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—ORAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

P&T Comments

A. NSAIDs Drug Class

Background Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the oral NSAIDs. There are 26 drugs in the class, comprised of 19 different chemical entities. Generic formulations are available for 21 drugs and there are 5 branded products: Celebrex, Arthrotec, Vimovo, Zipsor, and Cambia. Celecoxib (Celebrex) is the only cyclooxygenase-2 (COX-2) selective inhibitor available in the United States. Two fixed dose combinations (FDCs) of an NSAID with an anti-ulcer drug are available. Arthrotec is a combination of diclofenac and the prostaglandin analog misoprostol. Vimovo is the first FDC of an NSAID and a proton pump inhibitor (PPI) and is comprised of naproxen and esomeprazole. Diclofenac potassium liquid-filled capsules (Zipsor) contains 25 mg of diclofenac potassium, which is the lowest diclofenac dosage strength marketed; it is solely indicated for relief of mild-to-moderate acute pain. Cambia is a formulation of diclofenac potassium in powder packets for suspension. The partially COX-2-selective NSAIDs include meloxicam, nabumetone, and etodolac. The remaining drugs in the class are the non-COX-2-selective NSAIDs: diclofenac potassium tablets (Cataflam, generics), diclofenac sodium (Voltaren, generics), diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid (Ponstel, generics), naproxen (Naprosyn, generics), naproxen sodium (Anaprox, generics), naproxen sodium extended release (ER) (Naprelan CR, generics), oxaprozin, piroxicam, sulindac, and tolmetin.

The oral NSAIDs have not previously been reviewed; however, prior to implementation of the Uniform Formulary Rule in 2005, the following drugs were added to the Basic Core Formulary (BCF): ibuprofen, indomethacin, meloxicam, and naproxen. The clinical review focused on use of the oral NSAIDs for adults with chronic pain due to osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or anklylosing spondylitis. The review included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness— The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 1absent) the following conclusions for the Oral NSAIDs:

With regards to efficacy,

1. For short-term pain relief (less than 6 months), all of the oral NSAIDs have a similar effect on reducing chronic pain in adults due to osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis, based on systematic reviews from the Oregon Drug Effectiveness Review Project (DERP), and the Cochrane group.
2. There is no significant difference in efficacy of pain relief with celecoxib (Celebrex) versus the partially COX-2 selective or nonselective NSAIDs, based on results from randomized controlled trials, meta-analyses, and a systematic review from the Agency for Healthcare Research and Quality (AHRQ; Chou 2007).
3. Diclofenac potassium liquid-filled capsules (Zipsor) were superior to placebo for reducing pain following bunionectomy in two trials. There are no head-to-head trials comparing Zipsor to the other NSAIDs.
4. The FDC of naproxen with esomeprazole (Vimovo) was superior to placebo and non-inferior to celecoxib for reducing pain in patients with osteoarthritis of the knee in two trials.

With regard to gastrointestinal (GI) safety,

5. All the NSAIDs increase the risk of serious GI adverse reactions, including bleeding, inflammation, ulceration, and perforation of the stomach or intestines, which can be fatal.
6. Celecoxib showed benefit for short-term (therapy duration less than or equal to 6 months) GI safety versus nonselective NSAIDs based on meta-analyses (DERP and AHRQ) and the SUCCESS trial. However, celecoxib did not show benefit for long-term (therapy duration greater than 6 months) GI safety (CLASS trial; DERP and AHRQ meta-analyses; FDA analysis).
7. In one trial, celecoxib plus aspirin versus naproxen plus the PPI lansoprazole plus aspirin showed no significant difference for development

of endoscopically-confirmed ulcers at 12 weeks (short-term) (Goldstein 2007).

8. Celecoxib versus diclofenac plus the PPI omeprazole showed no significant differences in terms of recurrent ulcer bleeding at 6 months (short-term GI safety) (Chan 2002 New England Journal of Medicine).
9. The GI protective effects of celecoxib therapy alone versus NSAID plus PPI were recently evaluated in the CONDOR study. The results showed short-term GI safety benefit for celecoxib for the composite endpoint of upper and lower GI bleeds when compared to diclofenac plus omeprazole. The results were primarily due to a lower risk of a decrease in hemoglobin (due to presumed occult bleeding of GI origin in the small bowel) in the celecoxib group. (Chan 2010 Lancet)
10. For high-risk patients, taking celecoxib with a PPI may provide increased GI protection versus long-term celecoxib monotherapy. The results of one good-quality trial reported that celecoxib plus omeprazole significantly lowered recurrent GI bleeding in very high-risk GI patients (12-month trial) (Chan 2007 Lancet).
11. For the partially selective NSAIDs, nabumetone showed short-term GI safety benefit compared to nonselective NSAIDs in a single meta-analysis of fair quality (Huang 1999). Etodolac and meloxicam showed no consistent differences in conferring GI safety benefit as compared to nonselective NSAIDs, based on randomized controlled trials and observational studies.
12. For the non-COX-2-selective NSAIDs, clinical trial data suggest that all nonselective NSAIDs are associated with relatively similar risks of serious GI events.
13. Further study is needed to determine the comparative GI safety benefits of concomitant use of an NSAID with various gastroprotective agents (misoprostol, H2 blocker, PPI) in preventing clinical GI events. Misoprostol decreases the risk of clinically relevant GI events, but is associated with a significant increase in nausea, diarrhea, and abdominal pain.
14. In terms of endoscopically visualized gastric ulcers and discontinuation of therapy due to GI adverse events, Vimovo showed short-term GI safety benefit in patients taking low-dose aspirin versus enteric-coated naproxen alone in two trials.
15. There is insufficient data with Zipsor to assess GI risks.

With regard to cardiovascular (CV) safety,

16. NSAIDs may cause an increased risk of serious CV thrombotic events, myocardial infarction (MI), and stroke, which can be fatal.
17. Based on indirect analyses and observational studies, naproxen appears to be risk-neutral with regard to cardiovascular events; however, a black box warning is still present in the package insert for CV events.
18. Celecoxib, partially-selective NSAIDs, and nonselective NSAIDs have an increased risk of CV events, but there are no consistent differences in the incidence of CV events between them (with the exception of naproxen), based on clinical trials, and the DERP and AHRQ analyses.
19. No CV events related to Vimovo and Zipsor were reported in short-term clinical trials, but there is limited data available.

With regard to tolerability,

20. Relative to nonselective NSAIDs, COX-2 selective and partially selective NSAIDs demonstrated improved or similar tolerability profiles. There are no clear differences in tolerability between the nonselective NSAIDs
21. Vimovo showed a significant benefit in tolerability as compared to use of enteric-coated naproxen alone.

With regard to other factors,

22. Two NSAIDs are available over-the-counter without a prescription: ibuprofen and naproxen.
23. Four NSAIDs are formulated as oral suspensions: indomethacin, meloxicam, ibuprofen, and naproxen.

B. NSAIDs—Relative Cost-Effectiveness

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the oral NSAIDs. Based on the clinical findings regarding efficacy, safety, tolerability, and clinical outcomes with NSAIDs, a cost minimization analysis (CMA) was performed to compare the non-COX-2 selective/partially-COX-2 selective NSAIDs and NSAID/anti-ulcer FDCs. A cost-effectiveness analysis (CEA) was conducted to compare celecoxib (Celebrex) with the nonselective NSAIDs for treatment of osteoarthritis, and a budget impact analysis (BIA) was performed to compare competing formulary scenarios. 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 results for nonselective/partially-selective NSAIDs showed that these products are the most cost-effective option within the oral NSAID class and should be used prior to treatment with NSAID/anti-ulcer FDCs or celecoxib (Celebrex) when clinically appropriate. However, several specific

nonselective/partially-selective NSAIDs were recognized as not being cost-effective relative to the other agents in the class, including naproxen sodium ER (Naprelan CR, generic), diclofenac potassium liquid-filled capsules (Zipsor), diclofenac potassium powder packets (Cambia), and mefenamic acid (Ponstel, generic). The NSAID/anti-ulcer FDCs were comparable on costs with other agents in the oral NSAID class.

Results of the CEA demonstrated that celecoxib was more costly than the nonselective/partially-selective NSAIDs. Published clinical evidence suggested lower risk of GI events with celecoxib compared to nonselective NSAIDs in the short-term (less than or equal to 6 months). However, the cost of preventing an additional ulcer complication with celecoxib was high due to the large difference in cost and small risk reduction in the published clinical data with celecoxib compared to nonselective NSAIDs. Longer-term evidence (greater than 6 months) with celecoxib remains inconclusive with regards to GI risk. Based on these findings, celecoxib should be reserved for patients at high risk for adverse GI events.

The BIA compared several formulary scenarios, including a scenario with an automated PA (step therapy) requiring a trial of generic formulations of partially-selective or nonselective NSAIDs prior to use of celecoxib, and a scenario without an automated PA (no step therapy). The BIA results concluded that the no step-therapy scenario was more cost-effective than the scenario with step therapy for new users of celecoxib.

Relative Cost-Effectiveness Conclusion—Based on the results of the economic analysis and other clinical and cost considerations, the P&T Committee concluded (14 for, 0 opposed, 0 abstained, 1 absent) that the most cost-effective scenario designated the following with formulary status on the UF: diclofenac potassium, diclofenac sodium, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, meloxicam, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, sulindac, tolmetin, naproxen/esomeprazole (Vimovo), diclofenac/misoprostol (Arthrotec), and celecoxib (Celebrex).

C. NSAIDs—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 (13 for, 0 opposed, 1 abstained, 1 absent) the following remain formulary on the UF without step therapy: diclofenac potassium, diclofenac sodium, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, meloxicam, nabumetone, naproxen, naproxen sodium, oxaprozin,

piroxicam, sulindac, tolmetin, naproxen/esomeprazole (Vimovo), diclofenac/misoprostol (Arthrotec), and celecoxib (Celebrex). The P&T Committee recommended diclofenac potassium liquid-filled capsules (Zipsor), diclofenac potassium powder packets (Cambia), naproxen sodium ER (Naprelan CR), and mefenamic acid (Ponstel) be designated NF.

D. NSAIDs—UF Implementation Plan

The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 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—NSAIDs

BAP Comments

A. NSAIDs—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 the following remain formulary on the UF without step therapy: diclofenac potassium, diclofenac sodium, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, meloxicam, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, sulindac, tolmetin, Vimovo, Arthrotec, and Celebrex. The P&T Committee recommended Zipsor, Cambia, naproxen Naprelan and Ponstel be designated NF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. NSAIDs—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—CONTRACEPTIVE AGENTS

P&T Comments

A. Contraceptive Agents Drug Class

The P&T Committee evaluated the relative clinical effectiveness of the drugs in the Contraceptive Agents class. The clinical review for the contraceptive products included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1). The Contraceptives Agents class is comprised of three subclasses: oral contraceptive products (OCPs), miscellaneous contraceptives (transdermal patch, vaginal ring, medroxyprogesterone injections) and emergency contraceptives.

The Contraceptive Agents were previously reviewed in May 2006 for UF status. Generic formulations are available for several products (See Table 1). Four new OCPs have recently entered the market: drospirenone 3mg/ethinyl estradiol (EE) 20 mcg/levomefolate Ca 0.451mg (Beyaz), norethindrone acetate 1mg/EE 10mcg/ferrous fumerate 75mg (Lo Loestrin Fe), levonorgesterol 0.1mg/EE 20mcg and levonorgesterol 0.1mg/EE 10mcg for extended use (LoSeasonique), and drospirenone 3mg/EE 30mcg/levomefolate Ca 0.451mg (Safyral). One new emergency contraceptive is also available, ulipristal (Ella).

Several OCPs are available on the UF and BCF, and all the miscellaneous contraceptives are currently designated as UF. For the emergency contraceptives, in November 2009, levonorgestrel 0.75 mg (Next Choice, Plan B generic) was designated as BCF and levonorgestrel 1.5 mg (Plan B One Step) was designated formulary on the Uniform Formulary.

The Contraceptive Drug Class accounted for $87 million in MHS expenditures in FY 2010. In terms of MHS utilization, drospirenone 3mg/EE 20mcg (Yaz,

generics) is the most utilized contraceptive, followed by norgestimate 0.18mg/0.215mg/0.25mg/EE 25mcg (Ortho Tri-Cyclen Lo).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended the following conclusions for the contraceptives:

- **Oral Contraceptives Subclass—**For the OCPs subclass, the P&T Committee, voted (14 for, 0 against, 0 abstained, 1 absent) the following conclusions were made:

  1. The differences among the OCPs include estrogen content, progestogen content, regimen, phasic formulation, and non-contraceptive benefits (e.g., acne, premenstrual dysmorphic disorder). The most commonly utilized OCPs are the low-estrogen products containing 20-30 mcg of EE. OCPs commonly include an estrogen with a progestin (combined OCP).
  2. There are no clinically relevant differences in contraceptive effectiveness among the different OCPs, as they all have Pearl Indices (pregnancies per 100 woman-years of use) ranging from < 1 to <3. Current literature does not provide sufficient evidence that combined OCs containing ≤ 20 mcg EE differ from those with higher EE dosage in preventing pregnancy. However, combined OCs with ≤ 20 mcg EE are associated with higher rates of changes in bleeding and amenorrhea.
  3. The continuous and extended cycle products (Lybrel Seasonale, Seasonique, LoSeasonique), allow for shorter, fewer or no periods, and are very popular. The Cochrane reviewers concluded extended or continuous cycle contraceptives are reasonable options for women without contraindications to therapy. Of note, the same regimen can be reproduced by eliminating the pill-free interval of monophasic combined OCs for 2-3 cycles.
  4. Most if not all combined contraceptives offer non-contraceptive benefits, including control of heavy menstrual bleeding or irregular cycles, and reduction of acne, dysmenorrhea, endometriosis pain and menstrual migraines, regardless of FDA approval for uses other than pregnancy prevention.
  5. The most commonly reported adverse effects of oral contraceptives include breast tenderness, headache, migraine, nausea, nervousness, vomiting, dizziness, weight gain, fluid retention, tiredness, decline of libido, and increased blood pressure.
  6. The use of combined OCs confers an increased risk of VTE. Based on epidemiological data, the risk of VTE with drospirenone (found in Yaz, Yasmin, Sayfral and Beyaz) is about 2-3 times higher than

levonorgestrel-containing OCPs; this risk appears similar to the risk with the third-generation progestins (e.g., desogestrel). FDA is currently reviewing all available data regarding the increased VTE risk with drospirenone-containing oral contraceptives.

7. Comments regarding the newest OCPs include the following: dienogest 2mg/3mg/estradiol valerate 3mg/2mg/2mg/1mg, (Natazia) has complicated dosing instructions if a dose is missed, and the benefits of a quadraphasic OCP remain to be determined. For Beyaz and Safyral, these two products are similar to Yaz and Yasmin, respectively, with the exception of folate, which is added to decrease the risk of neural tube defects if a pregnancy occurs during therapy. Efficacy for both Beyaz and Sayfral was based on data with the innovator products, and clinical trial data is not available. Lo Loestrin Fe has the lowest dose of EE available in an OCP, and had a Pearl Index of 2.92 in the open-label trial used to gain FDA approval. LoSeasonique is a low-EE dose extended cycle OCP given for 91 days (84 days of estrogen and progesterone and 7 days of low dose estrogen).

- **Miscellaneous Contraceptives Subclass—**For the miscellaneous contraceptives subclass, the P&T Committee, based upon its collective professional judgment voted (15 for, 0 against, 0 abstained, 1 absent)

  1. Contraceptive products offer alternative routes of administration including depot medroxyprogesterone acetate (DMPA) injections, a transdermal patch (Ortho Evra), and a vaginal ring (Nuvaring).
  2. Trials have demonstrated similar contraceptive effectiveness for the patch or vaginal ring as the combined OCs. The injectable DMPA contraceptives are highly effective agents; no pregnancy was reported in the three, year-long trials used to gain FDA approval.
  3. Based on a comparative trial, adverse effects of the transdermal patch appear similar to the combined OC comparator, with the exception of a higher incidence of site application reactions, breast symptoms (e.g., breast tenderness), and dysmenorrhea. Other concerns with the Ortho Evra patch include adhesion problems and application site reactions. The OrthoEvra patch has a black box warning with respect to greater risk of VTE than oral contraceptives, and higher consistent estrogen blood levels (systemic exposure ~ 60% higher than combined OCs).
  4. The most common adverse effects of the vaginal ring were vaginitis, headache, vaginal secretion, weight gain, and nausea. One concern with Nuvaring is deployment limitations related to storage requirements.
  5. Women receiving injectable DMPA may lose significant bone mineral density, an effect which may not be completely reversible. Injectable

DMPA products carry a black box warning regarding this risk. Other concerns with injectable DMPA include progressive (and substantial) weight gain, amenorrhea, irregular menses and unpredictable spotting/bleeding; and lack of immediate reversibility (10 months to return to baseline fertility)

6. The miscellaneous contraceptives serve a niche role and are appropriate contraceptive options for select patients.

- **Emergency Contraceptives Subclass—**For the miscellaneous contraceptives subclass, the P&T Committee, (14 for, 1 against, 0 abstained, 0 absent)

1. Levonorgestrel (Next Choice, generic Plan B; Plan B One Step) has a 3-day window of effectiveness following unprotected intercourse or contraceptive failure, and is available over-the-counter (OTC) for women older than 17 years. Ulipristal (Ella) is a new prescription emergency contraceptive which is effective for up to 5 days after unprotected intercourse.
2. Levonorgestrel 0.75 mg taken in 2 doses 12 hours apart has an efficacy rate of about 95% if taken within 24 hours of unprotected intercourse. Efficacy decreases over time; the efficacy rate is 86% if taken within 25-48 hours, and 58% if taken within 49 to 72 hours of unprotected intercourse. The single-dose 1.5-mg levonorgestrel regimen is as effective as the two-dose regimen taken 12 hours apart.
3. Ulipristal (Ella) is effective at preventing pregnancy following unprotected intercourse, based on the two pivotal trials. Additionally, no decrease in efficacy occurred over the 120 hour period. Two head-to-head comparisons of Ella 30 mg with levonorgestrel 1.5mg, are available. In one study Ella was non-inferior to levonorgestrel at preventing pregnancy (Creinin 2006). The other study demonstrated that Ella prevented more unintended pregnancies than levonorgestrel when administered within 72 and 120 hours after unprotected intercourse (observed pregnancy rate with Ella 1.90, 95% CI 1.13-3.12, versus levonorgestrel 2.50, 95% CI 1.68-3.94; p = 0.037; (Glasier 2010).
4. Ella was well tolerated in the clinical trials and its side effect profile is similar to that of levonorgestrel. The most common adverse effects were headache, abdominal pain, nausea and dysmenorrhea. Long term safety with Ella remains unknown.

B. Contraceptive Agents—Relative Cost-Effectiveness

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the oral contraceptive products (OCPs), the miscellaneous

contraceptives (patch, vaginal ring, medroxyprogesterone injections), and the emergency contraceptives. CMAs and BIAs were performed based on clinical findings that the efficacy, safety, tolerability, and other factors among the OCPs were similar with regard to contraception when used correctly. CMAs were used to analyze the miscellaneous contraceptives. CEAs and CMAs were used to analyze the emergency contraceptives, as efficacy differences between the agents were noted in the clinical review. 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 OCPs were designated with formulary or NF status on the UF. Two of the selected products are currently designated with BCF status: Yaz, and Yasmin. Four new agents selected are currently designated with formulary status on the UF: Beyaz, Loestrin Fe, LoSeasonique, and Safyral. Cost scenarios evaluating the impact of designating selected agents on the BCF were also considered.
- CMA alone was performed on the miscellaneous contraceptives (patch, vaginal ring, and medroxyprogesterone intramuscular (IM) and subcutaneous formulations) because there is limited generic competition within the class.
- In the emergency contraceptives subclass, CEA and CMA analyses were used to assess potential impact of pregnancies avoided, based on the clinically reviewed differences between the agents. The relative drug costs of the various treatment regimens were also assessed.

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analyses, the P&T Committee concluded the following:

- **Oral Contraceptives Subclass—**For the OCPs subclass, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 against, 0 abstained, 1 absent) as follows: BIA showed the scenario where all current BCF agents were retained on the BCF, all current UF agents that had been previously reviewed were retained on the UF, and all current NF, as well as the four new agents, were designated with NF status resulted in the lowest cost estimate compared to current MHS expenditures.
- **Miscellaneous Contraceptives Subclass—**For the miscellaneous contraceptives subclass, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 against, 0 abstained, 0 absent) as follows: CMA results showed that the average weighted price per day of therapy at all three points of service for the miscellaneous contraceptives was comparable to formulary agents included in the OCPs subclass.

- **Emergency Contraceptives Subclass—**For the emergency contraceptives subclass, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 against, 0 abstained, 0 absent) as follows: CEA results for the emergency contraceptive agents showed that at current costs, the incremental cost effectiveness ratio with ulipristal (Ella) was less than the projected annual median cost of a live birth in the United States and treatment with ulipristal is a cost-effective alternative compared to levonorgestrel in the MHS. The CMA results showed that Next Choice was the most cost-effective agent, followed by Plan B One-Step and Ella.

C. Contraceptive Agents—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 the following:

- **OCPs Subclass—**
  - The P&T Committee voted that the Jolessa branded generic formulation of Seasonale should be added to the UF.
  - The P&T Committee voted that the following drugs and their generic equivalents should be retained on the UF:
    - Monophasics with 20 mcg of EE (Yaz, , Sronyx, Loestrin 1/20, Loestrin Fe 1/20)
    - Monphasics with 30 mcg of EE (Levora, Lo/Ovral, Desogen, Loestrin 1.5/30 , Loestrin with iron 1.5/30, 1+35, Yasmin)
    - Monophasics with 35 mcg EE (Mononessa, Modicon, Zovia 1/35)
    - Monphasics with 50 mcg EE or mestranol (Zovia 1/50E, Ogestrel)
    - Biphasics (Necon 10/11, Mircette)
    - Triphasics (Ortho-Tri Cyclen Lo, Trinessa, Trivora, Tri-Norinyl, Ortho-Novum 7/7/7 Cyclessa, Nor-Q-D)
  - The following OCPs were designated NF or retained NF status on the UF:
    - norethindrone acetate 1mg/EE 10mcg (Lo Loestrin Fe)
    - levonorgestrel 0.1mg/EE 20mcg + 10mcg (LoSeasonique)
    - drospirenone 3mg/EE 20mcg/levomefolate Ca 0.451mg (Beyaz)
    - drospirenone/EE 30mcg/levomefolate Ca 0.451mg (Safyral)
    - levonorgestrel 90mcg/EE 20mcg, continuous regimen (Lybrel, generic)

- norethindrone acetate 1mg/EE 20mg, extended regimen (Loestrin 24 Fe)
- norethindrone 0.4mg/EE 35mcg (Ovcon-35 generics; also includes Femcon Fe chewable and Zeosa chewable)
- norethindrone 1mg/EE 50mcg (Ovcon-50)
- levonorgestrel 0.15mg/EE 30mcg + 10mcg, extended regimen (Seasonique, generics)
- norethindrone 1mg/EE 20mcg/30mcg/35mcg/ferrous fumerate 75mg (Estrostep Fe, generics)
- dienogest 2mg/3mg/estradiol valerate 3mg/2mg/2mg/1mg, (Natazia)
- levonorgestrel 0.15mg/EE 30mcg, extended regimen (Seasonale, generics, including Introvale and Quasense), with the exception of Jolessa branded generic

- **Miscellaneous Contraceptive Subclass—**The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following drugs remain formulary on the UF: norelgestromin/EE 50 mcg transdermal (Ortho Evra), etonorgestrel/EE vaginal ring (NuvaRing), medroxyprogesterone acetate 150 mg/mL (Depo-Provera IM, generics), and medroxyprogesterone acetate 104 mg/0.65 mL (Depo-SubQ Provera 104). No miscellaneous contraceptive agent was recommended for NF placement.

- **Emergency Contraceptive Subclass—**The P&T Committee recommended (12 for, 0 opposed, 3 abstained, 0 absent) the following drugs remain formulary on the UF: levonorgestrel 0.75mg (Next Choice; Plan B generic), levonorgestrel 1.5mg (Plan B One Step), and that ulipristal (Ella) be designated formulary on the UF. No emergency contraceptive was recommended for NF placement.

D. Contraceptive Agents—UF Implementation Plan

The P&T Committee recommended (14 for, 0 against, 0 abstained, 1 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.

V. UF CLASS REVIEWS—CONTRACEPTIVE AGENTS

BAP Comments

A. Contraceptive Agents—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 the

following:

Oral Contraceptives

- The P&T Committee voted that the Jolessa branded generic formulation of Seasonale should be added to the UF.
- The P&T Committee voted that the following drugs and their generic equivalents should be retained on the UF:
  - Monophasics with 20 micrograms of EE (Yaz, Sronyx, Loestrin 1/20, Loestrin with iron 1/20)
  - Monphasics with 30 micrograms of EE (Levora, Lo/Ovral, Desogen, Loestrin 1.5/30 , Loestrin with iron 1.5/30, 1+35, Yasmin)
  - Monophasics with 35 micrograms EE (Mononessa, Modicon, Zovia 1/35)
  - Monphasics with 50 micrograms EE or mestranol (Zovia 1/50, Ogestrel
  - Biphasics (Necon 10/11, Mircette)
  - Triphasics (Ortho-Tri Cyclen Lo, Trinessa, Trivora, Tri-Norinyl, Ortho-Novum 7/7/7 Cyclessa, Nor-Q-D)
- The following OCPs were designated NF or retained NF status on the UF:
  - Lo Loestrin with iron
  - LoSeasonique
  - Beyaz
  - Safyral
  - Lybrel
  - Loestrin 24 with iron
  - Ovcon-35, Femcon with iron, and Zeosa
  - Ovcon-50
  - Seasonique
  - Estrostep with iron
  - Natazia
  - Seasonale, and generics including Introvale and Quasense; this excludes the Jolessa product
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BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

- **Miscellaneous Contraceptive Subclass—**The P&T Committee recommended the following drugs and their generic equivalents remain formulary on the UF: Ortho Evra patch, NuvaRing, Depo-Provera IM, and Depo- Provera 104).

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

- **Emergency Contraceptive Subclass—**The P&T Committee recommended the following drugs remain formulary on the UF: Next Choice; Plan B generic, Plan B One Step, and that Ella be designated formulary on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Contraceptive Agents—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:

VI. UF CLASS REVIEWS—PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS FOR ERECTILE DYSFUNCTION (ED)

P&T Comments

A. PDE-5 Inhibitors for ED—Relative Clinical Effectiveness

Relative Clinical Effectiveness—The P&T Committee evaluated the clinical effectiveness of the PDE-5 Inhibitors for the treatment of ED. The drugs in the class include sildenafil (Viagra), tadalafil (Cialis), vardenafil oral tablets (Levitra), and one new drug—vardenafil orally dissolving tablets (ODT) (Staxyn). The PDE-5s for ED were previously reviewed in August 2009; at that time, vardenafil was designated with BCF status, with an automated PA requiring a trial of vardenafil prior to sildenafil or tadalafil, which were designated NF. Quantity limits are in place for the PDE-5s for ED.

Vardenafil ODT (Staxyn) contains the same chemical ingredient as vardenafil oral tablets (Levitra). It is available in 10 mg ODT tablets, which is the recommended dose for all patients. In contrast, the starting dose for vardenafil oral tablets is 5 mg in patients older than age 65. Pharmacokinetic studies with vardenafil 10 mg ODT show a higher area under the curve compared to vardenafil 10 mg oral tablets. The two placebo-controlled trials used to obtain FDA approval reported superior efficacy with Staxyn in treating ED. Information regarding the safety, effectiveness, and clinical outcomes of the PDE-5s for ED subclass was considered. The clinical review included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 0 absent) the following conclusions for the PDE-5s for ED:

With regards to efficacy,

1. There are no head-to-head comparative trials between the PDE-5 inhibitors assessing efficacy for ED.
2. Based on meta-analyses by AHRQ, Cochrane, and BioMed Central, indirect comparisons suggest that there are similar improvements between vardenafil oral tablets, sildenafil, and tadalafil in the following endpoints: International Index of Erectile Function (IIEF) "EF" domain change, percentage of patients responding "Yes" to Global Assessment question 1 (which asks "Did this treatment improve your erections?"), and percentage of patients reporting improved erections.

3. The improvement in IIEF score with Staxyn appears similar to that seen in the AHRQ review based on indirect comparison.
4. The 2009 PDE-5 UF review reported there was insufficient evidence to conclude that daily therapy for ED was superior to on demand therapy. There is no new evidence to change this conclusion
5. The improvement in IIIEF score with Staxyn appears similar to that seen in the AHRQ review based on indirect comparison.

With regard to safety,

6. There is insufficient evidence to conclude that there are clinically relevant differences in safety between PDE-5 inhibitors for ED.
7. Clinical trials with vardenafil ODT have identified no safety issues that were not previously identified in the studies of the vardenafil film-coated tablets. However, unlike the other PDE-5s, vardenafil ODT is not recommended for use in patients with renal or hepatic impairment.

With regard to other factors,

The PDE-5 inhibitors are highly therapeutically interchangeable, when used for treating ED.

B. PDE-5 Inhibitors for ED—Relative Cost-Effectiveness and UF Recommendation

Relative Cost-Effectiveness, Relative Cost-Effectiveness Conclusion, UF Recommendation—Due to contract solicitation issues, the cost effectiveness review and P&T Committee conclusions for the PDE-5 inhibitors for ED will be presented at an interim meeting.

VII. UF CLASS REVIEWS PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS FOR ERECTILE DYSFUNCTION (ED)

BAP Comments

A. PDE-5 Inhibitors for ED—Clinical Review

Due to contract solicitation issues, the P&T Committee conclusions for the PDE-5 inhibitors for ED will be presented at an interim meeting.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

VIII. RECENTLY APPROVED U.S. FDA AGENTS—RENIN ANGIOTENSIN ANTIHYPERTENSIVES (RAAs)

P&T Comments

A. Azilsartan (Edarbi)—Relative Clinical Effectiveness

Relative Clinical Effectiveness—Azilsartan (Edarbi) is a once daily angiotensin receptor blocker (ARB), the eighth ARB to enter the market. It is classified in the RAAs drug class. The class was last reviewed in August 2010. The clinical evaluation for Edarbi included, but was not limited to, the requirements stated in 32 Code of Federal Regulations (CFR) 199.21(e)(1).

Edarbi is indicated for the management of hypertension, alone or in combination with other agents. It has no other FDA-approved indications and there are no clinical outcomes (e.g., reduction in heart failure hospitalization, death, or type 2 diabetic renal disease) studies completed, in-process, or planned. Because of corresponding published reductions in stroke and all-cause mortality, a reduction of either systolic or diastolic blood pressure (BP) of 2 mm Hg or more is considered clinically meaningful for this review.

In seven clinical trials—two published and five unpublished—Edarbi demonstrated efficacy in treating hypertension. In two studies, it demonstrated superiority to valsartan (Diovan), a step-preferred, BCF agent, at a clinically meaningful reduction in systolic BP of 3-5 mm Hg. Additionally, Edarbi showed non-inferiority and statistical superiority (and a potentially clinically meaningful systolic BP reduction of 1-2 mm Hg) to olmesartan (Benicar). In terms of safety, there is no evidence that Edarbi is more or less safe, on average, than any of the seven other ARBs.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 1 absent) azilsartan (Edarbi) offers a compelling therapeutic advantage over valsartan and possibly olmesartan, but does not have clinical outcomes studies available.

B. Azilsartan (Edarbi)—Relative Cost-Effectiveness

Although the clinical review concluded Edarbi produced a clinically relevant reduction in BP compared to other ARBs, CMA was used to compare its cost to the other ARBs, consistent with the cost analysis for the ARBs subclass conducted at the August 2010 UF review for the RAAs. CMA was performed to evaluate Edarbi's cost in comparison to other UF RAAs drugs, including generic losartan,

telmisartan (Micardis), valsartan (Diovan), irbesartan (Avapro), olmesartan (Benicar), and candesartan (Atacand). 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 (14 for, 0 opposed, 0 abstained, 1 absent) that Edarbi was more costly than telmisartan (Micardis), valsartan (Diovan), irbesartan (Avapro), olmesartan (Benicar), and less costly than Atacand (candesartan).

C. Azilsartan (Edarbi)—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 (13 for, 0 opposed, 1 abstained, 1 absent) azilsartan (Edarbi) remain formulary on the UF.

D. Azilsartan (Edarbi)—Prior Authorization (PA) Criteria

The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) that azilsartan (Edarbi) be designated non-step preferred requiring the following step-therapy/PA criteria. 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 losartan, losartan/HCTZ, telmisartan (Micardis), telmisartan/HCTZ (Micardis HCT) telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge), or valsartan/amlodipine/HCTZ (Exforge HCT) at any Military Health Service (MHS) pharmacy point of service [Military Treatment Facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.
    b) The patient has received a prescription for azilsartan (Edarbi) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

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

a) The patient has tried one of the preferred RAAs and was unable to tolerate treatment due to adverse effects.

b) The patient has tried one of the preferred RAAs and has had an inadequate response.

c) The patient has a contraindication to the preferred RAAs, which is not expected to occur with the non-preferred RAAs (e.g., history of angioedema).

E. Azilsartan (Edarbi)—UF and PA Implementation Plan

The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service.

IX. RECENTLY APPROVED U.S. FDA AGENTS—RAAs

BAP Comments

A. Azilsartan (Edarbi)—UF Recommendation

The P&T Committee, based upon its collective professional judgment, recommended Edarbi remain formulary on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Azilsartan (Edarbi)—PA Criteria

The P&T Committee recommended that Edarbi be designated non-step preferred and would require the Prior Authorization criteria as noted above.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

C. Azilsartan (Edarbi)—UF and PA Implementation Plan

The P&T Committee recommended 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:

X. RECENTLY APPROVED U.S. FDA AGENTS—RAAs

P&T Comments

A. Aliskiren/Amlodipine/Hydrochlorothiazide (Amturnide)—Relative Clinical Effectiveness

Relative Clinical Effectiveness—Amturnide is a once daily triple-FDC antihypertensive product. It contains aliskiren, a direct renin inhibitor (DRI), amlodipine, a dihydropyridine calcium channel blocker (DHP CCB), and hydrochlorothiazide (HCTZ), a thiazide-type diuretic. Amturnide is the third triple-combination antihypertensive to enter the market. It is classified in the RAAs drug class due to the aliskiren (DRI) component. This class was last reviewed in August 2010. The clinical evaluation for Amturnide included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

Amturnide is indicated for the management of hypertension as an add-on or switch from two of the components, or as a substitute for all three titrated components, but not for initial therapy. It has no other FDA-approved indications and there are no clinical outcomes studies completed, in-process, or planned. Aliskiren has outcomes studies underway, while amlodipine and HCTZ have well-established published outcomes data.

In three unpublished clinical trials, Amturnide demonstrated efficacy in treating hypertension versus the efficacy demonstrated by dual combinations of the individual component medications. In terms of safety, there is no evidence that

Amturnide is more or less safe, on average, than either of the two other triple FDCs, valsartan/amlodipine/HCTZ (Exforge HCT) and olmesartan/amlodipine/HCTZ (Tribenzor). The combination of these three drug classes (DRI, DHP CCB and thiazide diuretic) has no compelling advantage in terms of efficacy over giving other combinations (e.g., ARB/DHP CCB/HCTZ). In terms of safety, the Amturnide FDC partially offsets the peripheral edema common to CCBs, the hypokalemia common to diuretics, and the hyperkalemia sometimes seen with ARBs.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 1 absent) that Amturnide does not offer a compelling therapeutic advantage in terms of efficacy or safety over other antihypertensive FDCs currently on the UF.

B. Aliskiren/Amlodipine/HCTZ (Amturnide)—Relative Cost-Effectiveness

CMA was performed to evaluate the cost of aliskiren/amlodipine/HCTZ (Amturnide) in relation to the other UF RAAs drugs, including the following: aliskiren/HCTZ (Tekturna HCT) plus generic amlodipine, benazepril/amlodipine, telmisartan/amlodipine (Twynsta), olmesartan/HCTZ (Benicar HCT), valsartan/amlodipine (Exforge), valsartan/amlodipine/HCTZ (Exforge HCT), olmesartan/amlodipine (Azor), and olmesartan/amlodipine/HCTZ (Tribenzor). 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 (13 for, 0 opposed, 0 abstained, 2 absent) Amturnide was more costly, compared with other RAAs currently designated with BCF or UF status.

C. Aliskiren/Amlodipine/HCTZ (Amturnide)—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 (12 for, 0 opposed, 1 abstained, 2 absent) aliskiren/amlodipine/HCTZ (Amturnide) remain formulary on the UF, as the FDC of DRI/amlodipine/HCTZ may be necessary for hypertensive patients requiring 3 drugs who do not respond to other triple FDC RAAs

D. Aliskiren/Amlodipine/HCTZ (Amturnide)—PA Criteria

The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent)

aliskiren/amlodipine/HCTZ (Amturnide) be designated non-step preferred requiring the following step-therapy/PA criteria. 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 losartan, losartan/HCTZ, telmisartan (Micardis), telmisartan/HCTZ (Micardis HCT) telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge), or valsartan/amlodipine/HCTZ (Exforge HCT) 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 aliskiren/amlodipine/HCTZ (Amturnide) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

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

    a) The patient has tried one of the preferred RAAs and was unable to tolerate treatment due to adverse effects.

    b) The patient has tried one of the preferred RAAs and has had an inadequate response.

    c) The patient has a contraindication to the preferred RAAs, which is not expected to occur with the non-preferred RAAs (e.g., history of angioedema).

E. Aliskiren/Amlodipine/HCTZ (Amturnide)—UF and PA Implementation Plan

The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) 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—RAAs

BAP Comments

A. Aliskiren/Amlodipine/HCTZ (Amturnide)—UF Recommendation

The P&T Committee, based upon its collective professional judgment, recommended Amturnide remain formulary on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Aliskiren/Amlodipine/HCTZ (Amturnide)—PA Criteria

The P&T Committee recommended Amturnide be designated non-step preferred and would require the Prior Authorization criteria as noted above

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

C. Aliskiren/Amlodipine/HCTZ (Amturnide)—UF and PA Implementation Plan

The P&T Committee recommended 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. RECENTLY APPROVED U.S. FDA AGENTS—NON-INSULIN DIABETES DRUGS DOPAMINE AGONIST

P&T Comments

A. Bromocriptine Mesylate (Cycloset)—Relative Clinical Effectiveness

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of a newly approved formulation of bromocriptine, bromocriptine mesylate (Cycloset). The clinical review included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

Cycloset is a centrally-acting dopamine agonist (DA) and is the only DA approved for the treatment of diabetes. This agent falls into the new DA subclass of the Non-Insulin Diabetes Drugs, which was reviewed for UF placement in November 2010. The other subclasses include dipeptidyl-peptidase 4 inhibitors (DPP-4s), thiazolidinediones (TZDs), glucagon-like peptide-1 receptor agonists biguanides, sulfonylureas (SUs), meglitinides, and alpha-glucosidase inhibitors. Step therapy (automated PA) applies for the Non-Insulin Diabetes Drug Class, which requires a trial of metformin or a sulfonylurea.

Bromocriptine is an old drug with a new use. It was first approved in 1978 for the treatment of Parkinson's disease and has uses in other endocrine-related disorders such as hyperprolactinemia, acromegaly, and prolactin-secreting adenomas. Bromocriptine should not be used to suppress lactation since an increase in stroke and myocardial should not be used to suppress lactation, since myocardial infarction and stroke were reported in postpartum women. The new bromocriptine Cycloset product is a quick release formulation administered in the morning. Other bromocriptine mesylate formulations are available, including immediate release (IR) 2.5 tablets and scored tablets, and 5 mg IR capsules (Parlodel, generics). Decreased levels of dopamine may contribute to insulin resistance, and increasing dopamine activity in the morning is

effective at improving glucose dysregulation. Cycloset is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus (T2DM).

Relative Clinical Effectiveness Conclusion—The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 1 absent) the following conclusions for bromocriptine mesylate (Cycloset):

- Uptitration of Cycloset is required to achieve the maximum therapeutic benefit. Patients start with 0.8mg (1 tab) daily and increase by 0.8mg in weekly increments to a maximally tolerated dose of 4.8mg daily. The minimum therapeutic dose is 1.6mg daily.

- When used as monotherapy, Cycloset decreased glycosolated hemoglobin or hemoglobin A1c (HbA1c) 0.1% from baseline compared to placebo. Cycloset decreased HbA1c 0.1-0.4% from baseline when added to a SU and a produced a maximum 0.5% decrease from baseline when combined with both metformin and a SU.

- There are no head-to-head studies to date with other non-insulin diabetes medications and no long-term outcomes studies currently in progress.

- Bromocriptine mesylate is weight neutral; however, as with other medications, more weight gain is likely when administered with a SU or TZD. It may have a beneficial effect on lipid levels and BP.

- Nausea is the primary side effect (~31%) although bromocriptine mesylate is generally well tolerated. The incidence of serious adverse events is similar to placebo.

- There was a statistically significant decrease in major cardiovascular events with Cycloset noted in one 52-week study. However, the clinical relevance of this secondary endpoint is not clear.

- Many potential drug interactions exist with Cycloset, including strong CYP 3A4 inducers or inhibitors; highly protein-bound drugs (e.g. salicylates, sulfonamides, chloramphenicol, probenecid); dopamine receptor antagonists; ergot-related drugs and sympathomimetic drugs.

- According to current T2DM treatment guidelines, the place in therapy for bromocriptine mesylate (Cycloset) remains unknown.

B. Bromocriptine Mesylate (Cycloset)—Relative Cost Effectiveness

The P&T Committee evaluated the cost of bromocriptine mesylate (Cycloset). CMA was performed. 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 (13 for, 0 opposed, 0 abstained, 2 absent) Cycloset was more costly when compared to step-preferred UF agents (metformin, SU, DPP-4 inhibitors, TZDs) and generic bromocriptine mesylate IR.

C. Bromocriptine Mesylate (Cycloset)—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 (12 for, 1 opposed, 1 abstained, 1 absent) bromocriptine mesylate (Cycloset) be designated NF and non-step preferred.

D. Bromocriptine Mesylate (Cycloset)—PA Criteria

Step therapy applies to this new subclass (dopamine agonists) requiring prior trial of metformin or a sulfonylurea. Bromocriptine mesylate (Cycloset) is recommended to be designated as non-step preferred and NF. The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 absent) the following PA criteria should apply to bromocriptine mesylate (Cycloset).

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

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

    a) The patient has a confirmed diagnosis of T2DM.
    b) 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.

c) The patient has experienced the following adverse event while receiving a SU: hypoglycemia requiring medical treatment.
d) The patient has a contraindication or has had inadequate therapy to both metformin and a SU.

E. Bromocriptine Mesylate (Cycloset)—PA Criteria and UF Implementation Plan

The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 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 decision.

XIII. RECENTLY APPROVED U.S. FDA AGENTS—NON-INSULIN DIABETES DRUGS DOPAMINE AGONIST

BAP Comments

A. Bromocriptine Mesylate (Cycloset)—UF Recommendation

The P&T Committee, based upon its collective professional judgment, recommended Cycloset) be designated non formulary and non-step preferred.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Bromocriptine Mesylate (Cycloset)—PA Criteria

The P&T Committee recommended Cycloset would be designated as non-step preferred and would require the Prior Authorization criteria as noted above.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

C. Bromocriptine Mesylate (Cycloset)—PA Criteria and UF Implementation Plan

The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 1 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 decision.

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

XIV. RECENTLY APPROVED U.S. FDA AGENTS—NARCOTIC ANALGESICS

P&T Comments

A. Buprenorphine Transdermal System (Butrans)—Relative Clinical Effectiveness

Relative Clinical Effectiveness—Butrans is a transdermal formulation of buprenorphine, a semi-synthetic opioid with mixed agonist/antagonist activity at opioid receptors. It is a Schedule III drug, classified as a low-potency single analgesic agent in the Narcotic Analgesics Drug Class. The class was last reviewed in February 2007. The clinical evaluation for Butrans included, but was not limited to, the requirements stated in 32 CFR 199.21(e)(1).

There are other formulations of buprenorphine commercially available: parenteral formulations for post-operative pain management and sublingual tablets for the management of opioid-dependence. Butrans is indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock, opioid analgesic for an extended period of time. One transdermal system allows for systemic delivery of buprenorphine, continuously over seven days, which offers a convenient regimen for patients.

In two unpublished clinical trials, Butrans demonstrated efficacy in treating chronic low back pain. There are no direct head-to-head studies comparing it to other long-acting narcotic agents of similar potency marketed in the United States. In terms of safety, there are some additional concerns with Butrans compared to

other narcotics, particularly the risk of QTc prolongation at doses greater than 20mcg/hr, which will limit its use in patients with unstable cardiac disease. The major safety issue with Butrans is buprenorphine-induced respiratory depression. This poses a concern for elderly patients or those with impaired pulmonary function since the effects of buprenorphine are not completely reversible with naloxone (an opioid antagonist). Butrans is not intended for patients requiring treatment with high–dose opioids (>80 mg/day of morphine or equivalent), another factor that may limit its use in patients stable on alternative opioid analgesics. Butrans provides an additional treatment option when a long-acting, low-potency analgesic is needed.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) that other than the convenience of less frequent dosing, buprenorphine transdermal system (Butrans) offers no other compelling therapeutic advantages over the other low potency narcotic analgesics currently on the UF.

B. Buprenorphine Transdermal System (Butrans)—Relative Cost Effectiveness

The P&T Committee evaluated Butran's cost relative to the other low-potency agents in the Narcotic Analgesics Drug Class. CMA was performed based on clinical findings that efficacy, safety, tolerability, and factors other than patient convenience found among the agents in this class were similar at equipotent doses. 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—The P&T Committee, based upon its collective professional judgment, concluded (15 for, 0 opposed, 0 abstained, 0 absent) that buprenorphine transdermal system (Butrans) was more costly, based on an average weighted cost per day of therapy, than other low-potency single analgesic agents currently on the UF. However, Butrans was less costly than the sublingual formulations of buprenorphine already on the UF.

C. Buprenorphine Transdermal System (Butrans)—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 (12 for, 2 opposed, 1 abstained, 0 absent) buprenorphine transdermal system (Butrans) remain formulary on the UF with prior authorization to ensure appropriate use of the drug.

D. Buprenorphine Transdermal System (Butrans)—PA Criteria

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following PA criteria should apply to Butrans. Coverage would be approved if the patient met any of the following criteria:

1. Manual PA criteria:

    a) Coverage provided for patients ≥18 yrs with moderate-to-severe chronic pain requiring opioid therapy.

        (1) Opioid naïve patients (prior use of <30 mg/day of morphine or equivalent in past 60 days) are limited to Butrans 5 mcg/hr patch.

        (2) Opioid tolerant patients (prior use of 30mg/day to 80 mg/day of morphine or equivalent within past 60 days or Butrans 5 mcg/hr patch) can receive Butrans 10 mcg/hr and 20 mcg/hr patches.

        (3) Maximum dose of Butrans is 20 mcg/hr.

    b) Coverage NOT provided for treatment of opioid-dependence.

    c) Coverage NOT provided for patients:

        (1) Requiring >80 mg/day of morphine or equivalent for pain control;

        (2) With significant respiratory depression or severe bronchial asthma;

        (3) With long QT syndrome or family history of long QT syndrome;

        (4) On concurrent Class 1A (procainamide, quinidine) or Class III (dofetilide, amiodarone, sotalol) antiarrythmics.

E. Buprenorphine Transdermal System (Butrans)—PA Criteria and UF Implementation Plan

The P&T Committee recommended (14 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.

XV. RECENTLY APPROVED U.S. FDA AGENTS—NARCOTIC ANALGESICS

BAP Comments

A. Buprenorphine Transdermal System (Butrans)—UF Recommendation

The P&T Committee, based upon its collective professional judgment, recommended Butrans remain formulary on the UF with prior authorization to ensure appropriate use of the drug.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Buprenorphine Transdermal System (Butrans)—PA Criteria

The P&T Committee recommended the Prior Authorization criteria noted above should apply to Butrans.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

C. Buprenorphine Transdermal System (Butrans)—PA Criteria and 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.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

XVI. UTILIZATION MANAGEMENT

P&T Comments

A. Montelukast (Singulair)—PA Criteria

PA criteria were proposed for montelukast. National and international treatment guidelines, as well as pertinent published clinical literature, were used to define supportable indications for use of montelukast. Utilization data from the MHS population was presented to the P&T Committee with respect to indications deemed supportable.

The P&T Committee recommended (12 for, 1 opposed, 1 abstained, 1 absent) the following PA criteria should apply to montelukast. Montelukast will be approved only for patients under the age of 19 and patients 19 or older who show evidence of use for an FDA-approved and guideline-supported indication. All current and new users of montelukast must meet one of the following criteria to pass through the PA process.

1. Automated PA criteria:
    a) Patient is ≤18 years of age.
    b) Patient has received an inhaled corticosteroid or inhaled beta agonist during the previous 180 days at a MTF, retail network pharmacy, or the mail order pharmacy.
2. Manual PA criteria:
    a) Coverage approved if:
        (1) The patient/provider documents use of montelukast for seasonal allergic rhinitis (or nasal polyposis) with evidence of a inadequate therapy with a nasal corticosteroid dispensed during the previous 180 days at a MTF, a retail network pharmacy, or the mail order pharmacy; or

        (2) The patient/provider documents intolerance (due to experienced adverse events) or contraindication to either inhaled or intranasal corticosteroids.

B. Montelukast (Singulair)—PA Implementation Period

The P&T Committee recommended (12 for, 0 opposed, 2 abstained, 1 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all points of service; and 2) TMA send a letter to beneficiaries affected by this UF decision.

XVII. UTILIZATION MANAGEMENT/ITEMS FOR INFORMATION

BAP Comments

A. Montelukast (Singulair)—PA

The P&T Committee recommended the Prior Authorization criteria as noted above should apply to Singulair. Singulair will be approved only for patients under the age of 19 and patients 19 or older who show evidence of use for an FDA-approved and guideline-supported indication. All current and new users of Singulair must meet one of the criteria above to pass through the Prior Authorization process.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Montelukast (Singulair)—PA Implementation Period

The P&T Committee recommended 1) an effective date of the first Wednesday after a 90-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: