DOD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

INFORMATION FOR THE UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL

I. Uniform Formulary Review Process

Under 10 U.S.C. § 1074g, as implemented by 32 C.F.R. 199.21, the DoD P&T Committee is responsible for developing the Uniform Formulary (UF). Recommendations to the Director, TMA, on formulary status, pre-authorizations, and the effective date for a drug's change from formulary to non-formulary status receive comments from the Beneficiary Advisory Panel (BAP), which must be reviewed by the Director before making a final decision.

II. UNIFORM FORMULARY CLASS REVIEWS — BASAL INSULINS

P&T Comments

A. Basal Insulins — Relative Clinical Effectiveness

The P&T Committee evaluated the clinical effectiveness of the long-acting basal insulin analogues (e.g., basal insulins) for the treatment of diabetes mellitus (DM). Insulin detemir (Levemir) and insulin glargine (Lantus) were FDA approved on June 16, 2005, and April 30, 2000, respectively. Insulin detemir and insulin glargine are available in both vials and pre-filled pen devices (Lantus SoloStar and Levemir FlexPen). Insulin glargine vials are currently on the BCF. Information regarding the safety, effectiveness, and clinical outcomes of the long-acting basal insulin analogues was considered. Neutral Protamine Hagedon (NPH), an intermediate-acting basal insulin was not included in the review; it remains a BCF drug. The clinical review included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1). MHS expenditures for the long-acting basal insulin analogues exceeded $4M per month at the retail, mail order, and MTF POS from January 2008 to December 2009.

Relative Clinical Effectiveness Conclusion —The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions regarding the basal insulin drug class:

1. With regard to efficacy, the following conclusions were made:
    a) In pivotal trials, both Levemir and Lantus produced similar reductions in glycosylated hemoglobin A1c (HbA1c) when compared to NPH insulin, in subjects with type-1 or type-2 DM.

b) In head-to-head studies, there was a statistically significant difference in the reduction in fasting plasma glucose (FPG) values between Levemir and Lantus in subjects with type-1 DM; larger reductions in FPG were seen with Lantus. This difference was not observed in subjects with type-2 DM. The clinical significance of this finding is unknown.

c) In head-to-head studies, the total Levemir dose required to achieve goal HbA1C levels (<7%) was larger than the dose of Lantus used to achieve goal HbA1C levels in subjects with type-1 DM. Levemir was dosed twice-daily more often than once-daily in subjects with type-2 DM. The clinical significance of these findings is unknown.

2. With regard to safety and tolerability, the following conclusions were made:

   a) Existing evidence does not support clinically relevant differences concerning hypoglycemia or weight gain between Levemir and Lantus. In subjects with type-2 DM, once-daily dosing of insulin detemir produced less weight gain (absolute difference 1.4 kg) when compared to twice-daily dosing of Levemir. In subjects with type-2 DM, Lantus was less likely to cause weight gain when compared to Levemir (absolute difference 0.9 kg).

   b) There is insufficient evidence to determine if there are clinically relevant differences between Levemir and Lantus with respect to cancer risk. Observational studies raised concerns of an association between the use of Lantus and cancer incidence. These studies had inconsistent findings and many study design flaws. FDA is uncertain of this association.

3. With regard to other factors

   a) There are no clinically relevant differences between the pen devices for insulin glargine (Lantus SoloStar) and insulin detemir (Levemir FlexPen) in terms of refrigeration requirements and expiration date after opening.

   b) Patient preference studies report that patients overall prefer using insulin pen devices compared to insulin vials. Although one study reported patients preferred the insulin glargine pen device (Lantus SoloStar) compared to the insulin detemir pen device (Levemir FlexPen); other studies have shown no patient preferences among various pen devices.

   c) A request for input from MTF providers revealed that the majority of responders ranked Lantus as their first preference for a basal insulin, followed by Levemir as the second choice, primarily due to perceived differences in efficacy and availability on the local formulary. The majority of responders stated that availability of one basal insulin on the local formulary was adequate to meet their prescribing needs

B. BASAL INSULINS — Relative Cost-Effectiveness

Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following:

a) Cost minimization analysis (CMA) results of the basal insulin agents revealed that glargine vials (Lantus) and pen devices (Lantus SoloStar) were the most cost-effective basal insulin products based on cost per ml of treatment. Cost per ml of treatment was calculated using average quarterly consumption rates for glargine vials (Lantus) and pen devices (Lantus SoloStar) and detemir vials (Levemir) and pen devices (Levemir FlexPen).

b) The potential impact of scenarios with selected basal insulin agents designated formulary or non-formulary on the UF was evaluated using budget impact analysis (BIA). Scenarios evaluating the impact of designating basal insulins on the BCF were also considered. Results from the BIA for the basal insulins revealed that placing glargine vials (Lantus) and pen devices (Lantus SoloStar) on the BCF and UF, with detemir vials (Levemir) on the UF, and designating detemir pen devices (Levemir FlexPen) NF was the most cost-effective scenario overall.

c) BIA results showed that detemir vials (Levemir) and detemir pen devices (Levemir FlexPen) were more costly than glargine vials (Lantus) and glargine pen devices (Lantus SoloStar) in all scenarios that do not require automated prior authorization. Glargine vials (Lantus) and glargine pen devices (Lantus SoloStar) were more costly than detemir vials (Levemir) and detemir pen devices (Levemir FlexPen) in one scenario involving an automated prior authorization. However, The P&T Committee decided that an automated prior authorization was not clinically appropriate for the basal insulin class.

C. BASAL INSULINS — Uniform Formulary 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 (15 for, 0 opposed, 1 abstained, 0 absent) to recommend the following:

a) Insulin glargine vials (Lantus), insulin glargine pen devices (Lantus SoloStar) and insulin detemir vials (Levemir) remain classified as formulary on the UF.

b) Insulin detemir pen devices (Levemir FlexPen) be designated as non-formulary on the UF.

D. BASAL INSULINS — Uniform Formulary Implementation Plan

The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TRICARE Pharmacy Benefits Program (TPHARM), and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

III. UNIFORM FORMULARY CLASS REVIEWS — BASAL INSULINS

BAP Comments

A. BASAL INSULINS— Uniform Formulary Recommendation

In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the basal insulins, the P&T Committee voted to recommend insulin glargine vials (Lantus), insulin glargine pen devices (Lantus SoloStar) and insulin detemir vials (Levemir) remain classified as formulary on the UF, and insulin detemir pen devices (Levemir FlexPen) be designated as non-formulary under the UF, based on cost effectiveness.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. BASAL INSULINS — Uniform Formulary Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

IV. UNIFORM FORMULARY CLASS REVIEWS — ANTIHEMOPHILIC AGENTS – Factor VIII and Factor IX concentrates

P&T Comments

A. Antihemophilic Agents – Factor VIII and Factor IX concentrates — Relative Clinical Effectiveness

The P&T Committee evaluated the clinical effectiveness of the antihemophilic agents. The class was divided into the factor VIII and factor IX concentrates; and the factor VIII/von Willebrand (vWF) factor complexes; human prothrombin concentrate complexes; and inhibitor bypassing products. The antihemophilic agents have not previously been reviewed for UF placement; they are an extended core formulary (ECF) drug class.

Purified factor VIII drugs are used to treat hemophilia A and are manufactured from two sources: plasma-derived (human) and recombinant. The human factor VIII products include Hemofil M, Koate DVI, and Monoclate P. The recombinant factor VIII products include Advate, Helixate FS, Kogenate FS, Recombinate, Refacto, and Xyntha. Although Refacto is still available for use, it was no longer manufactured at the time of this review, and therefore, not considered for ECF status.

Purified factor IX drugs used to treat hemophilia B are likewise derived from two sources: human and recombinant. The human factor IX concentrates include AlphaNine SD and MonoNine. There is only one recombinant factor IX product: BeneFIX. Information was considered regarding the safety, effectiveness, and clinical outcomes of the factor VIII and factor IX subclasses of the antihemophilic agents. Only uses that pertain to the outpatient pharmacy benefit were considered. The clinical review included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Military Health System (MHS) expenditures for the all antihemophilic agents (factor VIII, factor IX, factor VIII/vWF complexes, prothrombin complex concentrates (PCCs), and inhibitor bypassing products) exceeded $39M from December 2008 to November 2009 predominantly at the retail point of service (POS). There are approximately 190 unique utilizers in the MHS. There were no MHS utilizers of Monoclate P or AlphaNine SD during this time period.

Relative Clinical Effectiveness Conclusion — The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions regarding purified factor VIII and IX concentrates:

1. With regard to efficacy, the following conclusions were made:

   a) There are no head-to-head comparative trials evaluating the factor VIII or factor IX products. Efficacy studies were limited to open-label clinical trials; there are no published comparator and pharmacokinetic studies.

   b) Many products obtained FDA approval based on pharmacokinetic demonstration of bioequivalence to previously approved (e.g., earlier generation) products following improvements in production and viral depletion or inactivation methods.

   c) There is no evidence to conclude that there are clinically relevant differences in efficacy between the respective factor VIII and factor IX concentrates.

2. With regard to safety and tolerability, the P&T Committee agreed that, although the overall risk is small, there is a lower risk of viral transmission with recombinant products than with plasma-derived products. There is insufficient evidence to conclude there are clinically relevant differences in safety between the recombinant factor VIII products.

3. With regard to other factors, the following conclusions were made:

   a) National professional group guidelines and national hemophilia patient advocacy groups caution against switching between products once a patient is stabilized, due to potentially detrimental outcomes, including development of immunogenicity.

   b) There are differences among the factor VIII and factor IX products with regard to viral deactivation/depletion methods, storage and refrigeration requirements, vial sizes available, reconstitution and administration kits, patient support programs, and stabilizers/cell culture media used in recombinant products

B. Antihemophilic Agents – Factor VIII and Factor IX concentrates — Relative Cost-Effectiveness

Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following:

a) CMA results for the antihemophilic factor VIII agents revealed that Xyntha was the most cost-effective recombinant factor VIII product based on cost per unit of treatment. Cost per unit of treatment was calculated using the average drug price per unit rates for Xyntha and the following antihemophilic factor VIII products: Advate, Helixate FS, Hemofil M, Koate DVI, Kogenate FS, Recombinate, and Refacto. The cost of Monoclate P could not be evaluated due to no MHS utilization.

b) CMA results for the antihemophilic factor IX agents revealed that BeneFIX was the most cost-effective antihemophilic recombinant factor IX product based on the cost per unit of treatment. Cost per unit of treatment was calculated using average drug price per unit rates for the recombinant factor IX products AlphaNine SD and MonoNine.

C. Antihemophilic Agents – Factor VIII and Factor IX concentrates — Uniform Formulary 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 (13 for, 0 opposed, 2 abstained, 1 absent):

a) The factor VIII products Koate DVI, Kogenate FS, Refacto, and Xyntha, and the factor IX products Alphanine SD and BeneFIX remain classified as formulary on the UF.

b) The factor VIII products Advate, Hemofil M, Helixate FS, Monoclate P, and Recombinate, and the factor IX product MonoNine be designated as non-formulary under the UF.

c) All factor VIII and factor IX products recommended for inclusion on the UF had existing Uniform Formulary Voluntary Agreement for Retail Refunds (UF VARR) submissions at or below the Federal Ceiling Price (FCP).

D. Antihemophilic Agents – Factor VIII and Factor IX concentrates — Uniform Formulary Implementation Plan

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 180-day implementation period in the TRICARE Pharmacy Benefits

Program (TPHARM), and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

V. UNIFORM FORMULARY CLASS REVIEWS — Antihemophilic Agents – Factor VIII and Factor IX concentrates

BAP Comments

A. Antihemophilic Agents – Factor VIII and Factor IX concentrates — Uniform Formulary 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:

a) The factor VIII products Koate DVI, Kogenate FS, Refacto, and Xyntha, and the factor IX products Alphanine SD and BeneFIX remain classified as formulary on the UF.

b) The factor VIII products Advate, Hemofil M, Helixate FS, Monoclate P, and Recombinate, and the factor IX product MonoNine be designated as non-formulary under the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Antihemophilic Agents – Factor VIII and Factor IX concentrates — Uniform Formulary Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday one week after the minutes are signed, following a 180-day implementation period in the TPHARM, and at MTFs no later than a 180-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

VI. UNIFORM FORMULARY CLASS REVIEWS — ANTIHEMOPHILIC AGENTS – Factor VIII/von Willebrand Factor Complexes, human Prothrombin Concentrate Complexes, and Inhibitor Bypassing Products

P&T Comments

A. Antihemophilic Agents – Factor VIII/von Willebrand Factor Complexes, human Prothrombin Concentrate Complexes, and Inhibitor Bypassing Products — Relative Clinical Effectiveness

The P&T Committee evaluated the clinical effectiveness of the remainder of the antihemophilic drug class, comprised of the human factor VIII/vWF complexes, the human PCCs, and the inhibitor bypassing products.

Humate-P and Alphanate are the two human factor VIII products containing a measured amount of vWF that are used to treat certain types of von Willebrand disease and to replace factor VIII in patients with hemophilia A. Human PCCs were formerly the treatment of choice for hemophilia B before highly purified products became available and now are used to treat factor II and factor X deficiency. The PCCs include Bebulin VH and Profilnine SD. The inhibitor bypassing products include one recombinant activated factor VII, NovoSeven RT, and one human activated prothrombin complex concentrate, Feiba VH. These two products are indicated for use in patients with hemophilia A or hemophilia B who have developed inhibitors, and are used to treat bleeding episodes, or to prevent bleeding episodes during surgical interventions.

Information was considered regarding the safety, effectiveness, and clinical outcomes of the factor VIII/vWF complexes, the PCCs, and the inhibitor bypassing subclass of the antihemophilic agents. Only uses that pertain to the outpatient drug benefit were considered. The clinical review included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1). There were no MHS utilizers of Humate-P or Profilnine from December 2008 to November 2009.

Relative Clinical Effectiveness Conclusion — The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 2 absent) the following clinical effectiveness conclusions:

1. With regard to efficacy, the following conclusions were made:

   a) There is no evidence to conclude that there are clinically relevant differences in efficacy between NovoSeven RT and Feiba VH in the outpatient treatment of bleeding episodes in hemophilia patients who have inhibitors.

   b) There is no evidence to conclude that there are clinically relevant differences in efficacy between Bebulin VH and Profilnine SD in the outpatient treatment of factor II or factor X deficiency.

   c) There is no evidence to conclude that there are clinically relevant differences in efficacy between Humate-P and Alphanate in the outpatient treatment of von Willebrand disease or hemophilia A.

2. With regard to safety and tolerability, the P&T Committee agreed that:

a) Although the risk is small, there is a lower risk of viral transmission with a recombinant product (NovoSeven RT) than with a plasma-derived product (Feiba VH). Feiba VH may also cause an anamnestic response in patients with inhibitors who are classified as high responders to therapy, and can cause anaphylaxis or nephrotic syndrome in hemophilia B patients who have developed inhibitors. Both products carry a very low risk of thrombotic complications. Feiba VH has a warning advising extreme caution when using in patients with hepatic impairment.

b) Bebulin VH contains heparin and may not be appropriate to use in patients with a history of type II heparin induced thrombocytopenia (HIT); otherwise, there is no evidence that there are clinically relevant differences in safety between Bebulin VH and Profilnine SD.

c) Alphanate contains heparin and may not be appropriate to use in patients with a history of type II HIT; otherwise, there is no evidence that there are clinically relevant differences in safety between Humate-P and Alphanate.

3. With regard to other factors:
   a) Feiba VH has a longer half-life than Novoseven RT and may be more appropriate when considering prophylactic treatment in a hemophilia patient who has developed inhibitors and is classified as a high responder to therapy.

   c) National professional group guidelines and national hemophilia patient advocacy groups caution against switching between products once a patient is stabilized, due to potentially detrimental outcomes, including development of immunogenicity.

d) There are differences among the factor VIII/vWF concentrates, the human PCCs, and the inhibitor bypassing products with regard to viral deactivation/depletion methods, storage and refrigeration requirements, vial sizes available, reconstitution and administration kits, and patient support programs

B. Antihemophilic Agents – Factor VIII/von Willebrand Factor Complexes, human Prothrombin Concentrate Complexes, and Inhibitor Bypassing Products — Relative Cost-Effectiveness

Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (13 for, 0 opposed, 2 abstained, 1 absent) the following:

a) CMA results for the Factor VIII/vWF antihemophilic subgroup revealed that Alphanate was the most cost-effective factor complex for this subclass based on cost per patient per year of treatment. Cost per patient per year of treatment was calculated using yearly consumption rates for Alphanate and Humate-P.

b) CMA results for the PCCs antihemophilic subgroup revealed that Profilnine SD was the most cost-effective factor complex for this subclass based on cost per patient per year of treatment. Cost per patient per year of treatment was calculated using yearly consumption rates for Bebulin VH and Profilnine SD.

c) CMA results for the inhibitor bypassing products antihemophilic subgroup revealed that NovoSeven RT was the most cost-effective factor complex based on a cost per patient per year of treatment. Cost per patient per year of treatment was calculated using yearly consumption rates for NovoSeven RT and Feiba VH.

C. Antihemophilic Agents – Factor VIII/von Willebrand Factor Complexes, human Prothrombin Concentrate Complexes, and Inhibitor Bypassing Products — Uniform Formulary 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 (13 for, 0 opposed, 2 abstained, 1 absent):

a) The factor VIII/vWF product Alphanate, the human PCC product Profilinine SD, and the inhibitor bypassing product NovoSeven RT remain classified as formulary on the UF.

b) The factor VIII/vWF product Humate-P, the human PCC product Bebulin VH, and the inhibitor bypassing product Feiba VH be designated as non-formulary under the UF.

c) All factor VIII/vWF, the human PCCs, and inhibitor bypassing product recommended for inclusion on the UF were covered by UF VARR submissions at or below the Federal Ceiling Price.

D. Antihemophilic Agents – Factor VIII/von Willebrand Factor Complexes, human Prothrombin Concentrate Complexes, and Inhibitor Bypassing Products — Uniform Formulary Implementation Plan

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 180-day implementation period in the TRICARE Pharmacy Benefits Program (TPHARM), and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

VII. UNIFORM FORMULARY CLASS REVIEWS — Antihemophilic Agents – Factor VIII/von Willebrand Factor Complexes, human Prothrombin Concentrate Complexes, and Inhibitor Bypassing Products

BAP Comments

A. Antihemophilic Agents – Factor VIII/von Willebrand Factor Complexes, human Prothrombin Concentrate Complexes, and Inhibitor Bypassing Products — Uniform Formulary 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, recommended:

a) The factor VIII/vWF product Alphanate, the human PCC product Profilinine SD, and the inhibitor bypassing product NovoSeven RT remain classified as formulary on the UF.

b) The factor VIII/vWF product Humate-P, the human PCC product Bebulin VH, and the inhibitor bypassing product Feiba VH be designated as non-formulary under the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Antihemophilic Agents – Factor VIII/von Willebrand Factor Complexes, human Prothrombin Concentrate Complexes, and Inhibitor Bypassing Products — Uniform Formulary Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday one week after the minutes are signed, following a 180-day implementation period in the TPHARM, and at MTFs no later than a 180-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

VIII. NEWLY APPROVED DRUGS — NARCOTIC ANALGESICS—Morphine sulfate extended release (ER)/naltrexone capsules (Embeda)

P&T Comments

A. Embeda— Relative Clinical Effectiveness

The clinical evaluation for Embeda included, but was not limited to, requirements stated in 32 Code of Federal Regulations (CFR) 199.21(e)(1). Embeda is the first abuse-deterrent formulation of morphine to reach the market. Each capsule

contains round pellets of morphine ER that surround a naltrexone core. Morphine sulfate ER/naltrexone is a Schedule II controlled substance and is classified as a high-potency single analgesic agent in the narcotic analgesic drug class, which was last reviewed in February 2007. Embeda is indicated for the treatment of moderate to severe pain in adults when continuous, around-the-clock analgesia is required for an extended period of time.

Morphine is a pure opioid agonist selective for the mu receptor, while naltrexone is a mu antagonist that reverses the effects of the mu agonists. When the capsules are taken whole as directed, the morphine provides analgesia, with no clinical effects from the naltrexone. Attempts to tamper with the pellets either by crushing or dissolving will cause a rapid release and absorption of the naltrexone, antagonizing the effects of the morphine released.

The unpublished trial used to gain FDA approval reported that Embeda was superior to placebo in relieving pain in patients with osteoarthritis. A study in recreational opioid users reported reduced drug liking for crushed Embeda capsules and whole Embeda capsules, when compared to immediate release morphine solution. The clinical significance of reduction in drug liking is unknown. The product labeling states, "There is no evidence that the naltrexone in Embeda reduces the abuse liability of Embeda." There are no other abuse deterrent opioids on the market yet, though several are currently in development.

The safety profile for Embeda reflects that of other morphine ER products and narcotic analgesics on the Uniform Formulary (UF). Crushing, chewing or dissolving pellets can cause fatal release of morphine or precipitate withdrawal in opioid-tolerant individuals.

The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) there was a potential benefit, though not yet proven, that morphine sulfate ER/naltrexone (Embeda) has a blunted drug-liking response, compared to other UF high-potency narcotic analgesics

B. Embeda— Relative Cost-Effectiveness

The P&T Committee evaluated the costs of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the other currently available narcotic analgesics. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Cost minimization analysis (CMA) was used to evaluate the relative cost-effectiveness of the agent. Results from the CMA showed the projected weighted average cost per day for Embeda is higher than the other formulary narcotic analgesics, including transdermal fentanyl, morphine sulfate ER (Avinza and MS Contin), oxycodone (OxyContin), and oxymorphone (Opana ER). However, the projected weighted average cost per day for Embeda was lower than the UF agent morphine sulfate (Kadian).

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 0 absent) morphine sulfate ER/Naltrexone HCl (Embeda) was cost effective relative to the other UF agents in the narcotic analgesics drug class.

C. Embeda — Uniform Formulary 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, recommended (12 for, 3 opposed, 1 abstained, 0 absent) morphine sulfate ER/naltrexone capsules (Embeda) be designated formulary on the UF.

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D Embeda — Uniform Formulary Implementation Plan – Not applicable

IX. NEWLY APPROVED DRUGS – NARCOTIC ANALGESICS—Morphine sulfate extended release (ER)/naltrexone capsules (Embeda)

BAP Comments

A. Embeda — Uniform Formulary 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, recommended morphine sulfate ER/naltrexone capsules (Embeda) be designated formulary on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Embeda — Uniform Formulary Implementation Plan – Not applicable

X. NEWLY APPROVED DRUGS — Attention Deficit/Hyperactivity Disorder (ADHD)—Guanfacine extended release (ER) tablets (Intuniv)

P&T Comments

A. Intuniv — Relative Clinical Effectiveness

Intuniv is indicated for the treatment of ADHD in children and adolescents aged 6 to 17 years. Intuniv is included in the ADHD/Narcolepsy drug class, which was reviewed in November 2006.

Guanfacine immediate release (IR) (Tenex, generics) is FDA-approved for treating hypertension, but is well accepted for off-label use in ADHD. Intuniv is dosed once daily for ADHD and is approved as monotherapy. Guanfacine IR is usually dosed twice daily for ADHD. Guanfacine is an alpha-2A agonist, and is not a scheduled substance, unlike the stimulants (methylphenidate and amphetamine). Clonidine is another alpha-2A agonist used off-label for ADHD. Clonidine is available in tablets and transdermal formulations. Intuniv has a longer half-life than clonidine and causes less sedative and hypotensive effects.

Atomoxetine (Strattera), another nonstimulant, is FDA-approved as monotherapy for children with ADHD and has a different mechanism of action (norepinephrine reuptake inhibitor) than guanfacine. Atomoxetine has more established efficacy data than Intuniv, but safety concerns include suicidal ideation and hepatotoxicity.

There are no direct comparative trials with Intuniv and other ADHD nonstimulants (guanfacine IR or atomoxetine). In two 8-week studies, Intuniv was superior to placebo in reducing symptoms associated with ADHD. Its efficacy in adolescents and the optimal dose for heavier adolescents remain to be determined. The duration of action of Intuniv ranged between 8 to 12 hours and was dose-dependent. Longer-term trials are necessary to delineate its place in therapy.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) that guanfacine ER (Intuniv) has a different mechanism of action and adverse effect profile than atomoxetine (Strattera). The P&T Committee acknowledged that Intuniv offers the convenience of once-daily dosing and a defined dosing regimen compared to guanfacine IR and clonidine, but there is insufficient data to suggest whether there are additional clinical advantages compared to the other UF nonstimulants.

B. Intuniv — Relative Cost-Effectiveness

The P&T Committee evaluated the cost of guanfacine ER (Intuniv) in relation to the efficacy, safety, tolerability, and clinical outcomes of the ADHD agents in the ADHD/Narcolepsy UF drug 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).

CMA was used to evaluate the relative cost-effectiveness of Intuniv relative to other UF ADHD agents. Results from the CMA showed the projected weighted average cost per day for Intuniv is higher than other formulary ADHD agents except clonidine patch.

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 1 absent) that guanfacine ER (Intuniv) is comparable in cost to branded stimulant and nonstimulant products in the ADHD/Narcolepsy drug class. In comparison to generics in this class, the P&T Committee determined that the higher daily cost for Intuniv was offset by its FDA-approved dosing regimen and once-daily administration

C. Intuniv — Uniform Formulary Recommendation

Taking into consideration the conclusions from the relative clinical effectiveness, relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (11 for, 3 opposed, 1 abstained, 1 absent) guanfacine ER tablets (Intuniv) be designated formulary on the UF.

D. Intuniv — Uniform Formulary Implementation Plan – Not applicable

XI. NEWLY APPROVED DRUGS — Attention Deficit/Hyperactivity Disorder (ADHD)—Guanfacine extended release (ER) tablets (Intuniv)

BAP Comments

A. Intuniv — Uniform Formulary Recommendation

Taking into consideration the conclusions from the relative clinical effectiveness, relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (11 for, 3 opposed, 1 abstained, 1 absent) guanfacine ER tablets (Intuniv) be designated formulary on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Intuniv — Uniform Formulary Implementation Plan – Not applicable

XII. NEWLY APPROVED DRUGS Newer Sedative Hypnotics—Zolpidem sublingual tablets (Edluar)

P&T Comments

A. Edluar — Relative Clinical Effectiveness

Zolpidem sublingual (SL) tablets (Edluar) is a newer sedative hypnotic approved for the short-term treatment of insomnia characterized by difficulties in sleep initiation. The newer sedative hypnotics were last reviewed in February 2007. Generic zolpidem immediate release (IR) oral tablets are currently included on the BCF.

Zolpidem SL tablets were approved under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act by demonstrating bioequivalence to Ambien tablets. The SL tablets disintegrate when placed under the tongue and are not swallowed. The pharmacokinetic profiles of zolpidem SL, zolpidem IR (Ambien), and zolpidem sustained release (Ambien CR) tablets are similar with regard to bioavailability, time to reach maximal concentration, half-life, protein binding, and elimination. There are no direct comparative trials evaluating the final commercially-marketed formulation of Edluar with zolpidem IR tablets or newer sedative hypnotics. Two small studies comparing an early zolpidem SL formulation with Ambien IR reported sleep onset measures were 6 to 7 minutes faster with the SL product than Ambien; however, the clinical relevance of this difference is unknown The safety profile of zolpidem SL reflects that of other zolpidem formulations (e.g., Ambien IR and Ambien CR).

Relative Clinical Effectiveness Conclusion—The P&T Committee voted (16 for, 0 against, 0 abstained, 0 absent) that although zolpidem SL tablets (Edluar) offer an alternative sedative hypnotic formulation for patients with swallowing difficulties, there is insufficient data to conclude Edluar offers improved efficacy, safety, or tolerability in the treatment of insomnia compared to zolpidem IR tablets

B. Edluar — Relative Cost-Effectiveness

The P&T Committee evaluated the costs of zolpidem SL tablets (Edluar) in relation to the efficacy, safety, tolerability, and clinical outcomes of the other newer sedative hypnotics. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of zolpidem SL tablets (Edluar). Results from the CMA showed the projected weighted average cost per day for Edluar is higher than the UF newer sedative hypnotics, zolpidem IR (Ambien), and non-formulary (NF) newer sedative hypnotics, ramelteon (Rozerem) and zaleplon (Sonata).

C. Edluar — Uniform Formulary Recommendation

Taking into consideration the conclusions from the relative clinical effectiveness, relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1 abstained, 0 absent) that zolpidem SL tablets (Edluar) be designated NF on the UF.

D. Edluar— Uniform Formulary Implementation Plan

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

XIII. NEWLY APPROVED DRUGS Newer Sedative Hypnotics—Zolpidem sublingual tablets (Edluar)

BAP Comments

A. Edluar — Uniform Formulary Recommendation

Taking into consideration the conclusions from the relative clinical effectiveness, relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended that zolpidem SL tablets (Edluar) be designated NF on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Edluar — Uniform Formulary Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

XIV. NEWLY APPROVED DRUGS — Renin Angiotensin Antihypertensive Agents (RAAs)—Telmisartan/amlodipine tablets (Twynsta)

P&T Comments

A. Twynsta — Relative Clinical Effectiveness

Twynsta is a fixed-dose combination product containing telmisartan (Micardis) and amlodipine (Norvasc, generics). It is the third two-drug combination product containing an angiotensin receptor blocker (ARB; Micardis) and dihydropyridine calcium channel blocker (DHP CCB; amlodipine) to reach the market. Azor (olmesartan [Benicar]/amlodipine) and Exforge (valsartan [Diovan]/amlodipine) were previously marketed. Telmisartan/amlodipine is solely indicated for treating hypertension; it can be substituted for the individual titrated components or used as initial therapy in patients likely to require two or more drugs to control blood pressure (BP). Current national guidelines for treating hypertension recommend when more than one drug is needed for BP control, one of the components should comprise a diuretic.

Telmisartan is currently designated as formulary on the UF; amlodipine is designated as BCF. Twynsta is included in the renin-angiotensin antihypertensive agents (RAAs) drug class, which is comprised of several subclasses (ARBs, angiotensin-converting enzyme (ACE) inhibitors, direct renin inhibitors and their combinations with CCBs or diuretics). The RAAs class will be re-evaluated at an upcoming meeting.

Treatment with various combinations of telmisartan/amlodipine was shown in one randomized trial to significantly reduce BP compared to baseline and placebo. There are no trials evaluating clinical outcomes of mortality or morbidity with Twynsta, although outcomes trials are available with the individual components.

The adverse reaction profile of Twynsta reflects that of the individual components. Although no studies are available specifically addressing the potential for increased compliance with Twynsta over the individual components administered together, other studies have shown an increase in persistence with fixed-dose antihypertensive combination products.

The clinical evaluation for Twynsta included, but was not limited to the requirements stated in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 1 absent) telmisartan/amlodipine (Twynsta) did not have a significant, clinically meaningful, therapeutic advantage in terms of safety, effectiveness, or clinical outcome over other antihypertensive drugs included on the UF.

B. Twynsta — Relative Cost Effectiveness

The P&T Committee evaluated the cost of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the combination antihypertensive agents in this class as well as the individual components, telmisartan and amlodipine. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of telmisartan/amlodipine (Twynsta) relative to other UF agents in this class. Results from the CMA showed the projected weighted average cost per day for telmisartan/amlodipine (Twynsta) is higher than the other formulary combination antihypertensive agents, including triple-therapy oral agent amlodipine/valsartan/hydrochlorothiazide (Exforge HCT) and the individual components amlodipine and telmisartan (Micardis).

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (15 for, 1 opposed, 0 abstained, 0 absent) telmisartan/amlodipine (Twynsta) is not cost effective relative to the other combination antihypertensive agents in this class. The P&T Committee evaluated the cost of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the anticholinergic agents in the overactive bladder (OAB) class.

C. Twynsta — Uniform Formulary 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, recommended (15

for, 0 opposed, 1 abstained, 0 absent) telmisartan/amlodipine (Twynsta) be designated NF on the UF.

D. Twynsta — Uniform Formulary Implementation Plan

The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA..

XV. NEWLY APPROVED DRUGS Renin Angiotensin Antihypertensive Agents (RAAs)—Telmisartan/amlodipine tablets (Twynsta)

BAP Comments

A. Twynsta — Uniform Formulary 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, recommended telmisartan/amlodipine (Twynsta) be designated NF on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Twynsta – Uniform Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

XVI. NEWLY APPROVED DRUGS — Renin Angiotensin Antihypertensive Agents (RAAs)—Aliskiren/valsartan tablets (Valturna)

P&T Comments

A. Valturna — Relative Clinical Effectiveness

Valturna is a fixed-dose combination product containing the ARB valsartan (Diovan) and aliskiren (Tekturna), a direct renin inhibitor. Tekturna is also available in a fixed-dose combination tablet containing the diuretic hydrochlorothiazide (HCTZ); both Tekturna and Tekturna HCT are designated as formulary on the UF. Valsartan (Diovan) is designated NF. Valturna is included in the renin-angiotensin antihypertensive agents (RAAs) drug class, which will be re-evaluated at an upcoming meeting.

Valturna is indicated for treating hypertension. It has other indications based on clinical trials showing positive clinical outcomes; outcomes trials with aliskiren are currently underway. Current national guidelines for treating hypertension have not yet addressed the place in therapy for direct renin inhibitors, although updated guidelines are anticipated later this year.

Treatment with Valturna was shown in one randomized trial to significantly reduce BP compared to and placebo or administering the components individually. However, the BP reduction seen with Valturna in this study was not as large as that seen in other studies evaluating fixed-dose antihypertensive combination products. The adverse reaction profile of Valturna reflects that of the individual components.

The clinical evaluation for Valturna included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) that although aliskiren/valsartan (Valturna) has a unique mechanism of action due to the direct renin inhibitor component and offers the potential for increased persistence, it did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other antihypertensive drugs included on the UF.

B. Valturna — Relative Cost Effectiveness

The P&T Committee evaluated the cost of the agent in relation to the efficacy, safety, tolerability, and clinical outcomes of the combination antihypertensive agents in this class as well as the individual components, aliskiren and valsartan. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

CMA was used to evaluate the relative cost-effectiveness of aliskiren/valsartan (Valturna) compared to other UF agents. Results from the CMA showed the projected weighted average cost per day for Valturna is higher than the other formulary combination antihypertensive agents, including triple-therapy oral agent amlodipine/valsartan/hydrochlorothiazide (Exforge HCT) and the individual components, aliskiren (Tekturna) and valsartan (Diovan).

Relative Cost-Effectiveness Conclusion—The P&T Committee voted (16 for, 0 opposed, 0 abstained, 0 absent) that aliskiren/valsartan (Valturna) is not cost effective relative to the other combination antihypertensive agents in this class

C. Valturna — Uniform Formulary 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, recommended (14 for, 0 opposed, 2 abstained, 0 absent) aliskiren/valsartan (Valturna) be designated NF on the UF.

D. Valturna — Uniform Formulary Implementation Plan

The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

XVII. NEWLY APPROVED DRUGS Narcotic Analgesics — Renin Angiotensin Antihypertensive Agents (RAAs)—Aliskiren/valsartan tablets (Valturna)

BAP Comments

A. Valturna — Uniform Formulary 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, recommended aliskiren/valsartan (Valturna) be designated NF on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Valturna – Uniform Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday one week after the minutes are signed, following a 60-day implementation period in the TPHARM, and at MTFs no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

XVIII. IMPLEMENTATION OF FEDERAL CEILING PRICE REGULATION – will be presented at the meeting.