DOD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

INFORMATION FOR THE UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL

I. UNIFORM FORMULARY REVIEW PROCESS

Under 10 United States Code § 1074g, as implemented by 32 Code of Federal Regulations (CFR) 199.21, the DoD Pharmacy and Therapeutics (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 nonformulary (NF) status receive comments from the Beneficiary Advisory Panel (BAP), which must be reviewed by the Director before making a final decision.

II. UF CLASS REVIEWS—ATYPICAL ANTIPSYCHOTIC (AAP) DRUGS

P&T Comments

A. AAP Drug Class

Background Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the drugs in the atypical antipsychotics (AAP) Drug Class. The clinical review for the oral AAP drugs included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1). The injectable AAPs were not included in the review.

The class is comprised of the following agents: clozapine (Clozapine, generics; Fazaclo), risperidone (Risperdal, Risperdal orally disintegrating tablet (ODT), generics), aripiprazole (Abilify, Abilify Discmelt), asenapine (Saphris), iloperidone (Fanapt), lurasidone (Latuda), olanzapine (Zyprexa, Zydis), olanzapine/fluoxetine (Symbyax), paliperidone (Invega), quetiapine IR and ER (Seroquel; Seroquel XR), and ziprasidone (Geodon).

The AAP Drug Class has not previously been reviewed for UF status, although quetiapine IR (Seroquel) and risperidone tablets were added to the Basic Core Formulary (BCF) in May 2003 (prior to implementation of the Uniform Formulary Rule). Clarifications were made in August 2007 to include quetiapine ER (Seroquel XR) on the BCF and to exclude risperidone ODT. Currently, risperidone is the only AAP drug available in a generic formulation. The anticipated generic entries in the class are Zyprexa, Geodon, Abilify, and Seroquel IR, with patents set to expire in 2011 to 2014.

The AAP Drug Class is associated with a significant cost within the Military Health System (MHS); expenditures exceed $200 million annually. In terms of MHS utilization, quetiapine is the most utilized AAP, followed by generic

risperidone. Aripiprazole is the third most utilized agent but accounts for most of the expenditures in the class.

The Pharmacy Outcomes Research Team (PORT) analyzed utilization and prescribing patterns in the MHS and noted that approximately 60% of AAP use in the MHS appears to be consistent with FDA-approved labeling. This estimate is higher than noted in the literature and may be overstated. The most common diagnosis codes for the AAPs differed by the population studied. For the active duty population, depression was the most commonly reported diagnosis code (53%, although it is unclear whether AAP use was for insomnia or to augment antidepressant effect). In the non-active duty population (ages 18–64 years), depression was the most commonly reported diagnosis code (61%). In contrast, attention deficit hyperactivity was the most commonly reported disorder diagnosis code in the pediatric population (62%), compared with the over-65 population, where dementia was the most common diagnosis code (52%).

Relative Clinical Effectiveness—The P&T Committee recommended (16 for, 0 against, 0 abstained, 1 absent) the following conclusions for the AAPs:

1. Schizophrenia: All AAPs are efficacious in treating schizophrenia. Data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial suggests that olanzapine is superior to the other AAPs in efficacy, but use is limited by adverse events. The four newest AAPs (asenapine, iloperidone, lurasidone, and paliperidone) are superior to placebo in treating schizophrenia, but the data is limited to small trials of short duration.
2. Bipolar Disorders: AAPs are used as adjunctive therapy to mood stabilizers in treating mania and mixed episodes. Six AAPs are FDA-approved for use in bipolar disorders (aripiprazole, asenapine, olanzapine, quetiapine, ziprasidone, and risperidone). Recommendations from the 2010 VA/DoD Clinical Practice Guideline (CPG) for bipolar disorder conclude olanzapine and quetiapine have more positive evidence than the other AAPs.
3. Major Depressive Disorder (MDD): For treatment-resistant MDD, AAPs are superior to placebo in augmenting antidepressant therapy. Three AAPs are FDA-approved for the treatment of MDD: aripiprazole, olanzapine/fluoxetine, and quetiapine ER. Data from systematic reviews suggests more positive evidence exists with quetiapine and aripiprazole for this indication. Risperidone also shows benefit in treating MDD, but is not FDA-approved.
4. Post-Traumatic Stress Disorder (PTSD): The available evidence from the 2010 VA/DoD CPG for PTSD and the American Psychiatric Association supports some benefit for the AAPs when used as adjunctive therapy to

cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs). The results of one meta-analysis show olanzapine and risperidone were more efficacious than placebo. None of the AAPs are FDA-approved for treating PTSD.

5. Dementia: There is evidence from systematic reviews that dementia symptoms of aggression and agitation are improved with AAPs (risperidone and olanzapine) but there is no benefit conferred in terms of cognition and functionality. Use of AAPs for psychiatric symptoms and behavioral disturbances in dementia patients is not approved by the FDA and is associated with significant risks of adverse events, including development of heart failure, cerebrovascular accident, and sudden cardiac death.
6. Insomnia: None of the AAPs are FDA-approved for treating insomnia. Current military guidance for deployment allows for the use of low-dose quetiapine (25 mg) for sleep with no waivers required. In the absence of other psychiatric comorbidities, the use of low-dose AAPs for primary insomnia should be discouraged due to the lack of supportive evidence, risk of adverse events (metabolic and cardiac), and lack of monitoring (e.g., EKG) for adverse events in-theatre. Other drug options to treat insomnia are available on the deployment formulary, which have a lower risk of adverse events than the AAPs.
    - The P&T Committee strongly recommends education of providers regarding the lack of evidence to support use of AAPs for primary insomnia and revision of current theater guidance.
7. With regards to safety, a black box warning applies to the entire class precluding use in elderly patients with behavioral and psychological symptoms of dementia due to increased mortality risk.
8. AAPs have different tolerability profiles as noted below:
    - Extrapyramidal symptoms are most likely to occur with risperidone (higher doses), paliperidone, and asenapine; and are least likely to occur with quetiapine, ziprasidone, aripiprazole, iloperidone, and olanzapine.
    - Diabetes and weight gain are most commonly associated with clozapine and olanzapine. These effects are less common with aripiprazole, lurasidone, and ziprasidone.
    - Hyperprolactinemia has been most commonly associated with risperidone and paliperidone. Aripiprazole, iloperidone, and quetiapine have the lowest risk of this adverse event.

- QTc interval prolongation is a concern with ziprasidone and iloperidone, but is least likely to occur with aripiprazole and lurasidone.

9. Adverse events are usually dose dependent and can be potentiated by patient characteristics such as age and comorbid conditions. AAP receptor binding affinities are associated with individual adverse events. Overall, the benefits conferred by AAPs are offset by limiting adverse effects.
10. For the pediatric population, the AAPs differ in their FDA-approved indications and ages. Aripiprazole, olanzapine, risperidone, paliperidone, and quetiapine are approved for use in the pediatric population.
11. In a request for provider opinion, most respondents wanted 4 or more AAPs on their local formulary. In addition to risperidone, most respondents requested aripiprazole and quetiapine for inclusion on the BCF.
12. The clinician's choice for selecting an AAP should be influenced by the relationship between the efficacy and tolerability profile of the drug as well as individual patient characteristics.

B. AAPs—Relative Cost-Effectiveness

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the AAP Drug Class. Although there are differences within the drug class regarding safety and tolerability profiles, cost minimization analyses (CMA) and budget impact analyses (BIA) were conducted, since clinically relevant differences in efficacy for schizophrenia are not apparent. 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 and BIA were used to assess the potential impact of cost scenarios where selected AAPs—aripiprazole (Abilify, Abilify Discmelt), asenapine (Saphris), clozapine (Clozaril, generics; Fazaclo), iloperidone (Fanapt), lurasidone (Latuda), olanzapine (Zyprexa, Zyprexa Zydis), olanzapine/fluoxetine (Symbyax), paliperidone (Invega), quetiapine IR and ER (Seroquel IR, Seroquel XR), risperidone (Risperdal, Risperdal ODT), and ziprasidone (Geodon)—were designated with formulary or NF status on the UF. Cost scenarios evaluating the impact of designating selected agents on the BCF were also considered.

Relative Cost-Effectiveness Conclusion—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, 1 absent) BIA results for the AAP agents showed that all investigated scenarios resulted in lower cost estimates compared to current MHS expenditures. Overall cost analyses indicated the most cost-effective scenario and operationally-appropriate choice placed clozapine (Clozaril, generics; Fazaclo), risperidone (Risperdal, Risperdal ODT, generics), aripiprazole (Abilify, Abilify

Discmelt), olanzapine (Zyprexa, Zyprexa Zydis), olanzapine/fluoxetine (Symbyax), paliperidone (Invega), quetiapine (Seroquel; Seroquel XR), and ziprasidone (Geodon) on the UF.

C. AAPs—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, recommended (9 for, 6 against, 2 abstained, 0 absent) clozapine (Clozaril, generics; Fazlaco), risperidone (Risperdal, Risperdal ODT, generics), aripiprazole (Abilify, Abilify Discmelt), olanzapine (Zyprexa, Zyprexa Zydis), olanzapine/fluoxetine (Symbyax), paliperidone (Invega), quetiapine (Seroquel; Seroquel XR), and ziprasidone (Geodon) remain formulary on the UF. The P&T Committee recommended iloperidone (Fanapt), asenapine (Saphris), and lurasidone (Latuda) be designated NF on the UF.

D. AAPs—UF Implementation Plan

The P&T Committee recommended (15 for, 0 against, 2 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision.

III. UF CLASS REVIEWS—AAPs

BAP Comments

A. AAPs—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, recommended clozapine (Clozaril, generics; Fazlaco), risperidone (Risperdal, Risperdal ODT, generics), aripiprazole (Abilify, Abilify Discmelt), olanzapine (Zyprexa, Zyprexa Zydis), olanzapine/fluoxetine (Symbyax), paliperidone (Invega), quetiapine (Seroquel; Seroquel XR), and ziprasidone (Geodon) remain formulary on the UF. The P&T Committee recommended iloperidone (Fanapt), asenapine (Saphris), and lurasidone (Latuda) be designated NF on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. AAPs—UF Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

IV. UF CLASS REVIEWS—NASAL ALLERGY DRUGS (NADs)

P&T Comments

A. NADs—Relative Clinical Effectiveness

The P&T Committee evaluated the clinical effectiveness of the NADs. The nasal corticosteroids were previously reviewed in November 2005, August 2007, and November 2008. The class is comprised of three subclasses as listed below.

- *Nasal Corticosteroids*: beclomethasone (Beconase AQ), budesonide (Rhinocort AQ), ciclesonide (Omnaris), flunisolide (generics), fluticasone furoate (Veramyst), fluticasone propionate (Flonase, generics), mometasone furoate (Nasonex), and triamcinolone (Nasacort AQ)
- *Nasal Antihistamines*: azelastine 0.1% (Astelin, generic), azelastine 0.15% with sucralose and sorbitol (Astepro), and olopatadine (Patanase)
- *Nasal Anticholinergics*: ipratropium (Atrovent, generics)

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 32 CFR 199.21(e)(1).

In terms of numbers of prescriptions dispensed, fluticasone propionate (Flonase, generics) is the highest utilized nasal allergy drug in the Military Treatment Facilities (MTFs), followed by mometasone (Nasonex), and azelastine 0.1% (Astelin). This utilization pattern is also seen in the Retail Network. The current BCF drug for the NAD Drug Class is azelastine 0.1%; fluticasone propionate was removed from the BCF in May 2010 due to supply issues.

Relative Clinical Effectiveness Conclusion—The P&T Committee voted (17 for, 0 opposed, 0 abstained, 0 absent) to accept the following clinical effectiveness conclusions:

Nasal Corticosteroids:

With regards to efficacy/clinical effectiveness of the nasal corticosteroids, the following conclusions were made:

- FDA-approved indications—The P&T Committee recognized that there were minor differences among the drugs with regard to FDA-approved uses for seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), prophylaxis of allergic rhinitis (AR) symptoms, nonallergic rhinitis, and nasal polyps. Additionally, the pediatric FDA-approved age ranges differ between the products.
- Clinical Practice Guidelines—Evidence-based guidelines from the 2008 American Academy of Allergy, Asthma and Immunology (AAAAI) and 2010 Allergic Rhinitis and its Impact on Asthma (ARIA) consider the nasal corticosteroids as the most effective drug class at reducing allergic rhinitis symptoms of sneezing, rhinorrhea, nasal congestion, and itching.
- Pharmacodynamic/pharmacokinetic properties—The AAAAI guidelines concluded that despite differences in topical potency, lipid solubility, receptor binding affinity, and systemic bioavailability, the overall clinical response does not appear to vary significantly between drugs.
- Efficacy for SAR/PAR—There was no compelling new data to change the conclusion from the 2008 P&T Committee Meeting review, which established there is no evidence of clinically relevant differences between the agents at relieving nasal or ocular symptoms of AR. However, ciclesonide lacks published evidence for reducing ocular symptoms.
- Nasal polyps—Mometasone and beclomethasone are FDA-approved for nasal polyps.

- There was no compelling new evidence to change previous conclusions.

With regards to regards to safety and tolerability, the following conclusions were made:

- Local effects—Nasal irritation, epistaxis, and rhinorrhea are the most common local adverse effects and are equally likely to occur with any of the nasal corticosteroids.
- Systemic effects—For systemic effects of hypothalamic pituitary adrenal-axis suppression, growth suppression, and ocular adverse events (cataracts/glaucoma), there is insufficient evidence to determine whether one nasal corticosteroid is more likely to cause these effects than another. When given in recommended doses, the nasal corticosteroids are not generally associated with clinically significant systemic adverse effects.
- Tolerability and patient preferences—Patient preferences may play a role in differentiating between the nasal corticosteroids. However, the available clinical data is poor, and no nasal corticosteroid has proven superior to the others in patient preference trials. Nevertheless, flunisolide is poorly tolerated and must be dosed three or four times daily while the others are dosed once or twice daily. Budesonide (Rhinocort AQ) is the only nasal corticosteroid with a pregnancy category B rating by the FDA. All the nasal corticosteroids have a class labeling that these drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nasal Antihistamines:

With regards to efficacy/clinical effectiveness of the nasal antihistamines, the following conclusions were made:

- FDA-approved indications—The P&T Committee recognized that there were minor differences between olopatadine (Patanase), azelastine 0.1% (Astelin, generic), and azelastine 0.15% (Astepro) with regard to FDA-approved uses for SAR and nonallergic rhinitis [e.g., vasomotor rhinitis (VMR)], and pediatric approval.
- Clinical Practice Guidelines—The 2010 ARIA guidelines suggest use of non-sedating oral antihistamines preferentially to nasal antihistamines. The 2008 AAAAI guidelines state that nasal antihistamines are generally less effective than nasal corticosteroids for treating AR, but may be considered for use as first-line treatment for AR and nonallergic

rhinitis. Nasal antihistamines are associated with a clinically significant effect on reducing nasal congestion.

- Efficacy for SAR—Azelastine and olopatadine are superior to placebo in relieving symptoms of SAR. There is no new compelling clinical data to suggest one product is more efficacious than the others.
- Head-to-head study—One head-to-head trial comparing the use of olopatadine with azelastine found no difference in relief of nasal symptoms, but suggests that olopatadine may be better tolerated by patients, as shown by a lower incidence of bitter taste.

With regards to safety and tolerability of the nasal antihistamines, the following conclusions were made:

- Local adverse effects—Somnolence is considered a class effect (AAAAI guidelines). Bitter taste has a higher incidence with azelastine, while epistaxis occurred with roughly equal frequency between olopatadine and azelastine.
- Patient preferences and tolerability—The available clinical data is sparse and is limited to manufacturer-sponsored studies, but tends to favor olopatadine. However, there is insufficient evidence to definitively conclude that clinically relevant differences exist between the nasal antihistamines.

Nasal Anticholinergics:

With regards to efficacy/clinical effectiveness, safety, tolerability, and other factors, of the ipratropium nasal spray (Atrovent, generics), the following conclusions were made:

- FDA-approved indications—Ipratropium is solely indicated for the relief of SAR in adults and children 12 years of age and older.
- Clinical Practice Guidelines—2010 AAAAI guidelines state that nasal anticholinergics may effectively reduce rhinorrhea, but have no effect on other nasal symptoms. Although adverse events are minimal, dryness of the nasal membranes may occur.
- Efficacy and Safety—No new efficacy or safety data have been published since the prior review. Ipratropium is rated Pregnancy Category B by the FDA.

B. NADs—Relative Cost-Effectiveness

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the NADs. CMAs and BIAs were performed based on findings

that there were no clinically relevant differences in efficacy, safety, tolerability, and other factors among the NADs. 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 and BIA were used to assess the potential impact of cost scenarios where selected nasal allergy agents were designated as formulary or NF on the UF. Cost scenarios evaluating the impact of designating selected agents on the BCF were also considered.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

BIA results for the NADs showed that six out of seven investigated scenarios resulted in lower cost estimates than current MHS expenditures. Scenarios where generic fluticasone propionate was selected as a BCF agent, with branded agents olopatadine (Patanase) and mometasone (Nasonex) on the UF were the most cost-effective scenarios overall. Sensitivity analysis results supported the above conclusion unless generic fluticasone propionate becomes unavailable for an extended period of time.

C. NADs—UF Recommendation

In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the NADs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 1 abstained, and 0 absent) to recommend that:

1. Fluticasone propionate (Flonase, generics), flunisolide (generics), mometasone (Nasonex), azelastine 0.1% (Astelin, generic), olopatadine (Patanase), and ipratropium (Atrovent, generics) be classified as formulary on the UF.

2. Azelastine 0.15% (Astepro), beclomethasone (Beconase AQ), budesonide (Rhinocort Aqua), ciclesonide (Omnaris), fluticasone furoate (Veramyst), and triamcinolone (Nasacort AQ) remain designated as NF on the UF.

D. NADs—UF Implementation Plan

Not applicable; no products moved from Uniform Formulary to Non-formulary.

V. UF CLASS REVIEWS—NADs

BAP Comments

A. NADs—UF Recommendation

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

1. Fluticasone propionate (Flonase, generics), flunisolide (generics), mometasone (Nasonex), azelastine 0.1% (Astelin, generic), olopatadine (Patanase), and ipratropium (Atrovent, generics) be classified as formulary on the UF.

2. Azelastine 0.15% (Astepro), beclomethasone (Beconase AQ), budesonide (Rhinocort Aqua), ciclesonide (Omnaris), fluticasone furoate (Veramyst), and triamcinolone (Nasacort AQ) remain designated as NF on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. NADs—UF Implementation Plan

Not applicable.

VI. RECENTLY APPROVED U.S. FDA AGENTS—DIPEPTIDYL PEPTIDASE-4 INHIBITOR (DPP-4)/BIGUANIDE FIXED-DOSE COMBINATION (FDC)

P&T Comments

A. Saxagliptin/Metformin XR (Kombiglyze XR)—Relative Clinical Effectiveness

Relative Clinical Effectiveness—Kombiglyze XR is a FDC product containing the DPP-4 inhibitor saxagliptin (Onglyza) and the biguanide metformin extended-release (ER) (generic Glucophage XR) in one tablet. This drug is the second FDA-approved DPP-4/metformin FDC product. The Non-Insulin Diabetes Drug Class, which included the DPP-4s and biguanides separately, as well as combinations, was reviewed during the November 2010 P&T Committee meeting.

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

Kombiglyze XR is approved for use as adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate. In November 2010, sitagliptin (Januvia) and sitagliptin/metformin immediate-release (IR) (Janumet) were designated with BCF status and saxagliptin was designated with UF status. Automated Prior Authorization or Step Therapy applies to the DPP-4 subclass, which requires a trial of metformin alone or a sulfonylurea (SU) prior to use of sitagliptin, sitagliptin/metformin IR, or saxagliptin. The generic metformin ER component of Kombiglyze XR is available on the BCF as a single agent.

Clinical trials with sitagliptin and saxagliptin when used as monotherapy show reduction in hemoglobin A1C (HbA1C) of 0.4 - 0.79%. The saxagliptin/metformin FDC provides a 2.5% decrease in HbA1c from baseline. There are no head-to-head trials comparing saxagliptin/metformin ER (Kombiglyze XR) and sitagliptin/metformin IR (Janumet). However, in a head-to-head non-inferiority trial, sitagliptin/metformin IR lowered HbA1c by approximately 0.1% more from baseline than saxagliptin/metformin IR. Saxagliptin was considered non-inferior to sitagliptin. While statistical significance was achieved, the difference between the two agents is not clinically significant. There are no clinically relevant differences between sitagliptin and saxagliptin when combined with metformin in terms of glycemic control, and changes in lipid profile, weight, or blood pressure.

The product labeling for Kombiglyze XR contains the same contraindications and warnings as metformin. Renal and hepatic impairment remains a concern as well as other conditions that increase the risk of developing lactic acidosis. Kombiglyze XR can be dosed once daily. To achieve the target dose of metformin, patients can take an additional dose of metformin or take two 2.5mg/1000mg Kombiglyze XR tablets together once daily.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) saxagliptin/metformin XR (Kombiglyze XR) offers no clinically meaningful therapeutic advantage over sitagliptin/metformin IR (Januvia) in terms of efficacy, safety, or tolerability.

B. Saxagliptin/Metformin XR (Kombiglyze XR)—Relative Cost-Effectiveness

CMA was performed to evaluate the cost of saxagliptin/metformin ER (Kombiglyze XR) in relation to the other UF DPP-4 inhibitor/biguanide FDC agent, sitagliptin/metformin IR (Janumet), and to generic metformin IR or ER in combination with sitagliptan (Januvia) or saxagliptan (Onglyza). Information

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

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that saxagliptin/metformin ER (Kombiglyze XR) tablets were more costly, compared with the other DPP-4s currently designated with BCF or UF status.

C. Saxagliptin/Metformin XR (Kombiglyze XR)—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, recommended (16 for, 0 opposed, 1 abstained, 0 absent) saxagliptin/metformin ER (Kombiglyze XR) remain formulary on the UF. Prior authorization/step therapy for the DPP-4s would require a trial of metformin or sulfonylurea prior to use of Kombiglyze XR for new patients.

D. Saxagliptin/Metformin XR (Kombiglyze XR)—PA Criteria

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) the following PA criteria should apply to Kombiglyze XR. Coverage would be approved if the patient met any of the following criteria:

1. Automated PA criteria:
    a) The patient has received a prescription for metformin or sulfonylurea at any MHS pharmacy point of service [(MTFs), retail network pharmacies, or mail order)] during the previous 180 days.

    b) The patient has received a prescription for a DPP-4 inhibitor (Januvia, Janumet, or Onglyza) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2. Manual PA criteria, if automated criteria are not met:
    a) The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis.
    b) The patient has experienced the following adverse event while receiving a SU: hypoglycemia requiring medical treatment.

c) The patient has a contraindication to both metformin and a SU.

E. Saxagliptin/Metformin XR (Kombiglyze XR)—UF and PA Implementation Plan

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service.

VII. RECENTLY APPROVED U.S. FDA AGENTS—DIPEPTIDYL PEPTIDASE-4 INHIBITOR (DPP-4)/BIGUANIDE FIXED-DOSE COMBINATION (FDC)

BAP Comments

A. Saxagliptin/Metformin XR (Kombiglyze XR)—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, recommended saxagliptin/metformin ER (Kombiglyze XR) remain formulary on the UF. Prior authorization/step therapy for the DPP-4s would require a trial of metformin or sulfonylurea prior to use of Kombiglyze XR for new patients.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Saxagliptin/Metformin XR (Kombiglyze XR)—PA Criteria

The P&T Committee recommended the following PA criteria should apply to Kombiglyze XR. Coverage would be approved if the patient met any of the following criteria:

1. Automated PA criteria:
    a) The patient has received a prescription for metformin or sulfonylurea at any MHS pharmacy point of service [(MTFs), retail network pharmacies, or mail order)] during the previous 180 days.

b) The patient has received a prescription for a DPP-4 inhibitor (Januvia, Janumet, or Onglyza) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2. Manual PA criteria, if automated criteria are not met:

a) The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis.

b) The patient has experienced the following adverse event while receiving a SU: hypoglycemia requiring medical treatment.

c) The patient has a contraindication to both metformin and a SU.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

C. Saxagliptin/Metformin XR (Kombiglyze XR)—UF and PA Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

VIII. RECENTLY APPROVED U.S. FDA AGENTS—Ophthalmic-1 Class

P&T Comments

A. Bromfenac 0.09% Ophthalmic Solution (Bromday)—Relative Clinical Effectiveness

Relative Clinical Effectiveness—Bromfenac 0.09% ophthalmic solution (Bromday) is a non-steroidal anti-inflammatory drug (NSAID). It is the only ophthalmic NSAID approved for once daily dosing. Bromday is the same formulation of bromfenac (Xibrom) that was previously a twice daily dosed product. The branded formulation Xibrom was withdrawn from the market in February 2011 by the manufacturer. At the time of the May 2011 P&T Committee meeting, no generic formulations of Xibrom were approved. The Ophthalmic-1 Class was reviewed at the August 2010 P&T Committee meeting. All the ophthalmic NSAIDs are designated with formulary status on the UF; none are designated with BCF status. The clinical evaluation included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Bromday was approved under a Supplemental New Drug Application using the data from Xibrom to change the dosing regimen to once daily dosing. Two Phase III placebo-controlled studies concluded that bromfenac dosed once daily for 16 days is effective for treating inflammation and pain in patients who have undergone cataract extraction with intraocular lens implantation. There are no head-to-head clinical trials comparing the bromfenac once-a-day formulation with the twice-a-day formulation. There are no studies comparing the bromfenac once daily formulation with any other ophthalmic NSAIDs. The safety profile of bromfenac is consistent with the other ophthalmic NSAIDs. The most common adverse events in the Phase III clinical trials that led to drug discontinuation and which occurred in a higher incidence than placebo were eye inflammation, photophobia, and eye pain. Based on the safety data from two Phase III studies, there are no clinically relevant differences between bromfenac ophthalmic solution and other ophthalmic NSAIDs.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) there is no published evidence to suggest that bromfenac ophthalmic solution 0.09% (Bromday) has a compelling clinical advantage over other ophthalmic NSAID products currently included on the UF.

B. Bromfenac 0.09% Ophthalmic Solution (Bromday)—Relative Cost-Effectiveness

The P&T Committee evaluated the cost of bromfenac 0.09% ophthalmic solution (Bromday) in relation to the efficacy, safety, tolerability, and clinical outcomes of the other Ophthalmic-1 NSAIDs prescribed for postoperative pain and

inflammation following cataract surgery. 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 Bromday compared to other UF agents. CMA results showed the projected weighted average cost per day for Bromday is higher than generic ophthalmic NSAIDs, but comparable in price to brand name ophthalmic NSAIDs.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) bromfenac 0.09% ophthalmic solution (Bromday) is cost-effective relative to the other branded Ophthalmic-1 NSAIDs in this class.

C. Bromfenac 0.09% Ophthalmic Solution (Bromday)—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, recommended (15 for, 0 opposed, 1 abstained, 1 absent) bromfenac 0.09% ophthalmic solution (Bromday) remain formulary on the UF.

D. Bromfenac 0.09% Ophthalmic Solution (Bromday)—UF Implementation Plan: Not Applicable

IX. RECENTLY APPROVED U.S. FDA AGENTS—Ophthalmic-1 Class

BAP Comments

A. Bromfenac 0.09% Ophthalmic Solution (Bromday)—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, recommended bromfenac 0.09% ophthalmic solution (Bromday) remain formulary on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Bromfenac 0.09% Ophthalmic Solution (Bromday)—UF Implementation Plan: Not Applicable

X. RECENTLY APPROVED U.S. FDA AGENTS—ALPHA BLOCKERS FOR BENIGN PROSTATIC HYPERPLASIA (BPH)

P&T Comments

A. Tamsulosin/Dutasteride (Jalyn)—Relative Clinical Effectiveness

Relative Clinical Effectiveness—Tamsulosin/dutasteride (Jalyn) is a FDC product containing tamsulosin (Flomax, generics), an uroselective alpha-1 blocker (A1B) and dutasteride (Avodart), a 5-alpha reductase inhibitor (5-ARI). Jalyn is the first combination product for BPH. The drug is indicated for treatment of symptomatic BPH in men who have an enlarged prostate (>30 mL prostate volume). Jalyn is classified in the A1B subclass of the BPH agents, which was last reviewed in May 2010. Automated PA/Step Therapy applies to the A1B subclass, which requires a trial of generic tamsulosin or alfuzosin (Uroxatral) for new patients. For the 5-ARI subclass, finasteride (Proscar, generics) is designated with BCF status, and dutasteride (Avodart) is nonformulary on the UF. The clinical evaluation for Jalyn included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

FDA approval for Jalyn is based on the large randomized controlled four-year study, Combination of Avodart and Tamsulosin (CombAT), which evaluated the combination versus individual components. Results from the CombAT study showed the combination of dutasteride and tamsulosin (Jalyn) was not superior to dutasteride monotherapy for males with BPH with an enlarged prostate (>30ml), in terms of objective clinical progression to acute urinary retention (AUR) or BPH-related surgery. The combination was superior to both tamsulosin and dutasteride monotherapy in terms of improvement of BPH-related symptoms.

The safety and tolerability data from the ComBAT study did not show a clinically relevant difference with Jalyn as compared to monotherapy with tamsulosin or dutasteride. There was a numerical increase in the incidence of cardiac failure with combination tamsulosin/dutasteride, however the FDA determined that co-

morbidities were more likely the cause than the drug effect. There was a higher incidence of sexual adverse events (e.g., erectile dysfunction, retrograde ejaculation) with Jalyn, but these did not lead to a higher discontinuation rate with Jalyn, compared to the single agents administered as monotherapy.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that the FDC tamsulosin/dutasteride (Jalyn) is superior to tamsulosin and dutasteride monotherapy in terms of delaying BPH symptoms. However, it was not superior to dutasteride in delaying clinical progression to AUR and BPH-related surgery. There were no clinically relevant differences for Jalyn as compared to tamsulosin or dutasteride monotherapy in terms of safety and tolerability. The P&T Committee also agreed there is a high degree of therapeutic interchangeability between Jalyn and other combinations of selective A1B and a 5-ARI (e.g., tamsulosin/finasteride).

B. Tamsulosin/Dutasteride (Jalyn)—Relative Cost-Effectiveness

The P&T Committee evaluated the cost of tamsulosin/dutasteride (Jalyn) in relation to the efficacy, safety, tolerability, and clinical outcomes of the other uroselective A1Bs and 5-ARIs used for BPH. 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 Jalyn compared to other UF agents. Results from the CMA showed the projected weighted average cost per day for Jalyn was higher than the most cost-effective combination—generic tamsulosin and generic finasteride. However, Jalyn was more cost-effective than its individual components taken separately.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) the combination of tamsulosin and finasteride administered together represents the most cost-effective combination of uroselective A1Bs and 5-ARIs for treatment of BPH. The FDC tamsulosin/dutasteride (Jalyn) is a cost-effective alternative relative to other combinations of A1Bs and dutasteride (Avodart).

C. Tamsulosin/Dutasteride (Jalyn)—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, recommended (14

for, 1 opposed, 1 abstained, 1 absent) tamsulosin/dutasteride (Jalyn) remain formulary on the UF, with automated PA/Step Therapy requiring generic tamsulosin or alfuzosin (Uroxatral) for new patients.

D. Tamsulosin/Dutasteride (Jalyn)—PA Criteria

Prior authorization for the A1Bs requires a trial of a step-preferred drug [tamsulosin or alfuzosin (Uroxatral)] prior to a non-step-preferred A1B [silodosin (Rapaflo)]. Tamsulosin/dutasteride (Jalyn) would be designated non-step-preferred. The P&T Committee recommended (13 for, 1 opposed, 2 abstained, 1 absent) the following PA criteria apply to tamsulosin/dutasteride (Jalyn):

1. Automated PA criteria:
    a) The patient has received a prescription for a preferred agent in the A1B subclass at any MHS pharmacy point of service (MTFs, retail network pharmacies, or home delivery) during the previous 180 days.

2. Manual (paper) PA criteria, if automated criteria are not met:
    a) The patient has received a trial of tamsulosin or alfuzosin and had an inadequate response and requires therapy with both an A1B and 5-ARI.
    b) The patient has received a trial of alfuzosin but was unable to tolerate it due to adverse effects but is expected to tolerate tamsulosin and requires therapy with both an A1B and 5-ARI.
    c) Treatment with alfuzosin is contraindicated for this patient (e.g., due to hypersensitivity) but tamsulosin is not contraindicated, and the patient requires therapy with both an A1B and 5-ARI.
    d) The patient requires therapy with both an A1B and 5-ARI and requires a fixed-dose combination (e.g., swallowing difficulties).

E. Tamsulosin/Dutasteride (Jalyn)—UF and PA Implementation Plan

The P&T Committee recommended (14 for, 0 opposed, 2 abstained, 1 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service.

XI. RECENTLY APPROVED U.S. FDA AGENTS—ALPHA BLOCKERS FOR BENIGN PROSTATIC HYPERPLASIA (BPH)

BAP Comments

A. Tamsulosin/Dutasteride (Jalyn)—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, recommended tamsulosin/dutasteride (Jalyn) remain formulary on the UF, with automated PA/Step Therapy requiring generic tamsulosin or alfuzosin (Uroxatral) for new patients.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Tamsulosin/Dutasteride (Jalyn)—PA Criteria

Prior authorization for the A1Bs requires a trial of a step-preferred drug [tamsulosin or alfuzosin (Uroxatral)] prior to a non-step-preferred A1B [silodosin (Rapaflo)]. Tamsulosin/dutasteride (Jalyn) would be designated non-step-preferred. The P&T Committee recommended the following PA criteria apply to tamsulosin/dutasteride (Jalyn):

1. Automated PA criteria:
    a) The patient has received a prescription for a preferred agent in the A1B subclass at any MHS pharmacy point of service (MTFs, retail network pharmacies, or home delivery) during the previous 180 days.

2. Manual (paper) PA criteria, if automated criteria are not met:
    a) The patient has received a trial of tamsulosin or alfuzosin and had an inadequate response and requires therapy with both an A1B and 5-ARI.
    b) The patient has received a trial of alfuzosin but was unable to tolerate it due to adverse effects but is expected to tolerate tamsulosin and requires therapy with both an A1B and 5-ARI.
    c) Treatment with alfuzosin is contraindicated for this patient (e.g., due to hypersensitivity) but tamsulosin is not contraindicated, and the patient requires therapy with both an A1B and 5-ARI.
    d) The patient requires therapy with both an A1B and 5-ARI and requires a fixed-dose combination (e.g., swallowing difficulties).

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

C. Tamsulosin/Dutasteride (Jalyn)—UF and PA Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

XII. ITEMS FOR INFORMATION

A. Dabigatran (Pradaxa)—Potential Prior Authorization: Dabigatran is the first oral anticoagulant to reach the market since warfarin (Coumadin). It is currently limited to use in patients with non-vavular atrial fibrillation to reduce the risk of stroke and systemic embolism. The P&T Committee reviewed the existing clinical data for dabigatran and its advantages and disadvantages versus warfarin. The P&T Committee also discussed whether prior authorization was required to ensure prescribing is consistent with the current FDA-approved indications. The P&T Committee agreed that Prior Authorization was not needed at this time. Dabigatran will be reviewed with the other anticoagulants at a future meeting.

B. Pharmacy Co-pay Changes: At the May 11-12, 2011 meeting, the Pharmacy &Therapeutics Committee, based on experience with the Uniform Formulary, changes in economic circumstances, and other appropriate factors, voted (14 for, 0 against, 3 abstain, 0 absent) to recommend an adjustment to the per prescription co-payments established in 32 C.F.R. §199.21(i)(2). The co-payment changes proposed in the President's FY 2012 budget for tiers 1 (generic)/2 (formulary)/3 (non-formulary) are $5/$12/$25 for up to a 30-day supply at the Retail Network and $0/$9/$25 for up to a 90-day supply at the Mail Order Pharmacy. These

adjusted amounts maintain compliance with the requirements of 10 U.S.C. §1074g(a)(6).

BAP Comments: