DEPARTMENT OF DEFENSE 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 199.21, the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee is responsible for developing the Uniform Formulary (UF). Recommendations to the Director, Defense Health Agency (DHA), 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—INHALED CORTICOSTEROIDS/LONG-ACTING BETA AGONISTS (ICS/LABAs) COMBINATIONS

P&T Comments

A. ICS/LABAs Combinations—Relative Clinical Effectiveness and Conclusion

The P&T Committee evaluated the clinical effectiveness of the ICS/LABA combinations, which were last reviewed for UF status in February 2009. Since the last review, one new drug, fluticasone/vilanterol (Breo Ellipta) has been marketed. Military Health System (MHS) expenditures for the class were $168 million in calendar year 2013. The P&T Committee agreed (16 for, 0 opposed, 0 abstained, 0 absent) with the following conclusions:

1. Fluticasone/salmeterol (Advair) and budesonide/formoterol (Symbicort) are highly therapeutically interchangeable for asthma. For asthma, head-to-head trials and systematic reviews show no significant differences in efficacy.
2. For chronic obstructive pulmonary disease (COPD), there is insufficient evidence to conclude that there are clinically relevant differences in efficacy between Advair and Symbicort.
3. Advair Diskus, Symbicort, and Breo Ellipta are all FDA-approved for maintenance treatment of COPD; however, only Advair Diskus and Breo Ellipta are specifically approved for decreasing COPD exacerbations. Symbicort does have data from observational studies showing decreases in COPD exacerbations.
4. For mometasone/formoterol (Dulera), there are no head-to-head trials with another ICS/LABA in asthma; clinically relevant differences in efficacy are not expected. Dulera is not approved for COPD; two trials have shown benefit in improving spirometric endpoints in COPD.
5. There is only limited data for Breo Ellipta in patients with asthma, and it is not FDA-approved for this indication.

6. Breo Ellipta offers the convenience of once-a-day dosing in COPD. However, the long-term safety of the LABA component vilanterol is not known. One large trial (SUMMIT) evaluating mortality as a primary endpoint is underway.
7. Advair Diskus in the only drug approved for treatment of asthma in children down to the age of four years; however, for this age range, a metered dose inhaler (MDI) with a spacer is more commonly used. It also has the advantage of availability in both a MDI [Advair hydrofluoroalkane (HFA)] and dry powder inhaler (Advair Diskus).
8. For safety, a systematic review did not show clinically relevant differences between Advair and Symbicort in asthma. Advair Diskus, Advair HFA, Symbicort, Dulera, and Breo Ellipta all contain the same black box warnings and precautions. All drugs containing a LABA carry a black box warning for the increased risk of death in asthma.
9. Breo Ellipta and Dulera have a lower degree of interchangeability with Advair and Symbicort, due to their limited FDA-approved indications.
10. The Pharmacy Outcomes Research Team (PORT) presented an analysis of the use of ICS/LABAs by indications and found that asthma represents the majority of MHS use (67% of beneficiaries had ICD-9 diagnosis codes indicative of asthma, while 37% had codes for COPD, and 17% had codes for neither diagnosis). However, there was considerable overlap between the COPD and asthma diagnosis codes.

B. ICS/LABAs Combinations—Relative Cost-Effectiveness Analysis and Conclusion

A pharmacoeconomic analysis and budget impact analysis (BIA) were performed to evaluate the ICS/LABAs. The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following:

- The pharmacoeconomic analysis showed that fluticasone/salmeterol (Advair Diskus/Advair HFA) was the most cost-effective agent in this class, followed by mometasone/formoterol (Dulera), budesonide/formoterol (Symbicort), and fluticasone/salmeterol (Breo Ellipta).
- A BIA was performed to evaluate the potential impact of scenarios, with selected agents designated step-preferred and formulary or non-preferred and NF on the UF. BIA results showed that the scenario where Advair Diskus and Advair HFA are designated as step-preferred and formulary, with Dulera, Symbicort, and Breo Ellipta designated as non-preferred and NF, was the most cost-effective option for the MHS.

C. ICS/LABAs Combinations—UF Recommendation

The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) the following for the ICA/LABAs, based on clinical and cost effectiveness:

- UF and step-preferred: fluticasone/salmeterol (Advair Diskus and Advair HFA)

- NF and non-preferred: budesonide/formoterol (Symbicort), mometasone/formoterol (Dulera), and fluticasone/vilanterol (Breo Ellipta)
- This recommendation includes step therapy, which requires a trial of Advair Diskus or Advair HFA in all new and current users of Symbicort, Dulera, and Breo Ellipta who are older than 12 years.

D. ICS/LABAs Combinations—Prior Authorization (PA) Criteria

The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) automated (step therapy) and manual PA criteria in all new and current users of Symbicort, Dulera, and Breo Ellipta who are older than 12 years of age; a trial of Advair Diskus or Advair HFA is required before the non-step preferred drugs.

Automated PA criteria

- The patient has filled a prescription for Advair or Advair HFA at any MHS pharmacy point of service [Military Treatment Facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.

  AND

Manual PA criteria—If automated criteria are not met, Symbicort, Dulera, or Breo Ellipta is approved (e.g., trial of Advair Diskus or Advair HFA is NOT required) if:

- Patient has experienced any of the following issues with either Advair Diskus or Advair HFA, which is not expected to occur with the non-preferred ICS/LABA combination drug:
  - inadequate response to Advair Diskus or Advair HFA
  - intolerable adverse effects
  - contraindication
  - patient previously responded to the nonformulary agent and changing to a formulary agent would incur unacceptable risk

E. ICS/LABAs Combinations—UF and PA Implementation Plan

The P&T Committee recommended (13 for, 2 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service (POS); and, 2) DHA send a letter to beneficiaries affected by the UF decision; and, 3) that the ICS/LABA Drug Class be added to the safety net program (Rapid Response Program).

III. UF CLASS REVIEWS—ICS/LABAs Combinations

BAP Comments

A. ICS/LABAs Combinations—UF Recommendation

The P&T Committee recommended the following for the ICA/LABAs, based on clinical and cost effectiveness:

- UF and step-preferred: fluticasone/salmeterol (Advair Diskus and Advair HFA)
- NF and non-preferred: budesonide/formoterol (Symbicort), mometasone/formoterol (Dulera), and fluticasone/vilanterol (Breo Ellipta)
- This recommendation includes step therapy, which requires a trial of Advair Diskus or Advair HFA in all new and current users of Symbicort, Dulera, and Breo Ellipta who are older than 12 years.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

B. ICS/LABAs Combinations—PA Criteria

The P&T Committee recommended automated (step therapy) and manual PA criteria in all new and current users of Symbicort, Dulera, and Breo Ellipta who are older than 12 years of age; a trial of Advair Diskus or Advair HFA is required before the non-step preferred drugs.

Automated PA criteria

- The patient has filled a prescription for Advair or Advair HFA at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

  AND

Manual PA criteria—If automated criteria are not met, Symbicort, Dulera, or Breo Ellipta is approved (e.g., trial of Advair Diskus or Advair HFA is NOT required) if:

- Patient has experienced any of the following issues with either Advair Diskus or Advair HFA, which is not expected to occur with the non-preferred ICS/LABA combination drug:
  - inadequate response to Advair Diskus or Advair HFA

- intolerable adverse effects
- contraindication
- patient previously responded to the nonformulary agent and changing to a formulary agent would incur unacceptable risk

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

C. ICS/LABAs Combinations—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 POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision; and, 3) that the ICS/LABA Drug Class be added to the safety net program (Rapid Response Program).

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

IV. UF CLASS REVIEWS—GASTROINTESTINAL (GI-1s) DRUG CLASS

P&T Comments

A. GI-1s: Oral Aminosalicylates Subclass—Relative Clinical Effectiveness and Conclusion

The P&T Committee evaluated the relative clinical effectiveness of the oral aminosalicylates, a subclass within the GI-1s Drug Class. The subclass is comprised of generic sulfasalazine and the 5-aminosalicylate (5-ASA) products [balsalazide (generic Colazal and Giazo), olsalazine (Dipentum), and mesalamine (Delzicol, Asacol HD, Pentasa, Lialda, and Apriso)].

The GI-1s were previously reviewed for UF placement in February 2011, and mesalamine delayed release (DR) tablets (Asacol), along with generic sulfasalazine, were recommended for BCF addition. Asacol was discontinued from the market in March 2013 due to safety concerns of dibutyl phthalate (DBP) present in the enteric coating of Asacol tablets. A new phthalate-free mesalamine DR formulation, Delzicol is now

available. At the May 2013 meeting, Asacol was removed from the BCF, pending a re-review of the subclass. Currently, the only aminosalicylate on the BCF is sulfasalazine.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) the following conclusions for the aminosalicylates drug class:

1. Sulfasalazine remains the first-line oral aminosalicylate. For the induction of remission in active ulcerative colitis (UC), evidence from two systematic reviews found no clinically relevant differences in efficacy between sulfasalazine and the newer 5-ASA formulations.
2. For maintenance of remission in UC, another systematic review showed a therapeutic advantage of sulfasalazine over the 5-ASA formulations. This advantage was offset by an increase in adverse events observed with sulfasalazine, due to the sulfapyridine moiety.
3. The newer 5-ASA formulations employ different release mechanisms, which deliver the active drug to various sites in the GI tract. These differences in drug release and site of release do not confer additional benefits in terms of clinical response.
4. The mesalamine product Delzicol is the phthalate-free replacement for Asacol that is bioequivalent to its predecessor; no clinical trials were conducted to evaluate efficacy or safety.
5. Giazo is a new balsalazide product with a higher strength per unit than the other balsalazide formulations (1,100 mg versus 750 mg with Colazal). It is not approved for use in women, and it offers no compelling advantage to the other balsalazide products commercially available.
6. The safety profile is similar for the 5-ASA products, based on systematic reviews. In clinical trials, females treated with Giazo reported more adverse events than males.
7. Lialda and Apriso are dosed once daily, which provides patient convenience, but have not been shown to have clinically relevant benefits in terms of adherence compared to 5-ASAs dosed twice or three times daily. Lialda and Apriso also have the lowest tablet burden.
8. The 5-ASA products are highly therapeutically interchangeable for treating UC. The choice of 5-ASA for UC will depend on other factors, such as location and extent of disease, as well as patient preference in terms of tablet burden and frequency of dosing.

B. GI-1s: Oral Aminosalicylates Subclass—Relative Cost-Effectiveness Analysis and Conclusion

Cost minimization analysis (CMA) and BIA were performed to evaluate the GI-1s Aminosalicylate Subclass. The P&T Committee concluded (15 for, 0 opposed, 1 abstained, 0 absent) the following:

- CMA results showed that generic sulfasalazine was the most cost-effective agent in this subclass, followed by balsalazide 750 mg (Colazal, generics), olsalazine (Dipentum), and the branded mesalamine agents Apriso, Lialda, Delzicol, Asacol HD, and Pentasa. Giazo (branded balsalazide 1,100 mg) was not cost-effective relative to other agents in this class.

- BIA was performed to evaluate the potential impact of scenarios with selected agents designated formulary or NF on the UF. BIA results showed the scenario with Apriso, Delzicol, and Lialda designated as formulary on the UF, with Asacol HD and Pentasa designated as NF, was the most cost-effective for the MHS.

C. GI-1s: Oral Aminosalicylates Subclass—UF Recommendation

The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) the following, based on the high degree of therapeutic interchangeability and cost-effectiveness:

- UF: sulfasalazine, balsalazide 750 mg (Colazal, generics), olsalazine (Dipentum), and the mesalamine products Delzicol, Lialda, and Apriso
- NF: Pentasa, Asacol HD and the balsalazide 1,100 mg product (Giazo)

D. GI-1s: Oral Aminosalicylates Subclass—UF Implementation Plan

The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision.

V. UF CLASS REVIEWS—GI-1s DRUG CLASS

BAP Comments

A. GI-1s: Oral Aminosalicylates Subclass—UF Recommendation

The P&T Committee recommended the following, based on the high degree of therapeutic interchangeability and cost-effectiveness:

- UF: sulfasalazine, balsalazide 750 mg (Colazal, generics), olsalazine (Dipentum), and the mesalamine products Delzicol, Lialda, and Apriso
- NF: Pentasa, Asacol HD and the balsalazide 1,100 mg product (Giazo)

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

B. 5-ARIs Subclass—UF Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision.

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

VI. UF CLASS REVIEWS—PANCREATIC ENZYME PRODUCTS (PEPs)

P&T Comments

A. PEPs—Relative Clinical Effectiveness and Conclusion

The P&T Committee evaluated the relative clinical effectiveness of the PEPs. The class was previously an extended core formulary class and last reviewed in February 2011. The PEPs were reviewed for the FDA-approved indication of exocrine pancreatic insufficiency (EPI) due to cystic fibrosis or other conditions; other uses (e.g., pain relief from pancreatitis) were not reviewed. Since the last review, three new products, Pertzye, Viokace, and Ultresa, have been marketed. The PEPs all contain various amounts of lipase, amylase, and protease.

The P&T Committee recommended (15 for, 1 opposed, 0 abstained, 0 absent) the following conclusions:

1. Based on clinical efficacy alone, Creon, Pancreaze, Zenpep, Viokace, Ultresa, and Pertzye are effective at increasing coefficient of fat absorption in patients with EPI, compared to placebo. Only limited clinical trial data is available.
2. Creon has the most indications and highest MHS utilization. Among the PEPs, Creon has an additional indication for EPI due to pancreatitis or pancreatectomy.
3. Zenpep has the most dosage strengths available, but it is solely approved for EPI due to cystic fibrosis.
4. Zenpep and Viokace have information for gastrostomy tube administration.
5. Viokace is an uncoated tablet that is not approved for use in pediatrics; it requires administration with a proton pump inhibitor, to prevent degradation in the stomach.

6. Creon, Pancreaze, and Zenpep have dosing recommendations for infants as young as 12 months of age while Pancreaze has dosing information in infants as young as 6 months.
7. Pertzye and Ultresa have limited data regarding efficacy in treating EPI and have limited dosage strengths available.
8. With regards to safety, the available evidence suggests there are no clinically relevant differences between any of the PEPs.
9. There is a high degree of therapeutic interchangeability among the class.

B. PEPs—Relative Cost-Effectiveness Analysis and Conclusion

CMA and BIA were performed to evaluate the PEPs Drug Class. The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 0 absent) the following:

- CMA results showed that Creon was the most cost-effective agent in this class, followed by Zenpep, Pancreaze, and Viokace. Ultresa and Pertzye were not cost-effective relative to other agents in this class.
- BIA was performed to evaluate the potential impact of scenarios with selected agents designated formulary or NF on the UF. BIA results showed the scenario with Creon, Zenpep, Pancreaze, and Viokace designated as formulary on the UF, with Ultresa and Pertzye designated as NF on the UF, was the most cost-effective for the MHS.

C. PEPs—UF Recommendation

The P&T Committee recommended (13 for, 2 opposed, 1 abstained, 0 absent) Creon, Pancreaze, Zenpep, and Viokace remain on the UF, and that Pertzye and Ultresa be designated as NF.

D. PEPs—UF Implementation Plan

The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision.

VII. UF CLASS REVIEWS—PEPs

BAP Comments

A. PEPs—UF Recommendation

The P&T Committee recommended Creon, Pancreaze, Zenpep, and Viokace remain on the UF, and that Pertzye and Ultresa be designated as NF.

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

B. PEPs—UF Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision.

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

VIII. RECENTLY APPROVED U.S. FDA AGENTS—ANTIDEPRESSANTS (AD-1s)

P&T Comments

A. AD-1s: Bupropion Extended Release (ER) 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), Levomilnacipran (Fetzima), and Vortioxetine (Brintellix)

The P&T Committee concluded (16 for, 0 against, 0 absent, 0 abstain) the following with regard to the clinical efficacy and safety of bupropion ER 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), levomilnacipran (Fetzima), and vortioxetine (Brintellix). All four drugs are indicated solely for the treatment of major depressive disorder (MDD).

1. Forfivo XL
    a) Forfivo XL is an extended-release 450 mg formulation of bupropion, a norepinephrine/dopamine reuptake inhibitor (NDRI). Several generic formulations of bupropion (Wellbutrin, Wellbutrin SR, and Wellbutrin XL) are on the BCF. There are no clinical trials with Forfivo XL; FDA approval was based on demonstrated bioequivalence to three tablets of 150 mg Wellbutrin XL.

    b) Limitations to the product include that patients must be titrated with another bupropion formulation first, and the dose cannot be adjusted in renal or hepatic impairment.

c) Forfivo XL has similar safety and tolerability concerns as other bupropion agents.

d) While Forfivo XL offers an alternative treatment option of one tablet administered once daily for patients requiring a high dose of bupropion, it offers no compelling clinical advantages over the other bupropion formulations on the BCF or UF.

2. Desvenlafaxine ER (Khedezla)

a) Khedezla is a serotonin/norepinephrine reuptake inhibitor (SNRI) that is an extended-release form of desvenlafaxine (Pristiq). Khedezla differs from Pristiq in the salt form (desvenlafaxine base versus desvenlafaxine succinate). Generic desvenlafaxine formulations are now available.

b) Khedezla has shown bioequivalence to Pristiq in three studies; there are no clinical trials available.

c) Khedezla offers no clinically relevant advantages over the venlafaxine products (Effexor, Effexor XR, generic) products on the UF.

3. Levomilnacipran (Fetzima)

a) Levomilnacipran is a SNRI and is an extended-release stereoisomer of milnacipran (Savella). Fetzima is indicated for MDD whereas Savella is indicated for fibromyalgia.

b) There are no head-to-head studies comparing levomilnacipran with other antidepressants.

c) In the three placebo-controlled studies used to gain FDA approval, all levomilnacipran doses produced a statistically significant change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS). However, varying effects on response rates (e.g., a 50% reduction in the MADRS score from baseline) have been reported, depending on the dose and study design. There was no difference from placebo in remission rate at any levomilnacipran dose.

d) The safety profile of levomilnacipran is similar to milnacipran (Savella) and carries the same warnings.

e) Levomilnacipran offers no clinically compelling advantages over the other AD-1s on the UF.

4. Vortioxetine (Brintellix)

a) There have been no head-to-head studies between vortioxetine and other antidepressants. In four of seven placebo-controlled studies, vortioxetine was superior to placebo in improving MADRS or HAMD (Hamilton Depression Rating Scale) scores from baseline.

b) In active comparator studies using duloxetine (Cymbalta) or venlafaxine (Effexor), vortioxetine showed similar clinical results in the endpoints of MADRS, HAMD, response, or remission.

c) The most common adverse events (AEs) with vortioxetine include nausea and vomiting. Vortioxetine has fewer known AEs and warnings compared to desvenlafaxine, duloxetine (Cymbalta), and levomilnacipran. However, vortioxetine is the newest AD-1 to reach the market and additional AEs may increase during post-marketing surveillance.

d) Although vortioxetine offers additional serotonergic effects in its mechanism of action and has fewer AEs overall than some of the other AD-1s, this has not translated into greater efficacy in treating depression.

B. AD-1s: Bupropion ER 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), Levomilnacipran (Fetzima), and Vortioxetine (Brintellix)—Relative Cost-Effectiveness Analysis and Conclusion

CMA was performed to evaluate new antidepressants bupropion ER 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), levomilnacipran (Fetzima), and vortioxetine (Brintellix) compared with other AD-1 subclasses, including selective serotonin reuptake inhibitors (SSRIs), SNRIs, and NDRIs. Based on the CMA results, the P&T Committee concluded (16 for, 0 against, 0 absent, 0 abstain) the following:

- For the NDRIs, the current BCF drugs—generic bupropion immediate release (IR), sustained release and ER formulations—were the most cost-effective agents, followed by the new entrant Forfivo XL and then followed by the NF branded product bupropion hydrobromide (Aplenzin).

- For the SNRIs and SSRIs subclasses, the BCF drugs citalopram and sertraline were the most cost-effective drugs, followed by generic venlafaxine IR and ER, and then followed by generic desvenlafaxine, Khedezla, generic duloxetine (Cymbalta), levomilnacipran (Fetzima), vortioxetine (Brintellix), and branded duloxetine (Cymbalta), ranked in order from most to least cost effective.

C. AD-1s: Bupropion ER 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), Levomilnacipran (Fetzima), and Vortioxetine (Brintellix)—UF Recommendation

The P&T Committee recommended (15 for, 0 against, 0 absent, 1 abstain) bupropion ER 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), levomilnacipran (Fetzima), and vortioxetine (Brintellix) be designated NF, based on clinical and cost effectiveness. Additionally, the P&T Committee recommended Khedezla, Fetzima, and Brintellix be non-step preferred ("behind the step"), which requires a trial of a formulary AD-1 prior to use in all current and new patients. See Prior Authorization section, below.

D. AD-1s: Bupropion ER 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), Levomilnacipran (Fetzima), and Vortioxetine (Brintellix)—PA Criteria

The P&T Committee recommended (15 for, 0 against, 0 absent, 1 abstain) PA criteria should apply to Khedezla, Fetzima, and Brintellix.

1. Desvenlafaxine ER (Khedezla): For all new users of Khedezla, patients are required to try venlafaxine IR or ER (Effexor, Effexor XR; generics) first.

2. Levomilnacipran (Fetzima) and vortioxetine (Brintellix): For new users of Fetzima or Brintellix, patients are required to try a generic SSRI, duloxetine, SNRI (except milnacipran), tricyclic antidepressant (TCA), mirtazapine, bupropion, serotonin antagonist reuptake inhibitor (trazodone or nefazodone), or mononamine oxidase inhibitor (MAOI) first.

- **Desvenlafaxine ER (Khedezla)—**PA criteria apply to all new users of Khedezla.

  Automated PA criteria

  - The patient has filled a prescription for venlafaxine IR or venlafaxine ER at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

    AND

  Manual PA criteria—If automated criteria are not met, Khedezla is approved in new users (e.g., trial of venlafaxine IR or venlafaxine ER is NOT required) if:

  - Use of the formulary SNRI (venlafaxine) is contraindicated (e.g., hypersensitivity to a dye or other inert ingredient) and use of any other formulary antidepressant is not clinically appropriate.
  - The patient has previously responded to Khedezla, and changing to a formulary medication would incur unacceptable risk (e.g., the patient is currently stabilized on therapy with Khedezla and changing to a formulary medication would present a risk of destabilization).
  - The patient is being treated for depression, requires treatment with a SNRI (e.g., due to failure of SSRI therapy), and has failed an adequate trial of venlafaxine. Note: an adequate trial is generally considered to be at least 4–8 weeks in duration, due to the delay in achieving maximal benefit.
  - The patient requires treatment with a SNRI (e.g., due to failure of SSRI therapy), and has been unable to tolerate venlafaxine.

- **Levomilnacipran (Fetzima) and vortioxetine (Brintellix)—**PA criteria apply to all new users of Fetzima and Brintellix.

  Automated PA criteria

  - The patient has filled a prescription for a formulary SSRI, duloxetine, SNRIs (except milnacipran), TCA, mirtazapine, buproprion, trazodone or nefazodone, or an MAOI at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

    AND

  Manual PA criteria—For new users, Fetzima or Brintellix is approved (e.g., trial of a formulary AD-1 listed above is NOT required) if:

  - Use of a formulary antidepressant (SSRI, duloxetine, SNRI (except milnacipran), TCA, mirtazapine, bupropion, trazodone or nefazodone, or MAOI) is contraindicated (e.g., hypersensitivity to a dye or other inert ingredient) and use of any other formulary antidepressant is not clinically appropriate.
  - The patient has previously responded to Fetzima or Brintellix, and changing to a formulary medication would incur unacceptable risk (e.g., the patient is currently stabilized on therapy with Fetzima or Brintellix and changing to a formulary medication would present a risk of destabilization).
  - The patient is being treated for depression and has failed therapy with the formulary antidepressants (SSRI, duloxetine, SNRI (except milnacipran), TCA, mirtazapine, bupropion, trazodone or nefazodone, or MAOI). Note: an adequate trial is generally considered to be at least 4–8 weeks in duration, due to the delay in achieving maximal benefit.
  - The patient is being treated for depression and has been unable to tolerate the formulary antidepressants (SSRI, duloxetine, SNRI (except milnacipran), TCA, mirtazapine, bupropion, trazodone or nefazodone, or MAOI).

E. AD-1s: Bupropion ER 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), Levomilnacipran (Fetzima), and Vortioxetine (Brintellix)—UF and PA Implementation Plan

The P&T Committee recommended (15 for, 0 against, 0 absent, 1 abstain) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2)

DHA send a letter to beneficiaries affected by the UF decision.

IX. RECENTLY APPROVED U.S. FDA AGENTS—AD-1s

BAP Comments

A. AD-1s: Bupropion ER 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), Levomilnacipran (Fetzima), and Vortioxetine (Brintellix)—UF Recommendation

The P&T Committee recommended bupropion ER 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), levomilnacipran (Fetzima), and vortioxetine (Brintellix) be designated NF, based on clinical and cost effectiveness. Additionally, the P&T Committee recommended Khedezla, Fetzima, and Brintellix be non-step preferred ("behind the step"), which requires a trial of a formulary AD-1 prior to use in all current and new patients. See Prior Authorization section, below.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

B. AD-1s: Bupropion ER 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), Levomilnacipran (Fetzima), and Vortioxetine (Brintellix)—PA Criteria

The P&T Committee recommended PA criteria should apply to Khedezla, Fetzima, and Brintellix.

1. Desvenlafaxine ER (Khedezla): For all new users of Khedezla, patients are required to try venlafaxine IR or ER (Effexor, Effexor XR; generics) first.
2. Levomilnacipran (Fetzima) and vortioxetine (Brintellix): For new users of Fetzima or Brintellix, patients are required to try a generic SSRI, duloxetine, SNRI (except milnacipran), TCA, mirtazapine, bupropion, serotonin antagonist reuptake inhibitor (trazodone or nefazodone), or MAOI first.

- **Desvenlafaxine ER (Khedezla)—**PA criteria apply to all new users of Khedezla.

  Automated PA criteria

  - The patient has filled a prescription for venlafaxine IR or venlafaxine ER at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

AND

Manual PA criteria—If automated criteria are not met, Khedezla is approved in new users (e.g., trial of venlafaxine IR or venlafaxine ER is NOT required) if:

- Use of the formulary SNRI (venlafaxine) is contraindicated (e.g., hypersensitivity to a dye or other inert ingredient) and use of any other formulary antidepressant is not clinically appropriate.
- The patient has previously responded to Khedezla, and changing to a formulary medication would incur unacceptable risk (e.g., the patient is currently stabilized on therapy with Khedezla and changing to a formulary medication would present a risk of destabilization).
- The patient is being treated for depression, requires treatment with a SNRI (e.g., due to failure of SSRI therapy), and has failed an adequate trial of venlafaxine. Note: an adequate trial is generally considered to be at least 4–8 weeks in duration, due to the delay in achieving maximal benefit.
- The patient requires treatment with a SNRI (e.g., due to failure of SSRI therapy), and has been unable to tolerate venlafaxine.

- **Levomilnacipran (Fetzima) and vortioxetine (Brintellix)—**PA criteria apply to all new users of Fetzima and Brintellix.

Automated PA criteria

- The patient has filled a prescription for a formulary SSRI, duloxetine, SNRIs (except milnacipran), TCA, mirtazapine, buproprion, trazodone or nefazodone, or an MAOI at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

AND

Manual PA criteria—For new users, Fetzima or Brintellix is approved (e.g., trial of a formulary AD-1 listed above is NOT required) if:

- Use of a formulary antidepressant (SSRI, duloxetine, SNRI (except milnacipran), TCA, mirtazapine, bupropion, trazodone or nefazodone, or MAOI) is contraindicated (e.g., hypersensitivity to a dye or other inert ingredient) and use of any other formulary antidepressant is not clinically appropriate.
- The patient has previously responded to Fetzima or Brintellix, and changing to a formulary medication would incur unacceptable risk

(e.g., the patient is currently stabilized on therapy with Fetzima or Brintellix and changing to a formulary medication would present a risk of destabilization).

- The patient is being treated for depression and has failed therapy with the formulary antidepressants (SSRI, duloxetine, SNRI (except milnacipran), TCA, mirtazapine, bupropion, trazodone or nefazodone, or MAOI). Note: an adequate trial is generally considered to be at least 4–8 weeks in duration, due to the delay in achieving maximal benefit.
- The patient is being treated for depression and has been unable to tolerate the formulary antidepressants (SSRI, duloxetine, SNRI (except milnacipran), TCA, mirtazapine, bupropion, trazodone or nefazodone, or MAOI).

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

C. AD-1s: Bupropion ER 450 mg (Forfivo XL), desvenlafaxine ER (Khedezla), Levomilnacipran (Fetzima), and Vortioxetine (Brintellix)—UF and PA Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday after a 90-day implementation period in all POS; and, 2) DHA send a letter to beneficiaries affected by the UF decision.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

X. UTILIZATION MANAGEMENT

P&T Comments

A. Overactive Bladder (OAB) Drugs: Mirabegron (Myrbetriq)—PA Criteria

Mirabegron was FDA-approved for OAB in June 2012 and launched in October 2013. It

will be reviewed as a new drug at an upcoming meeting. Mirabegron is a beta-3 agonist, which is a unique mechanism compared to the antimuscarinic OAB drugs (darifenacin, fesoterodine, tolterodine, oxybutynin, solifenacin, and trospium). In placebo-controlled trials, the efficacy of mirabegron on OAB symptoms appears similar to that of the other OAB drugs; however, mirabegron causes less anticholinergic AEs (dry mouth, constipation). The OAB drugs were reviewed for UF placement in November 2012, and automated PA (step therapy) was implemented, requiring a trial of a generic OAB drug or Detrol LA in all new and current users of an OAB drug.

The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 1 absent) PA criteria for all new users of mirabegron (Myrbetriq) for OAB.

- **Mirabegron (Myrbetriq)—**PA criteria apply to all new users of Myrbetriq.

  Automated PA criteria

  - The patient has filled a prescription for tolterodine ER (Detrol LA), oxybutynin ER, oxybutynin IR, or generic trospium IR (Sanctura) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

  Manual PA criteria—If automated criteria are not met, Myrbetriq is approved if:

  - Coverage is only approved for the FDA-approved indication of OAB with symptoms of urge incontinence, urgency, and urinary frequency
  - Patient has failed a 12-week trial with at least one of the following step-preferred OAB drugs (Detrol LA, oxybutynin ER, oxybutynin IR, or trospium IR) due to a treatment failure or intolerable adverse effects.
  - Patient has experienced central nervous system (CNS) adverse effects with oral OAB medications or is at increased risk for such CNS effects due to comorbid conditions or other medications.

B. Overactive Bladder (OAB) Drugs: Mirabegron (Myrbetriq)—PA Implementation

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday after a 30-day implementation period in all POS.

XI. UTILIZATION MANAGEMENT

BAP Comments

A. Overactive Bladder (OAB) Drugs: Mirabegron (Myrbetriq)—PA Criteria

The P&T Committee recommended PA criteria for all new users of mirabegron (Myrbetriq) for OAB.

- **Mirabegron (Myrbetriq)—**PA criteria apply to all new users of Myrbetriq.

  Automated PA criteria

  - The patient has filled a prescription for tolterodine ER (Detrol LA), oxybutynin ER, oxybutynin IR, or generic trospium IR (Sanctura) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

  Manual PA criteria—If automated criteria are not met, Myrbetriq is approved if:

  - Coverage is only approved for the FDA-approved indication of OAB with symptoms of urge incontinence, urgency, and urinary frequency
  - Patient has failed a 12-week trial with at least one of the following step-preferred OAB drugs (Detrol LA, oxybutynin ER, oxybutynin IR, or trospium IR) due to a treatment failure or intolerable adverse effects.
  - Patient has experienced central nervous system (CNS) adverse effects with oral OAB medications or is at increased risk for such CNS effects due to comorbid conditions or other medications.

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

B. OAB Drugs: Mirabegron (Myrbetriq)—PA Implementation

The P&T Committee recommended an effective date of the first Wednesday after a 30-day implementation period in all POS.

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

XII. UTILIZATION MANAGEMENT

P&T Comments

A. Phosphodiesterase-5 (PDE-5) Inhibitor: Avanafil (Stendra)—PA Criteria

Avanafil is a new PDE-5 inhibitor approved by the FDA in April 2012, but not launched until January 2014. It is only approved for erectile dysfunction (ED). Currently, automated PA (step therapy) applies to the class for ED; Viagra is the step-preferred PDE-5 for ED.

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 1 absent) PA criteria for all users of Avanafil (Stendra) for ED. A trial of sildenafil (Viagra) for ED is required prior to using Stendra. Uses other than ED, including benign prostatic hypertrophy, following prostatectomy, pulmonary arterial hypertension, or Raynaud's phenomenon are not allowed.

- **Avanafil (Stendra)—**PA applies to all new and current users of avanafil (Stendra).

  Automated PA criteria

  - The patient has received a prescription for sildenafil (Viagra) at any MHS point of service (MTFs, Retail Network or Mail Order) during the previous 180 days.
  - The patient is a male, aged 40 years of older with ED.

  Manual PA criteria—if automated criteria are not met. Stendra is approved if:

  - The patient has tried sildenafil (Viagra) and has had an inadequate response or was unable to tolerate treatment due to adverse effects.
  - Treatment with Viagra is contraindicated.

  Note: Coverage is approved only for erectile dysfunction (ED). Use for benign prostatic hyperplasia (BPH), following prostatectomy, pulmonary arterial hypertension, and Raynaud's phenomenon is not allowed. Additionally, use is not allowed for treatment of ED in males younger than age 18, for ED due to psychogenic origin, or in women for female sexual dysfunction.

XIII. UTILIZATION MANAGEMENT

BAP Comments

A. PDE-5 Inhibitor: Avanafil (Stendra)—PA Criteria

The P&T Committee recommended PA criteria for all users of Avanafil (Stendra) for ED. A trial of sildenafil (Viagra) for ED is required prior to using Stendra. Uses other than ED, including benign prostatic hypertrophy, following prostatectomy, pulmonary arterial hypertension, or Raynaud's phenomenon are not allowed.

- **Avanafil (Stendra)—**PA applies to all new and current users of avanafil (Stendra).

  Automated PA criteria

  - The patient has received a prescription for sildenafil (Viagra) at any MHS point of service (MTFs, Retail Network or Mail Order) during the previous 180 days.

  - The patient is a male, aged 40 years of older with ED.

  Manual PA criteria—if automated criteria are not met. Stendra is approved if:

  - The patient has tried sildenafil (Viagra) and has had an inadequate response or was unable to tolerate treatment due to adverse effects.

  - Treatment with Viagra is contraindicated.

    Note: Coverage is approved only for erectile dysfunction (ED). Use for benign prostatic hyperplasia (BPH), following prostatectomy, pulmonary arterial hypertension, and Raynaud's phenomenon is not allowed. Additionally, use is not allowed for treatment of ED in males younger than age 18, for ED due to psychogenic origin, or in women for female sexual dysfunction.

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

XIV. RE-EVALUATION OF NF AGENTS

P&T Comments

A. Duloxetine (Cymbalta)—UF Recommendation and Implementation

On an ongoing basis, the DHA Pharmacoeconomic Branch monitors changes in the clinical information, current costs, and utilization trends to determine whether the UF status of agents designated as NF needs to be readdressed. The P&T Committee's process for reevaluating NF agents was established at the May 2007 meeting and approved by the Director, TMA, on June 24, 2007.

The P&T Committee reevaluated the UF status of duloxetine (Cymbalta) in light of recent price reductions in generic formulations across all three POS. Additionally, automated PA (step therapy) requires a trial of a generic formulary antidepressant or generic non-opioid pain syndrome drug before receiving Cymbalta. As of the meeting,

the generic duloxetine products were not cost-effective relative to the price of branded Cymbalta.

The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 0 absent) maintaining Cymbalta as NF and continuing the current step therapy. When generic formulations of Cymbalta become cost-effective relative to the step-preferred agents, generic duloxetine will move to UF status, become step-preferred (e.g., "in front of the step"), and existing PA criteria will be removed without further action by the P&T Committee, Beneficiary Advisory Panel, or Director, DHA. A generic agent is cost-effective relative to step-preferred agents when the generic agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the step-preferred agent.

XV. RE-EVALUATION OF NF AGENTS

BAP Comments

A. Duloxetine (Cymbalta)—UF Recommendation and Implementation

The P&T Committee recommended maintaining Cymbalta as NF and continuing the current step therapy. When generic formulations of Cymbalta become cost-effective relative to the step-preferred agents, generic duloxetine will move to UF status, become step-preferred (e.g., "in front of the step"), and existing PA criteria will be removed without further action by the P&T Committee, Beneficiary Advisory Panel, or Director, DHA. A generic agent is cost-effective relative to step-preferred agents when the generic agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the step-preferred agent.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention