DECISION PAPER

DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

August 2007

1) **CONVENING**
2) **ATTENDANCE**
3) **REVIEW MINUTES OF LAST MEETING**
4) **ITEMS FOR INFORMATION**
5) **REVIEW OF RECENTLY APPROVED AGENTS**

A. Recently Approved Agents in Classes Not Yet Reviewed for the Uniform Formulary (UF) – The P&T Committee was briefed on four new drugs which were approved by the U.S Food and Drug Administration (FDA) (see Appendix B). The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee determined that these four new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed. The P&T Committee discussed the need for quantity limits (QLs) requirements for budesonide/formoterol (Symbicort) oral inhaler. (See paragraph 5A on page 20 of the P&T Committee minutes).

COMMITTEE ACTION: QUANTITY LIMITS – The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend QLs for budesonide/ formoterol of 1 inhaler per 30 days, 3 inhalers per 90 days.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: [illegible]

B. Renin Angiotensin Antihypertensive – Aliskiren (Tekturna)

Background – In May 2007, the P&T Committee re-classified the angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), ARB/calcium channel blockers combinations and any newly approved antihypertensive drugs affecting the renin system into a single drug class, the Renin-Angiotensin Antihypertensives (RAAs). Aliskiren is the first new drug in the RAA class.

Relative Clinical Effectiveness Conclusion – the P&T Committee voted (14 for, 1 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated below. The one opposing vote was due to the opinion that there was insufficient clinical experience with aliskiren.

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

b) Aliskiren's blood pressure (BP) 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.

Relative Cost Effectiveness Conclusion – the P&T Committee concluded (14 for, 0 opposed, 1 abstained, 2 absent) that:

Although aliskiren was somewhat more costly relative to the ARBs designated as formulary on the UF, the P&T Committee was reluctant to designate aliskiren 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 assess its value relative to other anti-hypertensives.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** –Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (10 for, 4 opposed, 1 abstained, 2 absent) to recommend that aliskiren be classified as formulary on the UF. The four opposing votes were cast due to the opinion that there was insufficient evidence to recommend formulary placement; the one abstaining vote was due to the opinion that there was a lack of sufficient cost effectiveness compared to the ARBs. (See paragraph 5B on pages 20-23 of the P&T Committee minutes).

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: On condition that active surveillance be initiated

C. Nasal Corticosteroid – Fluticasone Furoate (Veramyst)

Background – The P&T Committee reviewed the nasal corticosteroid drug class in November 2005; fluticasone propionate (Flonase, generics), mometasone furoate (Nasonex), and flunisolide (Nasarel) were designated as formulary on the UF, while beclomethasone dipropionate (Beconase AQ, Vancenase AQ), budesonide (Rhinocort AQ), and triamcinolone (Nasacort AQ, Nasacort HFA) were classified as non-formulary. Fluticasone furoate is a new nasal corticosteroid that replaces the

propionate ester of fluticasone propionate with a furoate ester. *In vitro* claims of enhanced glucocorticoid receptor binding *in-vitro* have not translated into enhanced clinical effectiveness.

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 Total Nasal Symptom Score. Veramyst's adverse effect profile appears similar to other nasal corticosteroids. The P&T 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 or mometasone furoate.

Relative Clinical Effectiveness Conclusion: The DoD P&T Committee concluded (12 for, 0 opposed, 1 abstained, 4 absent) that:

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

Relative Cost Effectiveness Conclusion: The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that:

> Fluticasone furoate was not cost effective relative to the UF nasal corticosteroids.

1) ***COMMITTEE ACTION: UF RECOMMENDATION*** – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of fluticasone furoate, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 1 abstained, 4 absent) to recommend that fluticasone furoate be classified as non-formulary under the UF. (See paragraph 5C on pages 23-25 of the P&T Committee minutes).

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

2) ***COMMITTEE ACTION: MEDICAL NECESSITY (MN) CRITERIA*** – Based on the clinical evaluation of fluticasone furoate and the conditions for establishing medical necessity of a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) medical necessity criteria for the nasal corticosteroids. (See paragraph 5C on page 26 of the P&T Committee minutes for the criteria).

   Director, TMA, Decision: ☒ Approved ☐ Disapproved

   Approved, but modified as follows:

3) ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend an

effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) and TRICARE Retail Pharmacy (TRRx) network, and at military treatment facilities (MTFs) no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TRICARE Management Activity (TMA). Committee members directed that if operationally feasible, the $22 co-pay should 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 fluticasone furoate users. (See paragraph 5C on page 26 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

4) ***COMMITTEE ACTION: QUANTITY LIMITS*** - The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend a QL for fluticasone furoate in the TRRx of 1 inhaler device per 30 days and a QL in the TMOP of 3 inhaler devices per 90 days. (See paragraph 5C on page 26 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

6) DRUG CLASS REVIEW – NEWER ANTIHISTAMINE (NA) DRUG CLASS

The P&T Committee evaluated the relative clinical effectiveness of the NA agents. The NA drug class includes the following agents: loratadine (Claritin, generics), acrivastine/ pseudoephedrine (Semprex-D), fexofenadine (Allegra, generics), cetirizine (Zyrtec), and desloratadine (Clarinex). The class also includes combinations of all of the single agent products with pseudoephedrine. As of June 2007, about three million Military Health System (MHS) prescriptions for these agents were filled annually. The NA drug class was ranked #5 in terms of expenditures ($178 million) in FY 2006 .

The brand-only agents in this class are desloratadine, acrivastine/pseudoephedrine and cetirizine. Loratadine and fexofenadine are available as generics. Loratadine is only available over-the-counter (OTC). Cetirizine is expected to become available OTC by the end of 2007 and generic cetirizine OTC products are expected to be marketed in the first quarter of calendar year 2008. Marketing for a very recently approved product, levocetirizine (Xyzal), is expected to begin in September/October of 2007.

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded (14 for, 0 opposed, 1 abstained, 2 absent) that:

1) Based on randomized placebo-controlled trials, cetirizine, desloratadine and loratadine are more efficacious than placebo for the symptomatic relief of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU). Fexofenadine is more efficacious than placebo for the

symptomatic relief of SAR and CIU. Acrivastine/pseudoephedrine is more efficacious than placebo for the symptomatic relief of SAR.

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

3) 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 may be more efficacious than loratadine with PAR.

4) For the treatment of CIU in adults, limited evidence based on two poor quality comparative trial suggests suggest that loratadine may be more efficacious than cetirizine for total symptom score reductions (but not response time), and cetirizine may be more efficacious than fexofenadine. In children, only cetirizine has evidence of efficacy for the treatment of CIU in children, based on both an active- and placebo-controlled trial.

5) 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.

6) No NA appears preferable in hepatic impaired, renal impaired and pediatric patients. Loratadine, cetirizine and acrivastine/pseudoephedrine are FDA pregnancy category B, while desloratadine, fexofenadine and the combination products containing pseudoephedrine are FDA pregnancy category C.

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

8) 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.

9) Loratadine has been identified as a candidate drug for the DoD OTC Demonstration Program.

Cost Effectiveness Conclusion – The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that:

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

2) The UF scenario that placed desloratadine and desloratadine/pseudoephedrine as non-formulary was the most cost effective scenario.

A. ***COMMITTEE ACTION: UF 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 (14 for, 0 opposed, 1 abstained, and 2 absent) to

recommend the following. (See paragraph 6C on page 33 of the P&T Committee minutes.)

1) Fexofenadine, fexofenadine/pseudoephedrine, cetirizine, cetirizine/ pseudoephedrine , and acrivastine/pseudoephedrine should be maintained as formulary on the UF.
2) Desloratadine and desloratadine/pseudoephedrine should be classified as non-formulary under the UF.
3) Loratadine and loratadine/pseudoephedrine should be added to the UF for purposes of the TRICARE OTC Demonstration Program.
4) At such time as cetirizine and cetirizine/pseudoephedrine are made available OTC, both products should be maintained on the UF for purposes of the TRICARE OTC Demonstration Program.
5) Desloratadine and desloratadine/pseudoephedrine should be reclassified as generic on the UF when the generic products are available and cost effective relative to similar agents in the newer antihistamine class.

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation for desloratadine and desloratadine/pseudoephedrine, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for desloratadine and desloratadine/pseudoephedrine. (See paragraph 6D on page 34 of the P&T Committee minutes.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period in the TMOP and TRRx, and no longer than a 90-day implementation period at MTFs. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 6E on page 34 of the P&T Committee minutes.)

Director, TMA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: BASIC CORE FORMULARY (BCF) RECOMMENDATION – Based on the results of the clinical and economic

evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that the current BCF listing for this class be maintained, requiring each MTF to carry at least one single ingredient agent from the NA class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use. (See paragraph 6F on page 34 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

7) DRUG CLASS REVIEW – LEUKOTRIENE MODIFIERS (LMs)

The P&T Committee evaluated the relative clinical effectiveness of the LM agents. The LM class is comprised of two leukotriene receptor antagonists, montelukast (Singulair) and zafirlukast (Accolate); and one 5-lipoxygenase inhibitor, zileuton (Zyflo). A controlled release formulation of zileuton (Zyflo CR) has been approved by the FDA, but is not yet commercially available.

Currently montelukast is the only BCF LM agent. None of the LMs are available in a generic formulation. The LM drug class accounted for $101 million dollars in MHS expenditures in FY 2006, and is ranked #16 in terms of total expenditures during that time period. Over 97% of the utilization is for montelukast; from June 2006 to May 2007, there were over 300,000 montelukast utilizers in the MHS, over 3,000 zafirlukast utilizers and only 300 zileuton utilizers.

Relative Clinical Effectiveness Conclusion: The P&T Committee voted (14 for, 0 opposed, 0 abstained, 3 absent) to accept the following clinical effectiveness conclusion:

a) For the treatment of asthma, National Heart, Lung and Blood Institute National Asthma Education Prevention Program guidelines include LMs as an alternative, but not preferred therapy. LMs are more effective than placebo in controlling asthma symptoms, but are less effective than inhaled corticosteroids (ICS), and are less effective when added on to long-acting beta agonist (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 forced expiratory volume in 1 second (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 ICS dose, or could be used in patients resistant to 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 (AR), 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 AR.

e) For AR, meta-analyses show that LMs are superior to placebo in clinically relevant AR endpoints such as rhinitis symptom 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 (NCS) are clinically superior to montelukast in all clinical endpoints studied. Combinations of an LM with an antihistamine are modestly more effective than either agent alone, but not superior to NCS in improving nasal symptoms of AR.

f) 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 in most of the endpoints studied.

g) In regard to safety and tolerability, zileuton has been associated with hepato-toxicity, requires liver function test 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 event reports and must be interpreted cautiously. Zafirlukast and zileuton are associated with more clinically significant drug interactions than montelukast.

h) 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.

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

Relative Cost Effectiveness Conclusion – the P&T Committee concluded (14 for, 0 opposed, 1 abstained, and 2 absent) that:

a) Zafirlukast was the least costly agent in the class; montelukast was more costly relative to zafirlukast 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 was not cost effective relative to the other products.

b) LMs are not cost effective in the treatment of AR relative to antihistamines and nasal corticosteroids and should not be considered as first-line therapy in the treatment of AR.

c) The Committee concluded that the UF scenario that placed zafirlukast and montelukast on formulary with a step therapy/prior authorization (PA) program required for use in AR was the scenario that resulted in the lowest expected expenditures in the LM class.

A. ***COMMITTEE ACTION: STEP THERAPY RECOMMENDATION*** – Although the committee agreed that the LMs are not cost effective for AR, the Committee voted (6 for, 8 opposed, 1 abstained, and 2 absent) against enacting a step therapy/PA policy for use of LMs in the management of AR. Similar policies have recently been initiated with other drug classes in the MHS and the Committee felt that the most prudent course of action at this time was to delay enacting another step therapy/PA policy. Instead, the PEC will gather additional evidence about the effect of the other step therapy/PA policies recently implemented in the MHS while educating MTF providers to minimize the use of LMs for the management of AR. The PEC will also monitor utilization in the LM class. If the use of LMs for AR continues to proliferate, the Committee will review the class again to determine if further action is required. (See paragraph 7C on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows: ASD(HA) urges that these pts be followed re: possible CV or oncologic benefits or AE's

B. ***COMMITTEE ACTION: UF 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 (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that zafirlukast and montelukast be maintained as formulary on the UF and that zileuton be classified as non-formulary under the UF. (See paragraph 7D on page 43 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. ***COMMITTEE ACTION: MN CRITERIA*** – Based on the clinical evaluation for zileuton and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) MN criteria for zileuton. (See paragraph 7E on pages 43-44 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and no later than a 90-day implementation period at MTFs. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 7F on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

E. COMMITTEE ACTION: BCF RECOMMENDATION – The P&T Committee considered the BCF status of the LM agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 1 opposed, 1 abstained, and 2 absent) to recommend that montelukast be retained on the BCF (specific formulations include tablets, chewable tablets, and oral granules). (See paragraph 7G on page 44 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

8) DRUG CLASS REVIEW – GROWTH STIMULATING AGENTS (GSAs)

The P&T Committee evaluated the relative clinical effectiveness of the GSAs. This class is divided into two subclasses: growth hormone (GH) agents (somatropin products) and insulin-like growth factor-1 (IGF-1) agents (mecasermin). The GSA drug class accounted for about $23 million in MHS expenditures in FY 2006.

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 GH deficiency (GHD), which is the most common use. 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).

Relative Clinical Effectiveness Conclusion: The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) 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 GH, 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 IGFD, 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 under the UF.

Relative Cost Effectiveness Conclusion: the P&T Committee concluded (15 for, 0 opposed, 0 abstained, and 2 absent) that:

a) Mecasermin (Increlex) and 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.

b) 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.

c) 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.

d) The budget impact analysis 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.

A. COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the GSAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 0 opposed, 1 abstained, 3 absent) 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 under the UF. (See paragraph 8C on page 57 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: MN CRITERIA – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) MN criteria for the somatropin products Genotropin, Humatrope, Saizen and Omnitrope. (See paragraph 8D on page 57 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. ***COMMITTEE ACTION: IMPLEMENTATION PERIOD*** – The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) 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 the approval by the Director, TMA. (See paragraph 8E on pages 57-58 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

D. ***COMMITTEE ACTION: PA CRITERIA*** – Currently, PA criteria apply to both GH (somatropin products) and mecasermin (Increlex). The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) PA criteria for GH (somatropin products) and mecasermin (Increlex). Changes from previous GH (somatropin) criteria are the addition of Noonan's Syndrome and Short Stature Homeobox gene (SHOX) deficiency as covered uses; no changes were recommended to mecasermin criteria. (See paragraph 8F on pages 58-59 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

E. ***COMMITTEE ACTION: EXTENDED CORE FORMULARY (ECF) RECOMMENDATION*** – Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 1 abstained, and 3 absent) to recommend that Norditropin and Norditropin / Nordiflex be added to the ECF. (See paragraph 8G on page 59 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

9) QUANTITY LIMITS

A. ***COMMITTEE ACTION: QL FOR RIZATRIPTAN (MAXALT)*** – The Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend changing the QL for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) to 12 tablets per 30 days, or 36 tablets per 90 days. (See paragraph 9A on page 59 of the P&T Committee minutes.)

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

10) BCF STATUS OF ROSIGLITAZONE

The PEC updated the P&T Committee on the two recent alerts issued by the FDA regarding rosiglitazone (Avandia). The P&T Committee discussed the advantages and disadvantages of removing rosiglitazone from the BCF. Ultimately, the P&T Committee determined that there was insufficient clinical evidence to justify removal of rosiglitazone from the BCF at this time. The PEC will update the P&T Committee as more information becomes available. (See paragraph 10 on pages 59-60 of the P&T Committee minutes.)

***COMMITTEE ACTION*:** The Committee voted (7 for, 6 opposed, 1 abstained, 3 absent) to retain rosiglitazone on the BCF at this time.

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

11) BCF / ECF REVIEW

The P&T Committee agreed with a plan to systematically review drug classes represented on the BCF and ECF over the next few meetings with the goals of: 1) removing obsolete medications, 2) defining BCF listings more specifically, 3) reframing or revising BCF listings to be compatible with drug classes as defined or outlined by the P&T Committee, and 4) assessing the need for future review.

The P&T Committee made initial recommendations for clarifying BCF listings in three drug classes or potential drug classes, including atypical antipsychotics (quetiapine and risperidone), osteoporosis agents (alendronate / vitamin D), and cough-cold medications (guaifenesin/pseudoephedrine).

COMMITTEE ACTION: The P&T Committee recommended the following changes to BCF / ECF listings. (See paragraph 11 on page 60 of the P&T Committee minutes and Appendix C).

Drug class or potential drug class	Current BCF / ECF listing	Recommendation	Vote			
			For	Opposed	Abstained	Absent
Atypical antipsychotics	BCF – "Quetiapine"	Clarify BCF listing to: "quetiapine tablets, immediate and extended release"	14	0	1	2
	BCF – "Risperidone oral; does not include orally disintegrating tablets (Risperdal Redi-tabs)"	Clarify BCF listing to: "Risperidone tablets and solution, does not include orally disintegrating tablets"	14	0	1	2
Osteoporosis agents	BCF – "Alendronate 70 mg / vitamin D 2800 IU (Fosamax Plus D)"	Clarify BCF listing to specify new product with higher strength of vitamin D – "Alendronate 70 mg/vitamin D 5600 IU tablets"	14	0	1	2
Cough-cold medications	BCF – "Guaifenesin 600 / PSE 120 mg ER oral"	Remove from BCF	14	0	1	2

Director, TMA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

Appendix A – Implementation Status of UF Recommendations/Decisions
Appendix B – Newly Approved Drugs
Appendix C – BCF Review
Appendix D – Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

S. Ward Casscells, III, M.D.
17 Oct 07

Department of Defense
Pharmacy and Therapeutics Committee Minutes
August 2007

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 14-15 Aug 2007 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P&T Committee Chair
LTC Brett Kelly, MSC, USA	DoD P&T Committee Recorder
CAPT William Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Capt Jeremy King, MC	Air Force, OB/GYN Physician
Lt Col Brian Crownover, MC	Air Force, Physician at Large
Col Everett McAllister, BSC	Air Force, Pharmacy Officer
LCDR Ronnie Garcia, MC *for* LCDR Michelle Perrelló, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatrics Physician Alternate
CDR David Tanen, MC	Navy, Physician at Large
CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
COL Karl R. Kerchief, MC	Army, Family Practice Physician
LTC Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CAPT Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
Mr. Joe Canzolino, RPh.	Department of Veterans Affairs

B. Voting Members Absent

Lt Col Roger Piepenbrink, MC	Air Force, Internal Medicine Physician
COL Ted Cieslak, MC	Army, Physician at Large

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Lt Col Paul Hoerner, BSC, USAF	Deputy Director, DoD Patient Safety Center
CDR Kim Lefebvre, MSC	Defense Supply Center Philadelphia
Major Pete Trang, BSC, USAF	Defense Supply Center Philadelphia
Mr. Howard Altschwager	Assistant General Counsel, TMA
LT Thomas Jenkins, MSC, USN	TMA Aurora

D. Non-Voting Members Absent

Martha Taft	Health Plans Operations, TMA

E. Others Present

Col Nancy Misel, BSC, USAF	IMA DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
LTC Chris Conrad, MC, USA	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
Maj Josh Devine, BSC, USAF	DoD Pharmacoeconomic Center
CPT Josh Napier, MC, USA	DoD Pharmacoeconomic Center
Shana Trice, Pharm.D.	DoD Pharmacoeconomic Center
David Bretzke, Pharm.D.	DoD Pharmacoeconomic Center
Angela Allerman, Pharm.D.	DoD Pharmacoeconomic Center
Eugene Moore, Pharm.D.	DoD Pharmacoeconomic Center
Julie Liss, Pharm.D.	DoD Pharmacoeconomic Center
Elizabeth Hearin, Pharm.D.	DoD Pharmacoeconomic Center
David Meade, Pharm.D.	DoD Pharmacoeconomic Center
Harsha Mistry, Pharm.D.	DoD Pharmacoeconomic Center
Todd Semla, Pharm.D.	VAPBM
Bill Coffenberry	TMA Contracting
Brenda Agner	TMA Contracting
Beth Spearman	TMA/POD
CDR Michael J. Contos	USPHS, IHS

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the Minutes – May 2007 DoD P&T Committee meeting minutes were approved as written, with no corrections noted.

B. Approval of May Minutes – Dr. Samuel Ward Casscells, III., M.D., approved the minutes of the May 2007 DoD P&T Committee meeting on 24 July 2007.

4. ITEMS FOR INFORMATION

TRICARE Management Activity (TMA) and DoD PEC staff members briefed the P&T Committee on the following:

A. Beneficiary Advisory Panel (BAP) Briefing – CAPT Buss briefed the members of the P&T Committee regarding the June 2007 BAP meeting. The P&T Committee was briefed on BAP comments regarding the DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

B. Implementation Status of UF Decisions – The PEC briefed the members of the P&T Committee on the progress of implementation for drug classes reviewed for UF status since February 2005.

C. Status of Newer Sedative Hypnotic Agents (SED-1) Step Therapy Program – The PEC briefed the members of the P&T Committee on a preliminary analysis of the SED-1 Step Therapy Program. The analysis examined the first week of SED-1 transactions (1 – 7 August) following the 1 August 2007 implementation date. During the observation period, 23,790 patients submitted a prescription for a SED-1. A total of 1,592 patients had claims stopped by the Step Therapy Program's automated profile review (APR) process. Of these patients, 771 (48%) subsequently received a SED-1 prescription through 10 August. This represents a window as short as 3 days and is unlikely to be a fair assessment of the Step Therapy Program; the PEC will continue to monitor as more data becomes available. Of patients who subsequently received a SED-1 prescription, 576 (75%) received the preferred product, Ambien IR.

D. Status of Fentanyl Patch Safety Program/Prior Authorization (PA) - The PEC briefed the members of the P&T Committee on a preliminary analysis of the Fentanyl Patch Safety Program. The analysis examined the first week of fentanyl patch transactions (1 – 7 August) following the 1 August 2007 implementation date. During the observation period, 2,732 patients submitted a fentanyl patch prescription. A total of 314 patients had claims stopped by the APR process. Of these patients, 255 (81%) subsequently received a fentanyl patch prescription and 59 (19%) did not, through 10 August (minimum 3-day window). Approximately 11% of patients (314/2732) were affected by the Fentanyl Patch Safety Program.

E. Administrative Actions – Modification of Medical Necessity (MN) Criteria for Duloxetine (Cymbalta) and Pregabalin (Lyrica) – Both of these medications recently gained U.S Food and Drug Administration (FDA) approval for new indications: duloxetine for the treatment of generalized anxiety disorder (February 2007) and pregabalin for the treatment of fibromyalgia (June 2007). MN criteria for these two non-formulary medications are interrelated, since duloxetine also has clinical evidence supporting efficacy in fibromyalgia. The PEC obtained input from members of the P&T Committee regarding the best way to make changes to the MN criteria for these two medications. Changes to MN criteria will be made administratively.

- *Duloxetine for Generalized Anxiety Disorder (GAD)* – Current duloxetine MN criteria allow for the use of the non-formulary serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine in patients treated for depression or other psychiatric illnesses who require treatment with an SNRI (e.g., due to failure of selective serotonin reuptake inhibitor [SSRI] therapy) and who have failed an adequate trial, been unable to tolerate, or have contraindications to the SNRI venlafaxine, which is on the UF. Both venlafaxine and duloxetine are FDA-approved for the treatment of GAD; other medications are FDA-approved either for GAD (e.g., paroxetine, escitalopram) or anxiety in general (e.g., buspirone, lorazepam, alprazolam), or have clinical evidence supporting their use (e.g., sertraline). Based on the results of one head-to-head trial [Hartford et al, 2007] and indirect evidence from placebo-controlled trials with duloxetine and venlafaxine, there is insufficient evidence to conclude that either agent is safer or more efficacious for the treatment of GAD; more clinical evidence is available for venlafaxine. Accordingly, the P&T Committee agreed that the MN criteria were adequate as stated.
- *Pregabalin for Fibromyalgia* – Fibromyalgia is a poorly understood, multifactorial condition that is diagnosed based on a history of widespread pain (bilateral, upper & lower body, spine) and often accompanied by fatigue, difficulty sleeping, and depression. American College of Rheumatology (ACR) criteria, which are based on the presence of excessive tenderness on applying pressure to 11 of 18 specific muscle-tendon sites, appear to be about 85% sensitive and specific for fibromyalgia. Prevalence in the U.S. is about 2% (3.4% women, 0.5% men).

  A 2004 American Pain Society guideline advises a stepwise approach to the treatment of fibromyalgia, including early evaluation and treatment of comorbid conditions (e.g., mood and sleep disturbances), an exercise program, and cognitive behavior therapy. The recommended sequence of drug treatment corresponds to the strength of clinical evidence available to guideline authors. It includes an initial trial of a low-dose tricyclic antidepressant (TCA) or cyclobenzaprine (a muscle relaxant structurally similar to the TCAs), which are considered to be supported by strong clinical evidence, followed by subsequent trials of SSRIs, SNRIs, or tramadol (modest evidence), and possible consideration of combination therapy or use of an anticonvulsant. None of these medications are FDA-approved for the treatment of fibromyalgia; pregabalin is the first medication with this FDA indication.

  Clinical trials evaluating pregabalin for the treatment of fibromyalgia include four randomized controlled trials (RCTs) and three open-label studies (based on information supplied by the manufacturer). One 14-week trial (n = 1077) compared three doses of pregabalin (300, 450, or 600 mg/d) to placebo for 14 weeks, resulting in a significant reduction in the mean pain score of about 1 point on an 11-point scale (0-10) compared to placebo [300 mg/d -0.71; 450 mg/d -0.98; 600 mg/d -1.00]. Withdrawals due to adverse effects were substantially higher with pregabalin than placebo and appeared to be dose-related [300 mg/d 16%; 450 mg/d 22%, 600 mg/d 26%; placebo 12%). Pregabalin was also

compared to placebo in a 6-month randomized withdrawal study (n=566). Significantly more patients on placebo had lost clinical response at endpoint (61%) compared to those on pregabalin (32%). The other two trials consist of a 13-week RCT, which reported about a 0.7 point reduction in endpoint mean pain score with 600 mg/d of pregabalin, compared to placebo ($p<0.05$), and an 8-week trial comparing 150-, 300-, or 450 mg/d of pregabalin to placebo that showed a significant reduction in mean pain score only for the 450 mg/d dose. The latter was not included as part of the FDA approval process; it is the only trial currently published [Crofford et al, 2006].

A small (n=75) placebo-controlled 12-week RCT evaluating gabapentin (a formulary anticonvulsant medication similar to pregabalin) for the treatment of fibromyalgia was recently published [Arnold et al, 2006]. The trial reported significantly greater improvements with gabapentin (1200 – 2400 mg/d) than with placebo at endpoint; results were not inconsistent with those reported during pregabalin trials. However, given the size of the trial and the lack of any comparative evidence, there is probably insufficient evidence to draw any conclusion regarding the relative efficacy or safety of pregabalin or gabapentin for the treatment of fibromyalgia; more clinical evidence is available for pregabalin.

The P&T Committee agreed that pregabalin should be considered medically necessary for patients diagnosed with fibromyalgia based on established criteria (e.g., ACR criteria) who have failed an adequate trial, been unable to tolerate, or for whom treatment with TCAs or cyclobenzaprine is contraindicated or clinically inappropriate (e.g., due to potential cardiac effects).

Duloxetine for Fibromyalgia – Although duloxetine is not FDA-approved for fibromyalgia, its use is supported by two placebo-controlled RCTs [Arnold et al, 2004; Arnold et al, 2005]. Results are not inconsistent with those reported during pregabalin trials, although there is probably insufficient evidence to draw any conclusion regarding relative efficacy or safety of the two agents for the treatment of fibromyalgia. Duloxetine's therapeutic effect in fibromyalgia is most likely due to a distinctly different mechanism than pregabalin and likely includes effects on comorbid conditions, such as depression and anxiety, as well as pain.

Current MN criteria for duloxetine allow for its use in patients who have failed an adequate trial, been unable to tolerate, or for whom treatment with at least one medication from at least two of the following four drug classes is contraindicated or clinically inappropriate: TCAs (e.g., amitriptyline); tricyclic muscle relaxants (cyclobenzaprine); SSRIs (e.g., fluoxetine); or opioids (e.g., tramadol). The P&T Committee agreed that, given the evidence for pregabalin and its recent FDA approval for this indication, duloxetine MN criteria should be changed accordingly. At the same time, the P&T Committee agreed that SSRIs and opioids should be dropped from MN criteria due to inconsistent clinical evidence supporting the use of SSRIs for fibromyalgia and the overly broad definition of opioids. The P&T Committee agreed that duloxetine should be considered medically necessary for patients diagnosed with fibromyalgia based on established criteria (e.g., ACR criteria), who have failed an adequate trial, been

unable to tolerate, or for whom treatment with both TCAs or cyclobenzaprine AND pregabalin is contraindicated or clinically inappropriate.

F. Administration Action – Modification of Mecasermin PA Criteria – The PEC reported an administrative change to mecasermin PA criteria to remove references to mecasermin rinfabate (Iplex) following its withdrawal from the market due to the outcome of litigation. Increlex is now the only mecasermin product on the market. The manufacturer of Iplex will continue to develop it for non-short stature indications (e.g., myotonic muscular dystrophy, Lou Gehrig's disease, HIV-associated adipose redistribution syndrome, and retinopathy of prematurity), but it is likely to be some time before data are available.

G. Statin Budget Impact Analysis (BIA) Review – The P&T Committee reviewed the performance of the Antilipidemic-1 (LIP-1) budget impact model used to estimate the outcome of potential formulary scenarios. The review compared actual Military Health System (MHS) pharmaceutical expenditures to the predicted expenditures that were reported at the August 2006 P&T meeting for the LIP-1 drug class. Data were collected for two quarters following UF implementation in January 2007. The results were compared directly and reported as a percent deviation from the actual values.

Study results showed that the model performed adequately during the first two quarters following the implementation date. The largest departure from actual spending occurred at the military treatment facility (MTF) point of service primarily because of conservative assumptions made about the price of generic simvastatin. The analysis assumed modest reductions in price for simvastatin after generic entry but in actuality the price fell more rapidly then what was predicted. More data will be collected in the future to determine if model performance is sustained. Furthermore, several findings from this review will be incorporated into future budget impact models to improve the validity and reliability of model results.

5. REVIEW OF RECENTLY APPROVED AGENTS

A. Recently Approved Agents in Classes Not Yet Reviewed for the UF

The P&T Committee was briefed on four new drugs which were approved by the FDA (see Appendix B). The P&T Committee determined that these four new drugs fall into drug classes that have not yet been reviewed for UF status; therefore, UF consideration was deferred until drug class reviews are completed. The P&T Committee discussed the need for quantity limits (QLs) for budesonide/formoterol (Symbicort) oral inhaler, based on existing QLs for other oral inhalation products and recommendations for use in product labeling.

COMMITTEE ACTION: QUANTITY LIMITS

The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to recommend QLs for budesonide/formoterol of 1 inhaler per 30 days, 3 inhalers per 90 days.

B. Renin Angiotensin Antihypertensive – Aliskiren (Tekturna)

1) Aliskiren Relative Clinical Effectiveness – The DoD P&T Committee evaluated the clinical effectiveness of aliskiren, a new direct renin inhibitor. Aliskiren is classified as a renin angiotensin antihypertensive agent (RAA). The RAA drug

class was defined at the May 2007 DoD P&T Committee meeting, and includes the following categories of drugs:

- *Angiotensin Receptor Blockers (ARBs) - May 2007*
  - **UF/Basic Core Formulary (BCF)**: telmisartan (Micardis), telmisartan/ hydrochlorothiazide (HCTZ) (Micardis HCT)
  - **UF:** candesartan (Atacand), candesartan HCTZ (Atacand HCT), losartan (Cozaar), losartan/HCTZ (Hyzaar)
  - **Non-Formulary**: eprosartan (Teveten), eprosartan/HCTZ (Teveten HCT), irbesartan (Avapro), irbesartan/HCTZ (Avalide), olmesartan (Benicar), olmesartan/HCTZ (Benicar HCT), valsartan (Diovan), valsartan/HCTZ (Diovan HCT)
- *ARB/Calcium Channel Blockers – February 2006*
  - **UF/BCF:** benazepril/amlodipine (Lotrel, generics)
  - **Non-Formulary:** enalapril/felodipine (Lexxel), trandolapril/verapamil sustained release (Tarka)
- *Angiotensin Converting Enzyme (ACE) inhibitors – August 2005*
  - **UF/BCF:** lisinopril (Prinivil, Zestril, generics), lisinopril/HCTZ (Prinzide, Zestoretic, generics), and captopril (Capoten, generics)
  - **UF**: captopril/HCTZ (Capozide, generics), benazepril (Lotensin, generics), benazepril/HCTZ (Lotensin HCT, generics), enalapril (Vasotec, generics), enalapril/HCTZ (Vasoretic, generics), fosinopril (Monopril, generics), fosinopril/HCTZ (Monopril-HCT, generics), trandolapril (Mavik)
  - **Non-Formulary:** ramipril (Altace), quinapril (Accupril, generics), quinapril/HCTZ (Accuretic, generics), perindopril (Aceon), moexipril (Univasc, generics), moexipril/HCTZ (Uniretic, generics)

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 diastolic BP 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 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 cytochrome P450 (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 BP 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 (14 for, 1 opposed, 0 abstained, 2 absent) to accept the clinical conclusions stated above. The one opposing vote was due to the opinion that there was insufficient clinical experience with aliskiren.

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

A cost minimization analysis (CMA) was employed to evaluate the cost effectiveness of aliskiren. The cost effectiveness of aliskiren 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 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 was somewhat more costly relative to the ARBs designated as formulary on the UF, the P&T Committee was reluctant to designate aliskiren 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.

The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to accept the cost effectiveness conclusions stated above.

3) *Aliskiren UF Recommendation*

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 (10 for, 4 opposed, 1 abstained, 2 absent) to recommend that aliskiren be designated as formulary on the UF.

4) *Aliskiren MN Criteria* – Since aliskiren was not recommended for non-formulary status under the UF, establishment of MN criteria is not applicable.

5) *Aliskiren Implementation Plan* – Since aliskiren was not recommended for non-formulary status under the UF, establishment of an implementation plan is not applicable.

C. Nasal Corticosteroid – Fluticasone Furoate (Veramyst)

1) *Fluticasone Furoate 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 is a new nasal corticosteroid marketed by GlaxoSmithKline, the manufacturer of fluticasone propionate, 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 fluticasone furoate and fluticasone propionate are FDA-approved for treating symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children. Fluticasone furoate and mometasone are approved for use in children down to the age of 2 years, compared to 4 years with Flonase. In contrast to mometasone furoate, 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 fluticasone furoate and fluticasone propionate. One head-to-head trial in patients older than 12 years of age with SAR showed that fluticasone furoate was not inferior to fluticasone propionate in terms of changes from baseline in TNSS.

Placebo-Controlled Trials – FDA-approval of fluticasone furoate was based on six placebo-controlled trials.

a) In the trials enrolling adults with SAR (three studies) or PAR (one study), fluticasone furoate 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, fluticasone furoate 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, fluticasone furoate 110 mcg but not 55 mcg showed a statistically significant improvement in rTNSS compared to placebo.

Efficacy in Treating Ocular Symptoms – Nasal corticosteroids have not shown efficacy at reducing ocular symptoms of AR, in contrast to benefits seen with oral

antihistamines. With fluticasone furoate, 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 fluticasone furoate is similar to other nasal corticosteroids. Common adverse events reported with fluticasone furoate included headache, epistaxis, and nasal ulceration. Administration of fluticasone furoate with ritonavir, a potent CYP3A4 inhibitor, is not recommended, due to the potential for increased systemic effects of fluticasone furoate.

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

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

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

The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusion stated above.

2) *Fluticasone Furoate Relative Cost Effectiveness* – The P&T Committee evaluated the relative cost effectiveness of fluticasone furoate 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 CMA was employed to evaluate the cost effectiveness of fluticasone furoate relative to the UF nasal corticosteroids. The results of the CMA showed that the projected weighted average daily cost of fluticasone furoate was significantly higher than weighted average daily cost of the UF nasal corticosteroids.

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

   > Fluticasone furoate was not cost effective relative to the UF nasal corticosteroids.

   The P&T Committee voted (12 for, 0 opposed, 1 abstained, 4 absent) to accept the cost effectiveness conclusion stated above

3) *Fluticasone Furoate UF Recommendation*

   Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of fluticasone furoate, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 1 abstained, 4 absent) to recommend that fluticasone furoate be classified as non-formulary under the UF.

4) *Fluticasone Furoate MN Criteria* – Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended maintaining the medical necessity criteria previously established for the nasal corticosteroid class. The following general MN criteria will be applied for fluticasone furoate:

   1) The use of formulary alternatives is contraindicated.

   2) The patient has experienced significant adverse effects from formulary alternatives.

   3) Formulary alternatives have resulted in therapeutic failure.

   COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

5) *Fluticasone Furoate Implementation Plan* – There have been approximately 650 prescriptions for fluticasone furoate in the MHS, all in the TRICARE Retail Pharmacy Network (TRRx), since market introduction. The Committee discussed the merits of a 60-day implementation period. Additionally, Committee members directed that if operationally feasible, the $22 co-pay should 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.

   COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) 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.

6) *Fluticasone Furoate QL* – The P&T Committee evaluated the need for QLs for fluticasone furoate. QLs are in effect for other nasal corticosteroids. Based on both adults and pediatric dosing in manufacturer labeling for fluticasone furoate, the number of doses in an inhaler (120 metered doses), and QLs for other nasal corticosteroids, the P&T Committee recommended QLs for fluticasone furoate.

   COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend QLs for fluticasone furoate in the TRRx for 1 inhaler device per 30 days and in the TMOP for 3 inhaler devices per 90 days.

6. DRUG CLASS REVIEW – NEWER ANTIHISTAMINES (NAs)

The P&T Committee evaluated the relative clinical effectiveness of the NA agents. The NA drug class includes the following agents (listed in order of FDA approval): loratadine (Claritin, generics), acrivastine/pseudoephedrine (Semprex-D), fexofenadine (Allegra, generics), cetirizine (Zyrtec), and desloratadine (Clarinex). The class also includes combinations of all of the single agent products with pseudoephedrine. Loratadine (Claritin, generics), cetirizine (Zyrtec), and desloratadine (Clarinex) are FDA-

indicated for the treatment of SAR, PAR, and chronic idiopathic urticaria (CIU). Fexofenadine is indicated for the treatment of SAR and CIU. Acrivastine/ pseudo-ephedrine is only indicated for the treatment of SAR.

All of the NAs are classified as inverse agonists of the H_1-receptor; they act to stabilize the H_1-receptor in its inactive conformation. Histamine is the main inflammatory mediator involved in the development of the majority of the symptoms seen in conditions treated with NAs.

As of June 2007, about three million MHS prescriptions for these agents were filled annually. The NA drug class was ranked #5 in terms of expenditures ($178 million) in FY 2006 . Across the MHS, cetirizine is the most commonly prescribed NA, followed by fexofenadine then loratadine. Usage of desloratadine and pseudoephedrine combination products is low and stable, while usage of acrivastine/pseudoephedrine is rare.

The brand-only agents are desloratadine, acrivastine/pseudoephedrine and cetirizine. Loratadine and fexofenadine are available as generics. Loratadine is only available over-the-counter (OTC). Brand-name cetirizine is expected to become available OTC by the end of 2007 and generic cetirizine OTC products are expected to be marketed in the first quarter of calendar year 2008. Marketing for the newly FDA approved product, levocetirizine (Xyzal), is expected to begin in September/October of 2007. Levocetirizine was not included in the current review; it will be addressed at a future meeting.

A. NAs – Relative Clinical Effectiveness

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

Allergic rhinitis (AR) affects an estimated 20 to 40 million people in the United States. Multiple symptoms are associated with AR, including sneezing, itching, nasal congestion and rhinorrhea. These symptoms arise from different allergens comprised of pollens, molds, dust mites, and animal dander. Although AR is a term collectively used to define these symptoms, there are two different classifications, SAR or intermittent AR, and PAR or persistent AR.

SAR or "hay fever" is the rapid and reproducible onset and offset of symptoms in association with pollen exposure. PAR is more difficult to diagnose, because the symptoms of PAR overlap with symptoms of chronic sinusitis, upper respiratory infections and vasomotor rhinitis. Patients with PAR are affected with symptoms at least 9 months of a year. It is estimated that about 20% of the patients with AR suffer

from SAR, 40% from PAR, and 40% with both SAR and PAR (PAR with seasonal exacerbations).

CIU is defined as the occurrence of daily, or almost daily, wheals and itching for at least 6 weeks, with no obvious cause. CIU has not been the subject of detailed epidemiological studies. Published figures for frequency are confounded by uncertainty of the diagnosis, since the term "chronic idiopathic urticaria" is often taken to encompass physical urticarias. It has been estimated that about 0.1% of the population suffers from CIU, and 50% of these patients have symptoms for more than a year. Up to 20% of patients with symptoms greater than one year go on to have symptoms for 20 years or more. CIU is a major affliction causing serious disability.

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 2007. 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 2002 Evidence and Technology Report/World Health Organization: Rhinitis; the European Dermatology Forum 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 SAR in adults that there was insufficient evidence to suggest clinically significant differences in efficacy between fexofenadine, loratadine and cetirizine or desloratadine and fexofenadine. There is insufficient evidence to compare acrivastine/ pseudoephedrine to the other agents in the treatment of SAR.

Five head-to-head comparative trials assessed the efficacy of various NAs 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 versus loratadine, cetirizine versus fexofenadine, or loratadine versus fexofenadine. The trials were too heterogeneous for meta-analysis. A recent head-to-head trial [Berger 2006] compared the efficacy of desloratadine and fexofenadine 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 5 mg, fexofenadine 180 mg once daily, or placebo. Mean daytime instantaneous TSS was significantly reduced from baseline by 28% with desloratadine, $p = 0.006$ and by 27% with fexofenadine, $p = 0.024$ 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, fexofenadine, and loratadine were more effective than placebo.

b) *Perennial Allergic Rhinitis*

Adults

The committee concluded that for the treatment of 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 versus cetirizine. The parent assessment results of this 4-week trial in 80 children, ages 2 to 6, showed cetirizine 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 and a placebo-controlled trial for loratadine showed the agents to be more effective than placebo in the treatment of PAR.

c) *Chronic Idiopathic Urticaria*

Adults

For CIU, the P&T Committee concluded that limited evidence suggests loratadine may be more effective than cetirizine and that cetirizine may be more effective than fexofenadine in adults.

Two fair quality head-to-head trials in adults with CIU were identified. One trial reported that loratadine 10 mg QD was more effective ($p<0.01$) in reducing TSS than cetirizine 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 10 mg QD was more effective (p-value not reported) than fexofenadine 180 mg QD in symptom-free patients [cetirizine 51.9% vs. Fexofenadine 4.4%].

Children

Only cetirizine 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 NAs 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 NAs generally cause less drowsiness and sedation than older antihistamines. Cetirizine has been shown to cause more sedation than fexofenadine and loratadine. Loratadine and desloratadine, while causing minimal sedation at recommended dosages, have shown to cause significant sedation at higher doses. Fexofenadine 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, fexofenadine and loratadine appear to have little potential to cause arrhythmias.

Pseudoephedrine-Containing Products – Combination products with pseudoephedrine can cause central nervous system 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 have alternative dosing recommendations for patients with moderate to severe renal failure. Acrivastine/pseudoephedrine is not recommended in patients with a creatinine clearance less than or equal to 48 mL per minute.
- *Hepatic Failure* – Cetirizine, desloratadine, and loratadine have alternative dosing recommendations for patients with hepatic failure. Because

fexofenadine is metabolized to a very small extent, dosing changes in patients with hepatic failure is not necessary. The manufacturers of acrivastine/ pseudoephedrine 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 and pseudoephedrine combination products, have indications for pediatric patients. Cetirizine, fexofenadine, and desloratadine have dosing recommendations for patients down to age 6 months. Loratadine has indications for patients to age 2 years and older.
- *Pregnancy and Lactation* – Acrivastine/pseudoephedrine, cetirizine and loratadine 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 (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, fexofenadine and the combination products containing pseudoephedrine are FDA pregnancy category C.

  The manufacturer states that loratadine 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 area under the curve of fexofenadine by ~43%. Acrivastine/ pseudoephedrine 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. 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, desloratadine and loratadine are more efficacious than placebo for the symptomatic relief of SAR, PAR and CIU. Fexofenadine is more efficacious than placebo for the

symptomatic relief of SAR, and CIU. Acrivastine/pseudoephedrine 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, fexofenadine, and loratadine, or desloratadine and fexofenadine. 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 may be more efficacious than loratadine with PAR.

d) For the treatment of CIU in adults, limited evidence based on two poor quality comparative trial suggests suggest that loratadine may be more efficacious than cetirizine for total symptom score reductions (but not response time), and cetirizine may be more efficacious than fexofenadine. In children, only cetirizine 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, cetirizine and acrivastine/pseudoephedrine are FDA pregnancy category B, while desloratadine, fexofenadine 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 one NA is sufficient for adequate clinical coverage, based on provider responses regarding prescribing practices and likely patient response.

i) Loratadine has been identified as a candidate drug for the DoD OTC Demonstration Program.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. NAs – Relative Cost Effectiveness

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

The 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, 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 and desloratadine/pseudoephedrine 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 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 P&T Committee concluded that:

1) Desloratadine and desloratadine/pseudoephedrine were not cost effective relative to other comparable agents in the newer antihistamine class.
2) The UF scenario that designated desloratadine and desloratadine/pseudoephedrine as non-formulary under the UF was the most cost effective scenario.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the cost effectiveness conclusion stated above.

C. NAs – UF Recommendations

COMMITTEE ACTION – 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 (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that:

1) Fexofenadine, fexofenadine/pseudoephedrine, cetirizine, cetirizine/pseudoephedrine, and acrivastine/pseudoephedrine should be maintained as formulary on the UF.
2) Desloratadine and desloratadine/pseudoephedrine should be classified as non-formulary under the UF.
3) Loratadine and loratadine/pseudoephedrine should be added to the UF for purposes of the TRICARE OTC Demonstration Program.
4) At such time as cetirizine and cetirizine/pseudoephedrine are made available over-the-counter, both products should be maintained on the UF for purposes of the TRICARE OTC Demonstration Program.
5) Desloratadine and desloratadine/pseudoephedrine should be reclassified as generic on the UF when the generic products are available and cost effective relative to similar agents in the newer antihistamine class.

D. NAs – MN Criteria

Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for desloratadine and desloratadine/pseudo-ephedrine:

1) The use of formulary alternatives is contraindicated.
2) The patient has experienced significant adverse effects from formulary alternatives.
3) Formulary alternatives have resulted in therapeutic failure.

The P&T Committee noted that acrivastine/pseudoephedrine, like other NA combination products with pseudoephedrine, is not indicated in children younger than 12 years of age.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

E. NAs – UF Implementation Period

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

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

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period in the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

F. NAs – BCF Review and Recommendations – The P&T Committee considered the BCF status of the NA agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that the current BCF listing for this class be maintained, requiring each MTF to carry at least one single-ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use. The P&T Committee noted that loratadine is the most cost effective NA in the MTFs, at approximately 1/12 the cost of the next most competitively priced agent.

7. DRUG CLASS REVIEW – LEUKOTRIENE MODIFIERS (LMs)

The P&T Committee evaluated the relative clinical effectiveness of the LMs. The LM class is comprised of two leukotriene receptor antagonists, montelukast (Singulair) and zafirlukast (Accolate); and one 5-lipoxygenase inhibitor, zileuton (Zyflo). A controlled release formulation of zileuton (Zyflo CR) has been approved by the FDA, but is not yet commercially available and was not included in the review.

Currently montelukast is the only BCF LM agent. None are available in a generic formulation. The LM drug class accounted for $101 million dollars in MHS expenditures in FY 2006, and is ranked #16 in terms of total expenditures during that time period. Over 97% of the utilization is for montelukast; from June 2006 to May 2007, there were over 300,000 montelukast utilizers in the MHS, over 3,000 zafirlukast utilizers and only 300 zileuton utilizers.

A. LMs – Relative Clinical Effectiveness

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

1) *FDA-approved indications*

a) Asthma

Montelukast, zafirlukast and zileuton 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 (ICSs) and long-acting beta agonists (LABAs).

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 April 2007, montelukast received approval for use in 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, ICSs 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 ICSs in reducing asthma exacerbations and improving forced expiratory volume in 1 second (FEV1) (RR 1.72; 95% CI 1.28-2.31).
- ICSs were also preferred in a Cochrane review (Ducharme, DiSilva) where patients taking LMs versus those taking ICSs 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 ICSs.
- 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) *Exercise Induced Bronchoconstriction*

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 April 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*

i) *Efficacy Measures* - Meta-analyses and clinical trials evaluating treatment for AR 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 NAs or nasal corticosteroids (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. NCS and 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 RCTs (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. 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 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 in Taiwanese children ranging in age from 2-6 years and 6-12 years with PAR. Cetirizine 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, fexofenadine, and desloratadine), two years (loratadine and mometasone), and 4 years (fluticasone propionate).

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 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 and zafirlukast 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 eight published cases linking zafirlukast with hepatic failure, two of which required transplant. Information received in response to a Freedom of Information Act request to 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 gastrointestinal 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 contra-indicated 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 ICS. 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 AR, and is specifically approved for both SAR and PAR. There are a few small clinical trials that evaluate zafirlukast in the treatment of AR, but they fail to consistently show efficacy. There is no data to support the use of zileuton in AR.

e) For AR, meta-analyses show that LMs are superior to placebo in clinically relevant AR 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. NCSs 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 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 (14 for, 0 opposed, 0 abstained, 3 absent) to accept the clinical effectiveness conclusions stated above.

B. LMs – Relative Cost Effectiveness

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

The 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, AR, and EIB. Moreover, the clinical review concluded that the LMs have a role in the management of asthma and are gaining acceptance in the treatment of EIB. However, the use of LMs in AR remains controversial. As a result, the pharmacoeconomic analysis first compared the LMs in a CMA 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 NAs and NCS in the treatment of AR. 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 was the least costly agent in the class. In comparison, montelukast 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.

In the treatment of AR, the cost effectiveness analysis showed that NA agents and NCS agents were the most cost effective options for the treatment of AR. The LMs were less effective than the NCS and provided comparable efficacy to the NAs. However, the LMs were significantly more costly per day of treatment than either the NAs or the NCS agents. Hence, pervasive use of LMs as first-line therapy in AR should be discouraged to optimize treatment of AR in the MHS.

Based on the results of the clinical review and the pharmacoeconomic evaluations, a BIA of a UF scenario that required a step therapy/PA program for use of LMs in allergic rhinitis (with no PA for other indications) was compared to a scenario with no PA 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 step therapy/PA policy for AR 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 was the least costly agent in the class; montelukast was more costly relative to zafirlukast 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 was not cost effective relative to the other products.
2) LMs are not cost effective in the treatment of AR relative to antihistamines and NCS agents and should not be considered as first-line therapy in the treatment of AR.

3) The Committee concluded that the UF scenario that placed zafirlukast and montelukast on formulary with a step therapy/PA required for use in AR was the scenario that resulted in the lowest expected expenditures in the LM class.

COMMITTEE ACTION: The DOD P&T Committee voted (14 for, 0 opposed, 1 abstained, and 2 absent) to accept the LM relative cost effectiveness analysis as presented by the PEC.

C. LMs – Step Therapy Consideration

For SAR and PAR (although montelukast is the only LM with this indication) the LMs are considered third-line agents after antihistamines and NCS. The Committee reviewed several programs utilized by civilian health plans to address use of the LMs for AR. Several plans allow unrestricted use of the LMs for asthma, but require PA for AR, primarily based on previous use of an antihistamine and/or NCS.

The Committee considered a step therapy/PA program where LMs would be allowed for MHS patients with asthma, but PA would be required for LM use in AR patients older than 5 years of age. Patients older than the age of 5 would require prior use of a NA and NCS, before LM use would be allowed.

COMMITTEE ACTION: Although the committee agreed that the LMs are not cost effective for AR, the Committee voted (6 for, 8 opposed, 1 abstained, and 2 absent) against enacting a step therapy/PA policy for use of LMs in the management of AR. Similar policies have recently been initiated with other drug classes in the MHS and the Committee felt that the most prudent course of action at this time was to delay enacting another step therapy/PA policy. Instead, the PEC will gather additional evidence about the effect of the other step therapy/PA policies recently implemented in the MHS while educating MTF providers to minimize the use of LMs for the management of AR. The PEC will also monitor utilization in the LM class. If the use of LMs for AR continues to proliferate, the Committee will review the class again to determine if further action is required.

D. LMs – UF Recommendations

COMMITTEE ACTION – 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 (14 for, 0 opposed, 1 abstained, and 2 absent) to recommend that zafirlukast and montelukast be maintained as formulary on the UF and that zileuton be classified as non-formulary under the UF.

E. LMs – MN Criteria

Based on the clinical evaluation for zileuton, and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for zileuton:

1) Use of formulary alternatives is contraindicated.

2) The patient has experienced significant adverse effects from formulary alternatives.

3) Formulary agents have resulted in therapeutic failure.

4) Patient previously responded to non-formulary agent and changing to a formulary agent would incur unacceptable risk.

With respect to criterion #4, the P&T Committee's primary concern was for asthma patients stabilized on zileuton, although this is likely to apply to very few patients considering the low usage of zileuton.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to approve the MN criteria outlined above.

F. LMs – UF Implementation Period

Approximately 145 beneficiaries (0.07% of those using agents in the LM class) will be affected by the UF decision. The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

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

COMMITTEE ACTION: The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 2 absent) an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

G. LMs – BCF Review and Recommendation

The P&T Committee considered the BCF status of the LM agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 1 opposed, 1 abstained, and 2 absent) to recommend that montelukast be retained on the BCF (specific formulations include tablets, chewable tablets, and oral granules).

8. DRUG CLASS REVIEW – GROWTH STIMULATING AGENTS (GSAs)

The P&T Committee evaluated the relative clinical effectiveness of the GSAs. This class is divided into two subclasses: growth hormone (GH) agents (somatropin products) and insulin-like growth factor-1 (IGF-1) agents (mecasermin). The GSA drug class accounted for about $23 million in MHS expenditures in FY 2006.

A. GSAs – Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the GSA agents currently marketed in the U.S. Information regarding the safety, effectiveness, and clinical outcomes of these drugs was considered. The clinical review included, but

was not limited to, the requirements stated in the UF Rule, 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

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

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 GH 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

GH 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 GH 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 +2 SD.
- *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

GH (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 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 GH 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 GHD, 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 GH 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 sShort Bowel Syndrome (SBS) in adults* – GH 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 Short Stature Homeobox gene (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)* – ISS, or non-GHD 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 GH 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 GH 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 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 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.

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	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

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.

- *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 June 2006 to July 2007 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 AST, alanine aminotransferase (ALT), and lactate dehydrogenase 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 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 thickening of soft tissues of the face and symptoms suggesting the occurrence of scoliosis due to a slipped 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 under the UF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions above.

B. GSAs – Relative Cost Effectiveness

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

The GSAs are divided into the IGF-1 and somatropin subclasses. The sole IGF-1 agent is mecasermin. 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, mecasermin, 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 GHD. As a result, 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 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 PA) 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 and two somatropin products (Zorbtive and Serostim) have a specific niche in therapy and are 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 P&T Committee voted (15 for, 0 opposed, 0 abstention, and 2 absent) to accept the GSA relative cost effectiveness analysis as presented by the PEC.

C. GSAs – UF Recommendations

COMMITTEE ACTION – 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 (13 for, 0 opposed, 1 abstained, 3 absent) to recommend that Tev-Tropin, Nutropin, Nutropin AQ, Norditropin, Nortropin Nordiflex, Serostim, Zorbtive, and mecasermin be maintained as formulary on the UF and that the Genotropin, Humatrope, Saizen and Omnitrope brands of somatropin be classified as non-formulary under the UF.

D. GSAs – MN Criteria

Based on the clinical evaluation and the conditions for establishing MN for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following general MN criteria for the somatropin products Genotropin, Humatrope, Saizen and Omnitrope:

1) Use of formulary alternatives is contraindicated.
2) The patient has experienced or is likely to experience significant adverse effects from formulary alternatives.

The P&T Committee noted that since the somatropin products all contain the same active ingredient, the most likely scenario under which criterion #2 would apply would be issues specific to specific formulations / preservatives (e.g., injection site reactions).

COMMITTEE ACTION: The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) to approve the MN criteria outlined above.

E. GSAs – UF 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.

MTFs will not be allowed to have the somatropin products Genotropin, Humatrope, Saizen and Omnitrope on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) MN is established. MTFs may (but are not required to) fill a prescription for a non-formulary Somatropin agent written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 3 absent) 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 the approval by the Director, TMA.

F. GSAs – PA Criteria

Currently, PA criteria apply to both GH (somatropin products) and mecasermin. The P&T Committee voted (13 for, 0 opposed, 1 abstained, 3 absent) that the following PA criteria should apply to GH and mecasermin. Changes from previous GH (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) GHD 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 Syndrome
   h) SHOX deficiency
2) *Mecasermin* – Coverage would be approved for the treatment of:
   a) Patients with severe primary IGFD defined by the following:
      i) Height standard deviation score $\leq$ -3
      ii) Basal IGF-1 standard deviation score $\leq$ -3
      iii) Normal or elevated GH levels

      OR
   b) Patients with GH gene deletion who have developed neutralizing antibodies to GH

   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 GHD, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroid

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend the PA criteria outlined above.

G. GSAs – Extended Core Formulary (ECF) Review and Recommendations

The P&T Committee considered the ECF status of the GSA agents. Based on the results of the clinical and economic evaluations presented, the P&T Committee voted (13 for, 0 opposed, 1 abstained, and 3 absent) to recommend that Norditropin / Norditropin Nordiflex be added to the ECF.

9. QUANTITY LIMITS

A. Rizatriptan (Maxalt) – The current QL for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) is 18 tablets per 30 days, or 36 tablets per 90 days. This QL was increased from 12 to 18 tablets per 30 days in May 2006 to accommodate a change in packaging (from 6 tablets per package to 9 tablets per package). Packaging for rizatriptan recently changed again, from 9 tablets per package to 12 tablets per package. QLs for triptans are based on the lack of safety evidence for treating more than 3-4 headaches per month with triptans, dosing recommendations, and package size.

***COMMITTEE ACTION*:** The Committee voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend changing the QL for rizatriptan tablets and orally disintegrating tablets to 12 tablets per 30 days, or 36 tablets per 90 days.

10. BCF STATUS OF ROSIGLITAZONE

Rosiglitazone (Avandia) – The PEC updated the P&T Committee on the two recent alerts issued by the FDA regarding rosiglitazone.

1) *FDA Alert #1: 8/14/2007:* Important revisions to the full prescribing information (labeling) highlighting increased risks of congestive heart failure associated with rosiglitazone. The updated information includes a new BOXED WARNING, and additional updated WARNINGS, PRECAUTIONS and CONTRAINDICATIONS to emphasize that rosiglitazone may cause or exacerbate heart failure, particularly in certain patient populations. *Source*: www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazone200707HCP.htm

2) FDA Alert #2: 5/21/2007**:** Ongoing FDA review of clinical data to assess a potential increased risk of ischemic cardiovascular events in patients taking rosiglitazone. FDA is aware of a potential safety issue related to rosiglitazone maleate. Safety data from a pooled analysis of controlled clinical trials have shown a significant increase in the risk of heart attack and heart-related deaths in patients taking rosiglitazone.

However, other published and unpublished data from long-term clinical trials of rosiglitazone provide contradictory evidence about the risk of ischemic cardiovascular events in patients taking rosiglitazone. FDA's review of all available data is ongoing. FDA has not confirmed the clinical significance of the reported increased risk of ischemic cardiovascular events in the context of other studies. Myocardial ischemic events are currently described in the WARNINGS section of the rosiglitazone label. FDA does not know whether the other approved medication in the same pharmacologic class or other oral drugs for treating type 2 diabetes have less, the same, or greater risks. Switching diabetic patients to other therapies also confers its own risks. For those reasons, FDA is providing this emerging information to prescribers so that they and their patients can make individualized treatment decisions. *Source:* www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazone200707HCP.htm

The P&T Committee discussed the advantages and disadvantages of removing rosiglitazone from the BCF. Ultimately, the P&T Committee determined that there was insufficient clinical evidence to justify removal of rosiglitazone from the BCF at this time. The PEC will update the P&T Committee as more information becomes available.

***COMMITTEE ACTION*:** The Committee voted (7 for, 6 opposed, 1 abstained, 3 absent) to not remove rosiglitazone from the BCF at this time.

11. BCF / ECF REVIEW

The P&T Committee agreed with the PEC's plan to systematically review drug classes represented on the BCF over the next few meetings with the goals of: 1) removing obsolete medications, 2) defining BCF listings more specifically, 3) reframing or revising BCF listings to be compatible with drug classes as defined or outlined by the P&T Committee, and 4) assessing the need for future review. The P&T Committee agreed that BCF/ECF listings will in the future be framed with greater specificity as drug classes are reviewed or reviewed.

The P&T Committee made initial recommendations for clarifying BCF listings in three drug classes or potential drug classes, including atypical antipsychotics (quetiapine and risperidone), osteoporosis agents (alendronate/vitamin D), and cough-cold medications (guaifenesin/pseudoephedrine). Details are outlined in Appendix C.

COMMITTEE ACTION: The P&T Committee recommended the following changes to BCF / ECF listings (see Appendix C for rationale):

Table 3: Recommended BCF / ECF Changes

Drug class or potential drug class	Current BCF / ECF listing	Recommendation	Vote			
			For	Opposed	Abstained	Absent
Atypical antipsychotics	BCF – "Quetiapine"	Clarify BCF listing to: "quetiapine tablets, immediate and extended release"	14	0	1	2
	BCF – "Risperidone oral; does not include orally disintegrating tablets (Risperdal Redi-tabs)"	Clarify BCF listing to: "Risperidone tablets and solution, does not include orally disintegrating tablets"	14	0	1	2
Osteoporosis agents	BCF – "Alendronate 70 mg / vitamin D 2800 IU (Fosamax Plus D)"	Clarify BCF listing to specify new product with higher strength of vitamin D – "Alendronate 70 mg/vitamin D 5600 IU tablets"	14	0	1	2
Cough-cold medications	BCF – "Guaifenesin 600 / PSE 120 mg ER oral"	Remove from BCF	14	0	1	2

12. CLASS OVERVIEWS

Class overviews for the osteoporosis agents were presented to the P&T Committee. The P&T Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review and developing the appropriate cost effectiveness models. The clinical and economic analyses of these classes will be completed during the February 2008 meeting; no action is necessary.

13. ADJOURNMENT

The second day of the meeting adjourned at 1700 hours on 15 August 2007. The next meeting will be 14-15 November 2007.

Patricia Buss

Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

Appendix A – Implementation Status of UF Class Review Recommendations / Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Aug 07	Newer Antihistamines	▪ desloratadine (Clarinex) ▪ desloratadine/pseudoephedrine (Clarinex D)	BCF	▪ MTFs required to carry at least one single ingredient agent from the newer antihistamine class (loratadine, cetirizine, or fexofenadine) on their local formulary, including at least one dosage form suitable for pediatric use	Pending approval	Pending approval
Aug 07	Leukotriene Modifiers	▪ Zileuton (Zyflo)	BCF	▪ montelukast (Singulair)	Pending approval	Pending approval
Aug 07	Growth Stimulating Agents	▪ somatropin (Genotropin, Genotropin Miniquick) ▪ somatropin (Humatrope) ▪ somatropin (Omnitrope) ▪ somatropin (Saizen)	ECF	▪ somatropin (Norditropin)	Pending approval	Pending approval
Nov 05 (updated for new drug Aug 07)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone propionate (Flonase)	19 Jan 06	19 Apr 06 (90 days)
		Recommended Aug 07 ▪ fluticasone furoate (Veramyst)			Pending approval	Pending approval
May 07 re-review (Feb 05 original)	PPIs	▪ lansoprazole (Prevacid) ▪ omeprazole/sodium bicarbonate (Zegerid) ▪ pantoprazole (Protonix) ▪ rabeprazole (Aciphex)	BCF	▪ generic omeprazole 10 mg and 20 mg (excludes Prilosec 40 mg) ▪ esomeprazole (Nexium)	24 July 07	24 Oct 07 (90 days)
May 07	Antilipidemic Agents II	▪ fenofibrate nanocrystallized (Tricor) ▪ fenofibrate micronized (Antara) ▪ omega-3 fatty acids (Omacor) ▪ colesevelam (Welchol)	BCF	▪ gemfibrozil ▪ fenofibrate IDD-P (Triglide)	24 July 07	21 Nov 07 (120 days)
May 07 re-review (Feb 05 original)	ARBs	▪ eprosartan (Teveten) ▪ eprosartan HCTZ (Teveten HCT) ▪ irbesartan (Avapro) ▪ irbesartan HCTZ (Avalide) ▪ olmesartan (Benicar) ▪ olmesartan HCTZ (Benicar HCT) ▪ valsartan (Diovan) ▪ valsartan HCTZ (Diovan HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan HCTZ (Micardis HCT)	24 July 07	21 Nov 07 (120 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
May 07	5-Alpha Reductase Inhibitors	▪ dutasteride (Avodart)	BCF	▪ finasteride	24 July 07	24 Oct 07 (90 days)
Feb 07	Newer Sedative Hypnotics	▪ zolpidem ER (Ambien CR) ▪ zaleplon (Sonata) ▪ ramelteon (Rozerem)	BCF	▪ zolpidem IR (Ambien)	02 May 07	01 Aug 07 (90 days)
Feb 07	Narcotic Analgesics	▪ tramadol ER (Ultram ER)	BCF	▪ morphine sulfate IR 15 mg, 30 mg ▪ morphine sulfate 12-hour ER (MS Contin or equivalent) 15, 30, 60 mg ▪ oxycodone/APAP 5/325 mg ▪ hydrocodone/APAP 5/500 mg ▪ codeine/APAP 30/300 mg ▪ codeine/APAP elixir 12/120 mg/5 mL ▪ tramadol IR	02 May 07	01 Aug 07 (90 days)
Feb 07	Ophthalmic Glaucoma Agents	▪ travoprost (Travatan, Travatan Z) ▪ timolol maleate for once daily dosing (Istalol) ▪ timolol hemihydrate (Betimol) ▪ brinzolamide (Azopt)	BCF	▪ latanoprost (Xalatan) ▪ brimonidine (Alphagan P); excludes 0.1% ▪ timolol maleate ▪ timolol maleate gel-forming solution ▪ pilocarpine	02 May 07	01 Aug 07 (90 days)
Nov 06	Older Sedative Hypnotics	-	BCF	▪ temazepam 15 and 30 mg	17 Jan 07	NA
Nov 06	ADHD Agents	▪ dexmethylphenidate IR (Focalin) ▪ dexmethylphenidate SODAS (Focalin XR) ▪ methylphenidate transdermal system (Daytrana)	BCF	▪ methylphenidate OROS (Concerta) ▪ mixed amphetamine salts ER (Adderall XR) ▪ methylphenidate IR (Ritalin)	17 Jan 07	18 Apr 07 (90 days)
Aug 06	TZDs	-	BCF	▪ rosiglitazone (Avandia) ▪ rosiglitazone / metformin (Avandamet)	23 Oct 06	NA
Aug 06	H2 Antagonists / GI protectants	-	BCF	▪ ranitidine (Zantac) – excludes gelcaps and effervescent tablets	23 Oct 06	NA
Aug 06	Antilipidemic Agents I	▪ rosuvastatin (Crestor) ▪ atorvastatin / amlodipine (Caduet)	BCF	▪ simvastatin (Zocor) ▪ pravastatin ▪ simvastatin / ezetimibe (Vytorin) ▪ niacin extended release (Niaspan)	23 Oct 06	1 Feb 07 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
May 06 (updated for new drugs Nov 06)	Contraceptives	▪ EE 30 mcg / levonorgestrel 0.15 mg in special packaging for extended use (Seasonale) ▪ EE 25 mcg / norethindrone 0.4 mg (Ovcon 35) ▪ EE 50 mcg / norethindrone 1 mg (Ovcon 50) ▪ EE 20/30/35 mcg / norethindrone 1 mg (Estrostep Fe)	BCF	▪ EE 20 mcg / 3 mg □rospirenone (Yaz) ▪ EE 20 mcg / 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent) ▪ EE 30 mcg / 3 mg drospirenone (Yasmin) ▪ EE 30 mcg / 0.15 mg levonorgestrel (Nordette or equivalent / excludes Seasonale) ▪ EE 35 mcg / 1 mg norethindrone (Ortho-Novum 1/35 or equivalent) ▪ EE 35 mcg / 0.25 mg norgestimate (Ortho-Cyclen or equivalent) ▪ EE 25 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo) ▪ EE 35 mcg / 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent) ▪ 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)	26 Jul 06	24 Jan 07 (180 days)
		Recommended Nov 06 ▪ EE 30/10 mcg / 0.15 mg levonorgestrel in special packaging for extended use (Seasonique) ▪ EE 20 mcg / 1 mg norethindrone (Loestrin 24 Fe)			17 Jan 07	18 Mar 07 (60 days)
May 06	Antiemetics	▪ dolasetron (Anzemet)	BCF	▪ promethazine (oral and rectal)	26 Jul 06	27 Sep 06 (60 days)
Feb 06	OABs	▪ tolterodine IR (Detrol) ▪ oxybutynin patch (Oxytrol) ▪ trospium (Sanctura)	BCF	▪ oxybutynin IR (Ditropan tabs/soln) ▪ tolterodine SR (Detrol LA)	26 Apr 06	26 Jul 06 (90 days)
Feb 06	Misc Antihypertensive Agents	▪ felodipine/enalapril (Lexxel) ▪ verapamil/trandolapril (Tarka)	BCF	▪ amlodipine/benazepril (Lotrel) ▪ hydralazine ▪ clonidine tablets	26 Apr 06	26 Jul 06 (90 days)
Feb 06	GABA-analogs	▪ pregabalin (Lyrica)	BCF	▪ gabapentin	26 Apr 06	28 Jun 06 (60 days)
Nov 05	Alzheimer's Drugs	▪ tacrine (Cognex)	ECF	▪ donepezil (Aricept)	19 Jan 06	19 Apr 06 (90 days)
Nov 05 (updated Aug 07)	Nasal Corticosteroids	▪ beclomethasone dipropionate (Beconase AQ, Vancenase AQ) ▪ budesonide (Rhinocort Aqua) ▪ triamcinolone (Nasacort AQ)	BCF	▪ fluticasone (Flonase)	19 Jan 06	19 Apr 06 (90 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
Nov 05	Macrolide/ Ketolide Antibiotics	▪ azithromycin 2 gm (Zmax) ▪ telithromycin (Ketek)	BCF	▪ azithromycin (Z-Pak) ▪ erythromycin salts and bases	19 Jan 06	22 Mar 06 (60 days)
Nov 05	Antidepressants I	▪ paroxetine HCl CR (Paxil) ▪ fluoxetine 90 mg for weekly administration (Prozac Weekly) ▪ fluoxetine in special packaging for PMDD (Sarafem) ▪ escitalopram (Lexapro) ▪ duloxetine (Cymbalta) ▪ bupropion extended release (Wellbutrin XL)	BCF	▪ citalopram ▪ fluoxetine (excluding weekly regimen and special packaging for PMDD) ▪ sertraline (Zoloft) ▪ trazodone ▪ bupropion sustained release	19 Jan 06	19 Jul 06 (180 days)
Aug 05	Alpha Blockers for BPH	▪ tamsulosin (Flomax)	BCF	▪ terazosin ▪ alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120 days)
Aug 05	CCBs	▪ amlodipine (Norvasc) ▪ isradipine IR (Dynacirc) ▪ isradipine ER (Dynacirc CR) ▪ nicardipine IR (Cardene, generics) ▪ nicardipine SR (Cardene SR) ▪ verapamil ER (Verelan) ▪ verapamil ER for bedtime dosing (Verelan PM, Covera HS) ▪ diltiazem ER for bedtime dosing (Cardizem LA)	BCF	▪ nifedipine ER (Adalat CC) ▪ verapamil SR ▪ diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150 days)
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	▪ moexipril (Univasc), ▪ moexipril / HCTZ (Uniretic) ▪ perindopril (Aceon) ▪ quinapril (Accupril) ▪ quinapril / HCTZ (Accuretic) ▪ ramipril (Altace)	BCF	▪ captopril ▪ lisinopril ▪ lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120 days)
May 05	PDE-5 Inhibitors	▪ sildenafil (Viagra) ▪ tadalafil (Cialis)	ECF	▪ vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90 days)
May 05 (updated for new drugs Nov 06)	Topical Antifungals*	▪ econazole ▪ ciclopirox ▪ oxiconazole (Oxistat) ▪ sertaconazole (Ertaczo) ▪ sulconazole (Exelderm)	BCF	▪ nystatin ▪ clotrimazole	14 Jul 05	17 Aug 05 (30 days)
		Recommended Nov 06: ▪ 0.25% miconazole / 15% zinc oxide / 81.35% white petrolatum ointment (Vusion)			17 Jan 07	18 Mar 07 (60 days)

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF Class	BCF/ECF Medications	Decision Date (DoD P&T minutes signed, effective date for BCF/ECF medications)	Effective Date for Non-Formulary Medications (Implementation period)
May 05	MS-DMDs	-	ECF	▪ interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-
Feb 05	ARBs – see May 07 for re-review	▪ eprosartan (Teveten) ▪ eprosartan/HCTZ (Teveten HCT)	BCF	▪ telmisartan (Micardis) ▪ telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90 days)
Feb 05	PPIs – see May 07 for re-review	▪ esomeprazole (Nexium)	BCF	▪ omeprazole ▪ rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90 days)

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = Uniform Formulary

ER = extended release; IR = immediate release; SR = sustained release; IDD-P = insoluble drug delivery-microParticle

ADHD = Attention Deficit Hyperactivity Disorder; ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hyperplasia; CCBs = Calcium Channel Blockers; EE = ethinyl estradiol; GI = gastrointestinal; GABA = gamma-aminobutyric acid; H2 = Histamine-2 receptor; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; OABs = Overactive Bladder Medications; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors; TZDs = thiazolidinediones

*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Newly Approved Drugs. August 2007 DoD P&T Committee Meeting

Medication (Brand name; manufacturer) mechanism of action	FDA Approval Date & FDA-Approved Indications	Committee Recommendation
Budesonide / formoterol inhaler (Symbicort, Astra Zeneca) corticosteroid with long-acting beta agonist	Jul 06 (launched Jul 07) ▪ Long term maintenance treatment of asthma in patients 12 years of age and older.	No UF recommendation at this meeting. Consideration of UF status deferred until inhalational asthma drugs are reviewed; UF review anticipated within the next 12 months. Quantity limits recommended: ▪ TMOP o #3 inhalers per 90 days ▪ Retail Network o #1 inhaler per 30 days
Rotigotine topical patch (Neupro; Schwarz Biosciences) non-ergoline D3/D2/D1 dopamine agonist	May 07 (launched Jul 07) ▪ Treatment of signs and symptoms of early stage idiopathic Parkinson's disease	No UF recommendation at this meeting. Consideration of UF status deferred until Parkinson's drugs are reviewed; UF review not anticipated in the next 12 months.
Estradiol 0.1% gel (Divigel; Upsher-Smith) estrogen for hormone replacement	Jun 07 (launched Aug 07) ▪ Treatment of moderate to severe hot flashes associated with menopause.	No UF recommendation at this meeting. Consideration of UF status deferred until hormone replacement therapies are reviewed; UF review not anticipated in the next 12 months.
Estradiol 0.06% gel (Elestrin; Bradley Pharmaceuticals) estrogen for hormone replacement	Dec 06 (launched Jun 07) Treatment of moderate to severe vasomotor symptoms associated with menopause.	No UF recommendation at this meeting. Consideration of UF status deferred until hormone replacement therapies are reviewed; UF review not anticipated in the next 12 months.

Appendix C – Basic / Extended Core Formulary (BCF/ECF) Review

Drug Class or Potential Drug Class	BCF / ECF listing	Recommendation/ Rationale
Atypical antipsychotics	BCF – "Quetiapine"	• ER formulation (Seroquel XR) approved May 07; manufacturer willing to supply at no higher cost than IR quetiapine; no generics anticipated for some time (~2011). • Available in IR tabs (6 strengths), ER tabs (4 strengths). • Recommendation: • Clarify BCF listing to "Quetiapine tablets, immediate and extended release."
	BCF – "Risperidone oral; does not include orally disintegrating tablets (Risperdal Redi-tabs)"	• Oral dosage forms available: solution, tablets (6 strengths), rapidly disintegrating tablets (5 strengths) • Several manufacturers have tentative ANDAs listed for risperidone solution and tablets; patent expires Dec 2007, pediatric exclusivity ends Jun 2008. Unclear when orally disintegrating tablets will become generically available. • Recommendation: • Clarify BCF listing to "Risperidone tablets and solution, does not include orally disintegrating tablets."
Osteoporosis agents	BCF – "Alendronate 70 mg / vitamin D 2800 IU (Fosamax Plus D)"	• Alendronate 70 mg / vitamin D 5600 IU approved Apr 07; manufacturer willing to extend current pricing agreement for Fosamax Plus D; class to be reviewed soon. • 5600 IU combination recommended for "most" osteoporotic patients. • Recommendation • Clarify BCF listing to specify product with higher strength of vitamin D – "Alendronate 70 mg/vitamin D 5600 IU tablets."
Cough-cold medications	BCF – "Guaifenesin 600 / PSE 120 mg ER oral" (Entex LA generic)	• Guaifenesin containing timed release prescription products targeted for regulatory action by FDA in May 2007. • Companies expected to stop manufacturing unapproved products containing timed-release guaifenesin within 90 days and must cease shipping them in interstate commerce within 180 days. • Only guaifenesin products expected to remain on market are Adams' Labs over-the-counter products (e.g., Mucinex D). • Recommendation: • Remove listing from BCF.

Appendix D – Table of Abbreviations

ACE	angiotensin converting enzyme
ACR	American College of Rheumatology
ALT	alanine aminotransferase
APR	automated profile review
ARB	angiotensin receptor blocker
AR	allergic rhinitis
ARIA	Allergic Rhinitis and Its Impact on Asthma
AST	aspartate aminotransferase
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BID	twice daily
BP	blood pressure
CEA	cost effectiveness analysis
CFR	Code of Federal Regulations
CI	confidence interval
CIU	chronic idiopathic urticaria
CMA	cost minimization analysis
CRI	chronic renal insufficiency
CYP	cytochrome (P450)
DERP	Drug Effectiveness Review Project (state of Oregon)
DoD	Department of Defense
EIB	exercise-induced bronchoconstriction
ER	extended release
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FY	fiscal year
GAD	generalized anxiety disorder
GH	growth hormone
GHD	growth hormone deficiency
GI	gastrointestinal
GSA	Growth Stimulating Agent (drug class)
HCTZ	hydrochlorothiazide
IGFD	insulin-like growth factor deficiency
ICS	inhaled corticosteroids
ISS	idiopathic short stature
LABA	long-acting beta agonists
LDL	low density lipoprotein
LFT	liver function test
LM	Leukotriene Modifier (drug class)
MAOI	monoamine oxidase inhibitor
MHS	Military Health System
MN	medical necessity
MTF	military treatment facility
NA	Newer Antihistamine (drug class)
NCS	nasal corticosteroids
NHLBI NAEPP	National Heart, Lung and Blood Institute National Asthma Education Prevention Program
OTC	over-the-counter
PA	prior authorization
PAR	perennial allergic rhinitis
P&T	Pharmacy and Therapeutics
PEC	Pharmacoeconomic Center

Appendix D – Table of Abbreviations (continued)

QD	once daily
QID	four times daily
RAAs	renin-angiotensin antihypertensive (drug class)
RCT	randomized controlled trial
RQLQ	rhinoconjunctivitis-specific quality of life
RR	relative risk
rTNSS	reflective Total Nasal Symptom Score
SAR	seasonal allergic rhinitis
SBS	Short bowel syndrome
SED-1	Sedative Hypnotic-1 (drug class)
SGA	small for gestational age
SHOX	Short Stature Homeobox gene
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TID	three times daily
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TNSS	Total Nasal Symptom Score
TRRx	TRICARE Retail Pharmacy Network
TS	Turner Syndrome
UF	Uniform Formulary
ULN	upper limit of normal

11 October 2007

Executive Summary

UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL COMMENTS
September 2007

The Uniform Formulary (UF) Beneficiary Advisory Panel (BAP) commented on the recommendations from the DoD Pharmacy & Therapeutics (P&T) Committee August 2007 meeting.

Comment from the Chairman of the Panel. Mr. Washington thanked Dr. Casscells for the recent changes made to the notification process that has resulted in beneficiaries being notified on time of the changes being made to the formulary status of drugs.

1. **Newer Antihistamine (NA) Drug Class:** The P&T Committee recommended the following:
    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 Over-the-Counter (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.
    5) 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.

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 the approval by the Director, TRICARE Management Activity (TMA).

Summary of Panel Vote/Comments:

- The Panel voted 11 Concur, 0 Non-Concur regarding the recommendations for formulary and non-formulary agents.
- The Panel voted 10 Concur, 1 Non-Concur regarding the recommended implementation period of 90 days.

- The Panel expressed the need to continue with targeted mailing to beneficiaries affected by moving drugs to the non-formulary tier.

Director, TMA:

☑ These comments were taken under consideration prior to my final decision.

2. **Leukotriene Modifiers (LM):** The P&T Committee recommended that zafirlukast (Accolate) and montelukast (Singulair) be maintained as formulary on the UF and that zileuton (Zyflo) be classified as non-formulary.

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.

Summary of Panel Vote/Comments:

- The Panel voted 11 Concur, 0 Non-Concur regarding the recommendations for formulary and non-formulary agents.
- The Panel voted 8 Concur, 3 Non-Concur regarding the recommended implementation period of 90 days.

Director, TMA:

☑ These comments were taken under consideration prior to my final decision.

3. **Growth Stimulating Agents (GSA):** The P&T Committee recommended 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.

The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

Summary of Panel Vote/Comments:

- The Panel voted 9 Concur, 2 Non-Concur regarding the recommendations for formulary and non-formulary agents.
- The Panel voted 0 Concur, 11 Non-Concur regarding the recommended implementation period of 60 days.

- The Panel recommended an implementation date of 90 to 120 days.

Director, TMA:

☑ These comments were taken under consideration prior to my final decision.

4. **Recently Approved Agents in Classes Reviewed for the Uniform Formulary:**

Tekturna: The P&T Committee recommended that aliskiren (Tekturna) be classified as formulary on the UF.

Veramyst: The P&T Committee recommended that fluticasone furoate (Veramyst) be classified as non-formulary.

The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

Summary of Panel Vote/Comments:

- **Veramyst:** The Panel voted 11 Concur, 0 Non-Concur regarding the recommendation of non-formulary status for Veramyst.
- The Panel voted 3 Concur, 8 Non-Concur regarding the recommended implementation period of 60 days.
- Two Panel members stated they would prefer a 30-day implementation period; one said 120 days.
- The Panel commented that its preference would be to prevent more people from getting on this product, which is going non-formulary, during the implementation period.

Director, TMA:

☑ These comments were taken under consideration prior to my final decision.