitrope	yes	yes		-			yes
Saizen		yes	yes, pen & needle-free pen	Required		Before initial use	yes
Serostim	yes	yes	yes, needle-free pen	Required		Before initial use	yes
Tev-Tropin		yes	*	-			yes
Zorbtive		yes		-			yes

*Approval of pen device anticipated

- *Educational material* – All manufacturers provide some type of educational material for their products, ranging from a hotline number for information and assistance to the patient or caregiver (provided by all manufacturers) to complete packages including a hotline number, website, nurse educator for initial instruction, and a safety registry website for physicians. The literature assessing the value of these educational programs is sparse. In MTFs, certain components of the educational programs are handled by MTF staff and manufacturer offerings such as nurse educators may be of little additional value.
- *Formulations* – The primary reason for the selection of preservatives is to prevent leaching of the drug into its glass or plastic container. The availability of a preservative-free product may be an advantage, although the need for such a product for use in infants should be rare. In addition, ready-to-use formulations that do not require reconstitution may increase accuracy of dosing.
- *Delivery Devices* – Availability of a product in a pen device allows for accuracy in dosing and may enhance compliance. Pens are available for these product lines: Genotropin, Humatrope, Norditropin, and Nutropin. Providers in general reported that patients prefer pens to vials; indeed, 67% of MHS utilization from Jun 06 to Jul 07 was for pens, followed by vials (26%) and disposable syringes (7%).

  Some pen devices conceal the needle from view, an advantage in children who fear needles. The Serono products, Saizen and Serostim, are the only products with a needle-free pen device. An additional consideration is the requirement for dose calculations on the part of the caregiver/patient; some pens require users to convert the milligram

dose prescribed to the units dosed on the pen. Products requiring conversions are the Nutropin product line, Saizen, and Serostim.

- *Drug Wastage* – Packaging for the two somatropin products that lack a GHD indication (Serostim and Zorbtive) is designed for dosage regimens used in AIDS/HIV wasting and SBS, not for use in GHD. Drug wastage would be inevitable if these products were used for GHD. In addition, educational materials available for these products do not address GHD.

b) Mecasermin

i. Serious Adverse Effects

- *Hypoglycemia* – Mecasermin can cause hypoglycemia due to its insulin-like effects. Hypoglycemia was reported in 30 of 71 patients in clinical trials (42%) at least once during their course of therapy. Most cases of hypoglycemia were mild or moderate in severity. Five patients had severe hypoglycemia that required assistance and treatment on one or more occasion, while four experienced hypoglycemic seizures/loss of consciousness on one or more occasion. Of the 30 patients reporting hypoglycemia, 14 (47%) had a history of hypoglycemia before treatment. The incidence of hypoglycemia was highest in the first month of therapy, and episodes were more frequent in younger children. Symptomatic hypoglycemia was usually avoided when a meal or snack was consumed either shortly (i.e., 20 minutes) before or after the administration of mecasermin.
- *Lymphoid tissue hypertrophy* – Hypertrophy of lymphoid tissues (e.g. tonsillar) can result in snoring, sleep apnea, and chronic middle-ear effusions. Tonsillar hypertrophy was noted in 11 (15%) subjects in the first 1 to 2 years of therapy with lesser tonsillar growth in succeeding years. Tonsillectomy or tonsillectomy/adenoidectomy was performed in 7 subjects; 3 of these had obstructive sleep apnea, which resolved after the surgery in all three cases.
- *Intracranial hypertension* – Intercranial hypertension with papilledema, visual changes, headache, nausea and/or vomiting have been reported with mecasermin (as with therapeutic GH administration). Intracranial hypertension occurred in three subjects, and in two subjects, resolved without interruption of mecasermin treatment. Mecasermin therapy was discontinued in the third subject and resumed later at a lower dose without recurrence.
- *Scoliosis* due to slipped capital femoral epiphysis can occur with rapid growth.

ii. Common Adverse Effects reported in the pooled mecasermin trials were hypoglycemia (42% of patients), lipohypertrophy, and tonsillar hypertrophy (15%). Other adverse effects occurring in at least 5% of patients include bruising, otitis media, headache, dizziness, convulsions,

vomiting, hypoacusis, fluid in the middle ear, ear pain, abnormal tympanometry, arthralgia, pain in extremity, and thymus hypertrophy. Adverse effects were generally mild to moderate and no patients withdrew from the pooled trials as a result.

Also reported during clinical trials were: mild elevations in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) not leading to treatment discontinuation; increases in cholesterol and triglycerides to above the upper limit of normal; increases in renal and/or splenic length reaching or surpassing the 95th percentile in some patients but not associated with impairments in renal function (as defined by serum creatinine and calculated creatinine clearance); echocardiographic evidence of cardiomegaly/valvulopathy without associated clinical symptoms ; and development of anti-IGF-1 antibodies with no apparent clinical consequence (e.g., allergic reactions or attenuation of growth).

iii. *Contraindications* – Mecasermin is contraindicated in patients whose epiphyses are already closed and those with active or suspected neoplasia. Mecasermin (Increlex) is not suitable for use in neonates due to its benzyl alcohol preservative.

iv. *Monitoring* – Preprandial glucose monitoring should be considered at treatment initiation, until a well tolerated dose is established, or if frequent or severe symptoms of hypoglycemia occur. Funduscopic exams are recommended at the start of therapy and periodically thereafter. Patients should also be monitored for *t*hickening of soft tissues of the face and symptoms suggesting the occurrence of scoliosis due to a *s*lipped capital femoral epiphysis.

v. *Special Populations* – Safety and effectiveness has not been established in children less than 2 years of age or in adults.

c) Safety/Tolerability Conclusion

i) Growth Hormone (Somatropin)

Serious adverse events of GH include benign intracranial hypertension, slipped capital femoral epiphyses, and retinopathy. Whether or not GH treatment has tumorigenic effects remains debatable, due to possible associations with underlying disease states. The most common adverse events are edema, arthralgias, injections site reactions, diabetogenic effects, and hypothyroidism. Consistent lab monitoring is necessary to decrease the potential for adverse effects from possible excessive dosing or exacerbation of other disease states; required monitoring does not differ among marketed products. GH is not recommended in critically ill patients.

Although all products contain the same molecular entity, reported rates of adverse events vary from product to product, possibly due to different dosing schemes for specific indications or differences between study

populations. There is limited evidence concerning differences between products attributable to excipients. Preservatives are primarily used as a way to prevent the drug leaching into the plastic or glass container. Products containing the preservative benzyl alcohol are not suitable for use in newborns; preservative-free products are available.

Since marketed somatropin products appear to be similar in efficacy and safety, the primary differences between products is based on educational materials; drug formulations / preservatives; delivery devices (pen or vial/syringe); and storage requirements (refrigeration vs. room temperature).

The biggest difference is in available delivery devices (e.g., a pen device, vial/syringe, needle-less system). A pen device is advantageous for ease of use and may increase accuracy in dosing. A pen device that does not require the caregiver or patient to convert from milligrams to "units" or "clicks" is more convenient and less likely to cause errors than one that requires conversion. Only one manufacturer, Serono, offers a needle-free device (for Saizen and Serostim).

Most of the products require refrigeration before and after initial use; products with room temperature storage may be advantageous in terms of limiting waste of the product and facilitating use while traveling. All products have a hotline number for patients and caregivers; other materials vary.

ii) Mecasermin

Mecasermin can cause disruptions in blood glucose and may require blood glucose monitoring. Lymphoid tissue hypertrophy, intracranial hypertension: and scoliosis due to slipped capital femoral epiphysis related to rapid growth can also occur.

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

a) Somatropin products appear to be safe and efficacious for the treatment of various growth-related conditions and for a few specialized non-growth related conditions.

b) There are no studies comparing any somatropin product to another for any given indication. Given that all of the products contain the same concentration (3 IU rhGH/mg) of bioidentical recombinant human growth hormone, they are unlikely to differ in efficacy for the treatment of growth-related or other disorders.

c) There are potential differences between somatropin products with respect to delivery devices, formulations, and stability/storage requirements. Differences that may favor particular products include availability of a pen device (preferably along with a vial/syringe product); the ability to use the pen device without having to do dose conversions, and the ability to store products at room temperature before or after initial use.

d) Mecasermin is safe and efficacious for severe IGF-1 deficiency, a much rarer condition than GHD. It is the only product available for the treatment of this condition.

e) Based on clinical issues alone, there are no compelling reasons to classify any of the GSA agents as non-formulary.

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

B. GSAs – Relative Cost Effectiveness

The GSAs are divided into the IGF-1 and somatropin subclasses. The sole IGF-1 agent is mecasermin (Increlex). It is indicated for the treatment of IGF-1 deficiency and therefore occupies a unique place in therapy within the GSAs. Among the somatropin products, two (Serostim and Zorbtive) are primarily used in disorders most commonly seen in adult patients (HIV wasting and short bowel syndrome). These two somatropin products are therefore available in dosage forms/concentrations that would make delivery of a pediatric dose difficult. For these reasons, Increlex, Serostim, and Zorbtive were excluded from the CMA and BIA. However, they were compared to the other GSAs on a cost per milligram basis.

The relative clinical effectiveness evaluation concluded that there was insufficient evidence to suggest that the remaining somatropin products within the GSA class differed in regards to efficacy, safety, tolerability, or clinical outcomes data in the treatment of growth hormone deficiency (GHD). As a result, cost minimization analysis (CMA) was performed to compare the relative cost effectiveness of these somatropin products.

Results from the somatropin CMA revealed: 1) Tev-Tropin was the most cost-effective somatropin product. However, Tev-Tropin does not offer some of the features (pen dosage forms, storage at room temperature, and ease of use) that some of the more costly products offer; 2) two product lines, Norditropin and Nutropin, are the most cost effective agents that offer physician- and patient-preferred features.

The budget impact analysis (BIA) evaluated the potential impact of various scenarios with one or more somatropin products designated as formulary on the UF. The BIA included a single agent in front of a step-edit (automated prior authorization) as well as two or more (up to all) somatropin products on the UF.

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

1) Mecasermin (Increlex) and the two somatropin products (Zorbtive and Serostim) have a specific niche in therapy and offer sufficient value on a cost/mg basis relative to the other agents within the therapeutic class.
2) Tev-Tropin was the most cost-effective somatropin agent based on cost-minimization analysis. However, the product offers fewer features than most other growth stimulating agent product lines.
3) Two somatropin product lines, Norditropin and Nutropin, offered more features (pen dosage forms, storage at room temperature, and ease of use) at a middle range of cost.
4) The BIA results showed that the most cost-effective formulary strategy for the somatropin products was the combination of the Tev-tropin and the Norditropin and Nutropin product lines.

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

C. Uniform Formulary Recommendation:

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the GSA agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that Tev-tropin, Nutropin, Nutropin AQ, Norditropin, Nortropin Nordiflex, Serostim, Zorbtive, and Increlex be maintained as formulary on the UF and that the Genotropin, Humatrope, Saizen and Omnitrope brands of somatropin be classified as non-formulary.

GSAs – PA Criteria

Currently, prior authorization criteria apply to both growth hormone (somatropin products) and mecasermin (Increlex). The P&T Committee voted that the following PA criteria should apply to growth hormone and mecasermin (Increlex). Changes from previous growth hormone (somatropin) criteria are the addition of Noonan's syndrome and SHOX deficiency as covered uses; no changes were recommended to mecasermin criteria.

1) *Growth Hormone (Somatropin)* – Coverage would be approved for the treatment of any of the following:
    a) Growth hormone deficiency in children and adults as a result of pituitary disease, hypothalamic disease, surgery or radiation therapy
    b) Chronic renal insufficiency before renal transplantation with associated short stature
    c) Other known renal indications: autorecessive polycystic kidney disease, cystinosis and hypophosphatemic rickets in the pediatric population
    d) Short stature in patients with Turner Syndrome or Prader-Willi syndrome

e) Infants born small for gestational age that have not reached age appropriate height by 24 months of age

f) Human immunodeficiency virus-associated wasting in adults

g) Noonan's syndrome

h) SHOX deficiency

2. *Mecasermin (Increlex)* – Coverage would be approved for the treatment of:

a) Patients with severe primary insulin-like growth factor (IGF)-1 deficiency (IGFD) defined by the following:

i. Height standard deviation score ≤ -3

ii. Basal IGF-1 standard deviation score ≤ -3

iii. Normal or elevated growth hormone levels

OR

b) Patients with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone

In addition, patients must meet the following criteria:

- Are receiving ongoing care under the guidance of a health care provider skilled in the diagnosis and management of patients with growth disorders (e.g., pediatric endocrinologist)
- Thyroid and nutritional deficiencies have been corrected before initiating mecasermin treatment
- Have been educated on monitoring and management of hypoglycemia

Coverage is NOT provided for:

- Patients with closed epiphyses (bone growth plates)
- Patients with active or suspected neoplasia (therapy should be discontinued if evidence of neoplasia develops)
- Patients with other causes of growth failure (secondary forms of IGF-1 deficiency, such as growth hormone deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroid

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

D. Implementation Period

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

VII. GSAs (cont.)

BAP Comments

A. **Uniform Formulary Recommendation:** The P&T Committee, based upon its collective professional judgment, voted to recommend that Tev-tropin, Nutropin, Nutropin AQ, Norditropin, Nortropin Nordiflex, Serostim, Zorbtive, and Increlex be maintained as formulary on the UF and that the Genotropin, Humatrope, Saizen and Omnitrope brands of somatropin be classified as non-formulary. Currently, prior authorization criteria apply to both growth hormone (somatropin products) and mecasermin (Increlex). The P&T Committee voted that the following PA criteria should apply to growth hormone and mecasermin (Increlex). Changes from previous growth hormone (somatropin) criteria are the addition of Noonan's syndrome and SHOX deficiency as covered uses; no changes were recommended to mecasermin criteria.

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

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

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

VIII. RECENTLY APPROVED AGENTS - Aliskiren (Tekturna)

A. Relative Clinical Effectiveness – The DoD P&T Committee evaluated the clinical effectiveness of aliskiren (Tekturna), a new direct renin inhibitor.

Pharmacology – Aliskiren is the first direct oral renin inhibitor marketed in the U.S. It decreases plasma renin activity and inhibits the conversion of angiotensinogen to angiotensin I. The correlation between decreased plasma renin activity and improved clinical outcomes is unclear.

Efficacy Measures – Clinical trials evaluating efficacy of aliskiren (typically 8 weeks in duration) have only assessed blood pressure (BP) reductions as the primary endpoint. Clinical trials have included patients with mild to moderate hypertension (mean DBP 95-110 mm Hg); patients with severe hypertension have been excluded from clinical trials, along with patients with severe cardiac disease or renal impairment.

Efficacy Results – A pooled analysis from eight randomized trials reported mean reductions in seated BP with aliskiren 150 mg of 8.7-12/7.8-10.2 mm Hg and with aliskiren 300 mg of 14.1-15.9/10.3-12.3 mm Hg (not placebo adjusted). Aliskiren has been compared to ARBs (irbesartan, losartan and valsartan), diuretics (HCTZ) and the ACE inhibitor ramipril, as monotherapy and as combination therapy. Overall, BP reductions with aliskiren were dose-related and were similar to that seen with the other drugs used as monotherapy; combination therapy produced additional BP reductions.

Outcomes Trials - Outcomes trials are currently underway, but results are not yet available. Trials are evaluating efficacy and safety of aliskiren in heart failure, post-myocardial infarction, diabetic nephropathy, left ventricular hypertrophy, diabetes, and metabolic syndrome. Initial results are expected in November 2007 for a study evaluating change in urinary albumin to creatinine ratio with aliskiren compared to losartan plus placebo (AVOID study) and a study evaluating reductions in brain natiuretic peptide (BNP) in patients with hypertension and stable heart failure (ALOFT).

Safety – Available clinical data suggest that aliskiren most closely resembles an ARB in terms of adverse effects. Angioedema and hyperkalemia have been reported. Pooled data from clinical trials reported a discontinuation rate due to adverse effects of 2.2% with aliskiren vs. 3.5% with placebo. Dose-related diarrhea is the most common adverse effect. Clinically, aliskiren does not appear to inhibit or induce CYP450 enzymes. Drug interactions have been reported with furosemide (decreased diuretic blood concentrations), and ketoconazole (increased aliskiren concentrations).

Place in Therapy – The exact place in therapy for aliskiren for treating hypertension is unknown at this time. Although aliskiren is indicated for use as monotherapy, it will likely be used as adjunctive therapy with other antihypertensive drugs (e.g., ACE inhibitors, ARBs, diuretics). A potential role for aliskiren would be in patients requiring double blockade of the renin-angiotensin aldosterone system; clinical trials with an ACE inhibitor plus an ARB in both heart failure and in patients with diabetic renal disease have suggested benefit; aliskiren could potentially be substituted for the ACE inhibitor in these settings.

Clinical Effectiveness Conclusion – The DoD P&T Committee concluded that:

a) Aliskiren is a new antihypertensive agent with a novel mechanism of action as a direct renin inhibitor.

b) Aliskiren's blood pressure lowering effects are similar to those achieved with other antihypertensives, but it does not show improved efficacy compared to other classes of antihypertensive agents.

c) Combination therapy of aliskiren with ACE inhibitors, diuretics and ARBs has shown additive BP lowering effects compared to monotherapy with other antihypertensive agents.

d) Several other safe, once-daily, less costly antihypertensive drugs are available that have proven clinical outcomes (e.g., ACE inhibitors, ARBs, diuretics).

e) The long-term adverse event profile of aliskiren is unknown; diarrhea is the most commonly reported adverse event and the discontinuation rate is similar to placebo.

f) Clinical outcomes of aliskiren are unknown. Trials are underway, with initial results anticipated in November 2007.

The P&T Committee voted to accept the clinical conclusions stated above. The one opposing vote was due to the opinion that there was insufficient clinical experience with aliskiren.

B. Relative Cost Effectiveness - Aliskiren (Tekturna)

The P&T Committee evaluated the relative cost-effectiveness of aliskiren (Tekturna) in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class, particularly the angiotensin receptor blockers (ARBs).

A cost minimization analysis (CMA) was employed to evaluate the cost effectiveness of aliskiren (Tekturna). The cost-effectiveness of aliskiren (Tekturna) was evaluated relative to ARBs, which were recently evaluated at the May 2007 DoD P&T Committee meeting.

The results of the CMA showed that the projected weighted average daily cost of aliskiren (Tekturna) was higher than the weighted average daily cost of the ARBs designated as formulary on the UF.

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

Although aliskiren (Tekturna) was somewhat more costly relative to the ARBs designated as formulary on the UF, the P&T Committee was reluctant to designate aliskiren (Tekturna) non-formulary at this time given its novel mechanism of action and the anticipated availability of clinical outcomes data that would enable the P&T Committee to more definitively asses its value relative to other antihypertensives.

C. Uniform Formulary Recommendations

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

D. **Uniform Formulary Implementation Period**

Not applicable.

IX. RECENTLY APPROVED AGENTS - Aliskiren (Tekturna)

BAP Comments

A. Uniform Formulary Recommendations. P&T Committee, based upon its collective professional judgment, voted to recommend that aliskiren (Tekturna) be maintained as formulary on the UF.

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

X. RECENTLY APPROVED AGENTS - Fluticasone Furoate (Veramyst)

A. Relative Clinical Effectiveness – The P&T Committee reviewed the nasal corticosteroid drug class in November 2005. Nasal corticosteroids on the UF include fluticasone propionate (Flonase, generics), mometasone furoate (Nasonex) and flunisolide (Nasarel). Fluticasone propionate is classified as the BCF agent. The non-formulary nasal corticosteroid agents are beclomethasone dipropionate (Beconase AQ, Vancenase AQ), budesonide (Rhinocort AQ), and triamcinolone (Nasacort AQ, Nasacort HFA).

Pharmacology – Fluticasone furoate (Veramyst) is a new nasal corticosteroid marketed by GlaxoSmithKline (GSK), the manufacturer of fluticasone propionate (Flonase), which has been available in a generic formulation since February 2006. Veramyst is structurally different from Flonase in that fluticasone propionate ester has been replaced with fluticasone furoate ester. Fluticasone furoate is active as the intact molecule and is not a prodrug or alternative salt of fluticasone. The structural change is responsible for higher glucocorticoid receptor binding affinity. However, *in vitro* claims of enhanced receptor binding have not translated into improved clinical effectiveness.

FDA-Approved Indications – Both Veramyst and Flonase are FDA-approved for treating symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis

(PAR) in adults and children. Veramyst and mometasone (Nasonex) are approved for use in children down to the age of 2 years, compared to 4 years with Flonase. In contrast to mometasone furoate (Nasonex), Veramyst is not currently approved for treatment of nasal polyps.

Efficacy – Efficacy assessment was based on the total nasal symptom score (TNSS), which was calculated based on the sum of a patient's score for four individual nasal symptoms (rhinorrhea, nasal congestion, sneezing, nasal itching). This was often reported as a reflective total nasal symptom score (rTNSS), which averages previous daytime and nighttime TNSSs over a certain time period.

Head-to-Head Trial - There is insufficient evidence to determine if there are clinically relevant differences between Veramyst and Flonase; one head-to-head trial in patients older than 12 years of age with SAR showed that Veramyst was not inferior to Flonase in terms of changes from baseline in TNSS.

Placebo-Controlled Trials - FDA-approval of Veramyst was based on six placebo-controlled trials.

a) In the trials enrolling adults with SAR (three studies) or PAR (one study), Veramyst 110 mcg/day showed statistically significant improvement in rTNSS when compared to placebo.

b) In one study in children younger than 12 years with PAR, Veramyst 55 mcg showed a statistically significant improvement in nasal symptom scores (rTNSS) compared to placebo; however there was no difference between placebo and Veramyst 110 mcg.

c) In the one pediatric study in patients with SAR, Veramyst 110 mcg but not 55 mcg showed a statistically significant improvement in nasal symptom scores (rTNSS) compared to placebo.

Efficacy in Treating Ocular Symptoms – Nasal corticosteroids have not shown efficacy at reducing ocular symptoms of allergic rhinitis, in contrast to benefits seen with oral antihistamines. With Veramyst, although some improvements were noted in individual ocular symptoms evaluated as secondary endpoints (e.g., eye watering/tearing, eye itching/burning, and eye redness), there was no difference from placebo when reflective total ocular symptom score was evaluated as a primary endpoint.

Safety – The adverse event profile of Veramyst is similar to other nasal corticosteroids. Common adverse events reported with Veramyst included headache, epistaxis, and nasal ulceration. Administration of Veramyst with ritonavir, a potent CYP3A4 inhibitor, is not recommended, due to the potential for increased systemic effects of Veramyst.

Delivery Device – The Committee also evaluated differences in the delivery device, ease of administration, and particle size of Veramyst compared to other nasal corticosteroids, but did not find a unique advantage or disadvantage relative to fluticasone propionate (Flonase, generics) or mometasone furoate (Nasonex).

Clinical Effectiveness Conclusion – The DoD P&T Committee concluded that:

Veramyst has no clinically significant differences with respect to safety, efficacy, or tolerability, when compared to other nasal corticosteroids included on the UF.

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

B. Fluticasone Furoate (Veramyst) Relative Cost Effectiveness – The P&T Committee evaluated the relative cost-effectiveness of fluticasone furoate (Veramyst) in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

A cost minimization analysis (CMA) was employed to evaluate the cost effectiveness of fluticasone furoate (Veramyst) relative to the UF nasal corticosteroids. The results of the CMA showed that the projected weighted average daily cost of fluticasone furoate (Veramyst) was significantly higher than weighted average daily cost of the UF nasal corticosteroids.

Cost Effectiveness Conclusion – Fluticasone furoate (Veramyst) is not cost-effective relative to the UF nasal corticosteroids.

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

C. Fluticasone Furoate (Veramyst) UF Recommendation

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of Fluticasone furoate (Veramyst), and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that fluticasone furoate (Veramyst) be classified as non-formulary.

D. Implementation period. The P&T Committee voted to recommend an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA. If determined to be operationally feasible, the $22 co-pay would start immediately upon signing of the minutes for new users; the $22 co-pay would go into effect after the 60-day implementation date for current Veramyst users.

XI. RECENTLY APPROVED AGENTS - Fluticasone Furoate (Veramyst)

BAP Comments

A. Uniform Formulary Recommendations. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of Fluticasone furoate (Veramyst), and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that fluticasone furoate (Veramyst) be classified as non-formulary.

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

B. Implmentation Period. The P&T Committee voted to recommend an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 60-day implementation period.

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