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—DEPRESSION AND NON-OPIOID PAIN SYNDROME AGENTS

P&T Comments

A. Depression and Non-Opioid Pain Syndrome Agents

Background Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the Depression and Non-Opioid Pain Syndrome Drug Class. The class is comprised of the former UF Antidepressants-1 (AD-1s) Drug Class [selective serotonin reuptake inhibitors (SSRIs), selective serotonin/norepinephrine reuptake inhibitors (SNRIs), serotonin antagonist reuptake inhibitors (SARIs), norepinephrine/dopamine reuptake inhibitors (NDRIs), alpha-2 receptor antagonists (A2RAs), serotonin partial agonist/reuptake inhibitors (SPARIs)]; the gamma-aminobutyric acid (GABA) analogs; and the tricyclic antidepressants (TCAs). Military Health System (MHS) expenditures for the Depression and Non-Opioid Pain Syndrome Drug Class exceed $490 million annually.

The class as a whole has not been previously reviewed; however, the AD-1s were reviewed in November 2005, and the GABA analogs were reviewed in February 2006. The drugs in this class are:

- SSRIs: citalopram, escitalopram (Lexapro), fluoxetine, fluoxetine 90 mg weekly regimen (Prozac Weekly), fluoxetine in special packaging (Sarafem), fluvoxamine, paroxetine hydrochloride (HCl) IR, paroxetine HCl controlled release (CR), paroxetine mesylate (Pexeva), sertraline

- SNRIs: duloxetine (Cymbalta), desvenlafaxine (Pristiq), milnacipran (Savella), venlafaxine IR, venlafaxine extended release (ER) capsules, venlafaxine ER tablets
- SARIs: nefazodone, trazodone IR, trazodone ER (Oleptro)
- NDRIs: bupropion HCl IR, bupropion HCl SR, bupropion ER, bupropion hydrobromide (HBr) (Aplenzin)
- A2RAs: mirtazapine tablets, mirtazapine ODT
- SPARIs: vilazodone (Viibryd)
- GABAs: gabapentin, pregabalin (Lyrica)
- TCAs: amitriptyline, desipramine, doxepin, imipramine HCl, imipramine pamoate, nortriptyline, protriptyline

The two newest entrants to the class are trazodone ER (Oleptro) and vilazodone (Viibryd). Two new gabapentin formulations have been approved by the FDA, gabapentin ER (Gralise) and gabapentin encarbil ER (Horizant), but will be reviewed at an upcoming DoD P&T Committee meeting.

For the clinical and cost effectiveness reviews, the Depression and Non-Opioid Pain Syndrome drugs were also evaluated in relation to the skeletal muscle relaxant cyclobenzaprine, and the monoamine oxidase inhibitors (MAOIs), when appropriate.

In order to support the clinical and cost-effectiveness evaluations in this complex class, the Pharmacy Outcomes Research Team (PORT) analyzed prior use of agents in this class among DoD beneficiaries initiating treatment with desvenlafaxine, duloxetine, milnacipran, or pregabalin between April 1, 2011, and June 30, 2011. A total of 135,402 new users (defined as no use of the index medication during the prior 180 days) of one of these four agents were included in the analysis.

The four study medications (desvenlafaxine, duloxetine, milnacipran, pregabalin) were chosen for analysis based on both clinical and economic considerations: all four are widely used or have potential for wide use, have alternatives that offer equal or greater clinical value, and offer the potential for minimizing costs with neutral or beneficial effects on patient outcomes. The analysis was undertaken to estimate new user rates, understand prescribing patterns, and to assess the number of beneficiaries likely to be affected by step therapy programs involving these agents.

Drugs in the class were divided into three groups (with some overlap) for purposes of the analysis:

- Group A (the four study medications): desvenlafaxine, duloxetine, milnacipran, pregabalin;

- Group B (medications used for depression): SSRIS, SNRIs (except milnacipran), TCAs, mirtazapine, bupropion, SARIs, MAOIs; and
- Group C (medications used for non-opioid pain syndromes): SNRIs including milnacipran, TCAs, cyclobenzaprine, GABA analogs (gabapentin and pregabalin).

For purposes of estimating the potential impact of step therapy programs for each of these agents, the "step-preferred" agents (medications that must be tried prior to receiving the study medication) were defined based on clinical considerations, available alternatives, and patterns of prior use.

- Desvenlafaxine is the active metabolite of venlafaxine. For the majority of patients, it offers no clinical advantage compared to the parent compound. Of 15,009 patients for whom desvenlafaxine was the index medication, only about 20% (3,057 patients) were new users; of these, 10% (299 patients) had received a previous prescription for venlafaxine. Looking back 2 years, desvenlafaxine was the first SNRI (venlafaxine, desvenlafaxine, or duloxetine) in 73% of patients, and the first medication for depression (Group B) medication in 25%. About ~11,000 new users annually could be affected by a requirement to try venlafaxine before desvenlafaxine.

- Duloxetine is an SNRI used both for depression and non-opioid pain syndromes, including fibromyalgia. Due to the complexity of depression and non-opioid pain treatment pathways and technical considerations of the step therapy look-back period, a conservative approach was taken with regard to step therapy requirements: the only patients affected are those for whom duloxetine is the first Group B or Group C medication prescribed in the last 180 days. Of 67,375 patients with duloxetine as their index medication, about 18% were new users. Of these, 64% had either a Group B or C medication. This leaves 36% of all new duloxetine users who would potentially be affected by a step therapy program that requires trial of any other Group B or C medication prior to receiving duloxetine.

- Milnacipran is an SNRI; however, in the United States it is indicated only for fibromyalgia. Accordingly, milnacipran was compared to the Group C medications, which includes other medications used for fibromyalgia. Of the 4,536 patients with milnacipran as their index medication, 26% were new users (no milnacipran in the last 180 days). Of these, 58% had a Group C medication in the last 180 days, leaving 42% of new milnacipran users who would potentially be affected by a step therapy program that requires a trial of any other Group C medication prior to receiving milnacipran.

- Pregabalin is a GABA analog similar to gabapentin, which is generically available. Both are used for neuropathic pain syndromes; there is little clinical evidence to support a substantial difference in efficacy or safety between the two. Of 48,482 patients with pregabalin as their index medication, about 23% were new users (no pregabalin in the last 180 days). Of these, only 24% had a gabapentin Rx in the last 180 days, leaving 76% of new pregabalin users who would potentially be affected by a step therapy program that requires a trial of gabapentin prior to receiving pregabalin.

Relative Clinical Effectiveness

1. The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 1 absent) upon the following conclusions regarding drugs used for depression, anxiety and other disorders (SSRIs, SNRIs, SARIs, NDRIs, A2RAs, SPARIs):
    - There are no compelling differences in efficacy to clearly differentiate one agent over the others.
    - High nonresponder rates in major depressive disorder (MDD) and anxiety disorders for each of the agents necessitate including a variety of agents on the UF.
    - Fluoxetine, and possibly escitalopram, are the only agents found to have a favorable risk to benefit profile in the treatment of MDD in children and adolescents.
    - Trials with duloxetine show no differences in efficacy with the comparator agents (fluoxetine, paroxetine, and venlafaxine), despite maximal doses of duloxetine and submaximal doses of the comparators.
    - Vilazodone is efficacious versus placebo for the treatment of MDD. Its unique mix of receptors may be beneficial to some patients. There are no head-to-head trials comparing vilazodone efficacy to other antidepressant agents and long-term data is limited.
    - Trazodone ER is efficacious versus placebo for the treatment of MDD. The effect appears to be heavily influenced by its sedating properties.
    - Mirtazapine consistently demonstrates the most rapid onset of action.
    - Beyond the FDA-indications, there is insufficient evidence to draw conclusions regarding the comparative efficacy of the antidepressants with respect to generalized anxiety disorder,

obsessive-compulsive disorder, panic disorder, or post-traumatic stress disorder.

- There is a high degree of therapeutic interchangeability for the majority of the antidepressants, when used for MDD.
- Discontinuation rates due to adverse events (AEs) are similar between agents.
- There is wide variation in the specific AE profiles of the antidepressant agents, which is due to their differences in receptor binding properties.
- Factors including activation/sedation properties, weight changes, sexual dysfunction, drug interactions (most commonly based on protein-binding, cytochrome P-450 CYP isoenzyme induction/inhibition), or therapeutic duplication may guide treatment decisions in individual patients.
- Rare serious AEs for mirtazapine, nefazodone, and trazodone typically limit these drugs to second-line status.
- Minor differences in other factors including different salt forms (HCl versus HBr), delivery mechanisms (IR versus ER), or active metabolites of the parent compound (desvenlafaxine versus venlafaxine) may reduce the number of drugs with the same active ingredient that are required for inclusion on the UF.

2. The P&T Committee agreed (18 for, 0 opposed, 0 abstained, 0 absent) upon the following conclusions regarding drugs used for non-opioid pain syndromes.
    - No published, direct head-to-head studies are available that compare duloxetine, milnacipran, and pregabalin for the treatment of diabetic peripheral neuropathy (DPN), fibromyalgia (FM), or post-herpetic neuralgia (PHN). Meta-analyses and systematic reviews are the primary sources for data analysis among agents.
    - Definitive statements about comparative clinical effectiveness between duloxetine and pregabalin are difficult to make given the lack of head-to-head studies.
    - The TCAs (particularly amitriptyline) and cyclobenzaprine have substantial data supporting their use, at low doses, in several pain syndromes, and are supported as first-line therapy by many clinical practice guidelines.

- *Fibromyalgia:*
    - A meta-analysis published in JAMA 2009 concluded the following:
        - There is strong evidence for the efficacy of antidepressants (TCAs, SNRIs, SSRIs, MAOIs) in the treatment of FM.
        - Antidepressants were shown to decrease pain, sleep disturbance, and depressed mood and improve HRQoL. The effect sizes were smaller for SNRIs, SSRIs, and MAOIs than for TCAs. There is strong evidence against a favorable effect of antidepressants on improving fatigue.
    - A systematic review from the Oregon Drug Effectiveness Review Project (DERP) showed the following:
        - Paroxetine IR was superior to the TCA amitriptyline in decreasing pain and sleep disturbance in one head-to-head study.
        - Amitriptyline was similar to duloxetine, milnacipran, and pregabalin on outcomes of relieving pain and fatigue. There was insufficient data on other outcomes (changes in patient rating scales) to compare the drugs.
        - Milnacipran was inferior to duloxetine on outcomes of pain, depressed mood, and health-related quality of life (HRQoL), and inferior to both duloxetine and pregabalin on improving sleep disturbance.
        - Duloxetine was not effective in reducing pain in male, nonwhite, and older patients.
    - In a meta-analysis by Straube and colleagues, 24% of FM patients taking pregabalin at higher doses (450mg–600mg) obtained at least 50% pain relief based on the patient global impression of change rating scale. The pregabalin dose-response relationship for efficacy in FM was not as striking as that seen in other conditions.
- *Post-Herpetic Neuralgia*: According to the PLoS Medicine systematic review (2005), there is evidence of analgesic efficacy (number needed to treat < 5.0) in PHN for TCAs, opioids, gabapentin, tramadol, and pregabalin.

- *Chronic Low Back Pain* (CLBP):
    - Duloxetine has received an indication for chronic musculoskeletal pain based on studies in CLBP and osteoarthritis of the knee. Duloxetine should not be used first line for CLBP. Acetaminophen, NSAIDs, and a trial of a TCA should be used prior to use of duloxetine for this indication.
    - In the clinical trials used to obtain FDA approval for CLBP, half of the patients treated with duloxetine achieved at least a 30% improvement in pain, which is statistically significant but not clinically significant. There is a significant placebo response (~ 40%) compared to duloxetine when used for CLBP.
    - Treating 5–8 patients with duloxetine resulted in modest improvement in pain (a minimally perceptible difference) in one patient treated for 13 weeks.
- *Phantom Limb Pain*
    - Only limited information is available. Current VA/DoD guidelines recommend pregabalin, gabapentin, antidepressants (e.g., SSRIs, or TCAs).
    - Two small trials (<45 patients) reported in the DERP review showed a moderate benefit with gabapentin compared to placebo.
    - There is no published data with pregabalin and a clinical trial with duloxetine was terminated early.
- Safety and Tolerability
    - Duloxetine: An additional safety warning exists regarding use in patients with hepatic impairment. Withdrawals due to AEs occurred more often with duloxetine (15%) than placebo (8%). Duloxetine is more likely to cause nausea, somnolence, constipation, and decreased appetite versus placebo.
    - Pregabalin is similar to gabapentin in AEs, although more peripheral edema and weight gain are likely with pregabalin compared to gabapentin. Pregabalin causes more dizziness and somnolence compared to placebo.

    - For both duloxetine and pregabalin, more patients with neuropathic pain discontinue taking the active drug compared with placebo.
    - Titration and tapering is required with all of the agents.
- Other factors that differentiate the drugs: Duloxetine is dosed once daily and its patent is expected to expire December 2013; pregabalin is dosed three times daily and is a controlled medication. All agents must be dosed based on either renal or hepatic concerns. Most pharmacy benefit managers have some form of restriction in place for duloxetine, milnacipran and pregabalin.

3. The P&T Committee agreed (18 for, 0 opposed, 0 abstained, 0 absent) upon the following conclusions regarding the TCAs:
    - *Depression*
        - In the primary care setting, based on one meta-analysis (McGillivray), there was a trend in favor of TCAs over SSRIs, although the p-value was not significant in terms of the weighted mean difference in depression scores. There was no significant difference between TCAs and SSRIs in terms of improvement in the Clinical Global Impression (CGI) scale.
        - Another meta-analysis (Arroll) showed that there were no apparent differences between SSRIs and TCAs in terms of an indirect comparison of the CGI, as the relative risks versus placebo were similar (1.37 with SSRIs versus 1.26 with TCAs) and the confidence intervals overlapped.
        - Use of TCAs for depression has largely been replaced by the SSRIs and SNRIs due to safety issues.
    - *DPN*: One meta-analysis (Wong) showed TCAs were significantly more effective than placebo in terms of the odds ratio for 50% decrease in pain over 3–6 weeks.
    - *Fibromyalgia*: The JAMA meta-analysis showed TCAs have large effect sizes for reducing pain, fatigue, and sleep disturbances compared to SSRIs, SNRIs, and MAOIs. There were no significant differences when amitriptyline was compared with cyclobenzaprine and nortriptyline in the DERP review.
    - *PHN*: TCAs are significantly more effective than placebo.

B. Depression and Non-Opioid Pain Syndrome Agents—Relative Cost-Effectiveness

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the depression and non-opioid pain syndrome agents. Based on the clinical findings regarding efficacy, safety, tolerability, other factors, and clinical outcomes with these agents, CMAs were performed to compare individual agents as well as combinations of these agents primarily used in the treatment of depression, non-opioid pain syndromes, or both. Budget impact analyses (BIAs) were also performed to compare competing formulary scenarios in the evaluation of the cost-effectiveness of the various groupings of these agents. Various scenarios incorporating step therapy were also evaluated, based on clinical considerations, available alternatives, and patterns of prior use derived from the PORT analysis outlined above.

Depression Analysis: One analysis evaluated the drugs for depression, including the SSRIs, NDRIs, and the SARIs. The cost of these agents was compared across therapeutic classes in a CMA. The A2RAs, SPARIs, and TCAs were also included in this CMA.

Depression Analysis—desvenlafaxine (Pristiq) versus venlafaxine: The SNRIs (desvenlafaxine and venlafaxine) were also modeled individually in a CMA and BIA to evaluate use of step therapy, where a trial of venlafaxine would be required for new users of desvenlafaxine.

Non-Opioid Pain Syndromes Analysis—pregabalin (Lyrica) versus gabapentin: This analysis included the GABA analogs, pregabalin, and gabapentin. The cost-effectiveness of pregabalin (Lyrica) versus gabapentin was determined in a CMA and BIA to evaluate use of step therapy, where a trial of gabapentin would be required for new users of pregabalin.

Depression and Non-Opioid Pain Syndromes Analysis—duloxetine (Cymbalta) and milnacipran (Savella): CMA and BIA were used to evaluate the cost-effectiveness of duloxetine and milnacipran. The combined depression and non-opioid pain syndromes analyses were grouped into the same categories outlined in the PORT analysis. The depression analysis group ("Group B drugs") included the SSRIs, SNRIs (except milnacipran), TCAs, mirtazapine, bupropion, SARIs, and MAOIs. The non-opioid pain syndrome analysis group ("Group C drugs") included the SNRIs (with milnacipran), TCAs, cyclobenzaprine, and GABA analogs (gabapentin and pregabalin). The final analysis compared the depression and non-opioid pain syndrome drugs together. Costs for each of the subgroups, along with the individual weighted average costs for duloxetine and milnacipran, were used in the CMAs and BIAs to evaluate various step therapy scenarios for the drugs of interest: duloxetine (Cymbalta) versus the depression

and non-opioid pain syndrome drugs, and milnacipran (Savella) versus the non-opioid pain syndrome drugs.

Relative Cost-Effectiveness Conclusion—Based on the results of the economic analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 against, 0 abstained, 0 absent) the following for the depression and/or non-opioid pain syndrome agents:

Depression Analysis: CMA results for the depression drugs [SSRIs, SARIs, NDRIs, A2RAs, SPARIs, TCAs, and MAOIs, (not including the SNRIs)], showed the following ranking, from least costly to most costly: SARIs (predominantly generic trazodone) <TCAs < A2RAs < SSRIs (using current prices for escitalopram) < NDRIs < MAOIs < SPARIs. When looking specifically at new entrants to the class, trazodone ER (Oleptro) and vilazodone (Viibryd) were less cost-effective than other antidepressants. The same is true of bupropion HBr (Aplenzin). Several current NF antidepressants are now available or are expected to become available in cost-effective generic formulations, including escitalopram (Lexapro), fluoxetine in special packaging (Sarafem), fluoxetine weekly (Prozac weekly), and paroxetine CR (Paxil CR).

Desvenlafaxine (Pristiq) versus venlafaxine: CMA results for desvenlafaxine and venlafaxine versus the other depression drugs showed SARIs, TCAs, A2RAs, SSRIs, and NDRIs to be less costly than the SNRIs. Among the SNRIs, venlafaxine was more cost-effective than desvenlafaxine, based on cost per day of treatment. BIA was used to assess the potential impact of cost scenarios where selected agents were designated formulary or NF on the UF. Cost scenarios evaluating the impact of designating agents on the BCF were also considered. BIA results showed the most cost-effective scenario was venlafaxine IR/ER as step-preferred on the UF/BCF, with desvenlafaxine (Pristiq) designated NF and non-step-preferred; a trial of venlafaxine IR/ER would be required for new users of desvenlafaxine. Cost-effective generic formulations of venlafaxine ER capsules are now available.

Non-Opioid Pain Syndromes Analysis and pregabalin (Lyrica) versus gabapentin: CMA results specifically focusing on pregabalin (Lyrica) versus gabapentin for non-opioid pain syndromes showed that TCAs and cyclobenzaprine, which are predominantly generic were less costly than the GABA analogs. Among the GABA analogs, gabapentin was more cost-effective than pregabalin (Lyrica), based on the cost per day of treatment between these two agents. BIA was used to assess the potential impact of cost scenarios where selected agents were designated formulary or NF on the UF. Cost scenarios evaluating the impact of designating agents on the BCF were also considered. BIA results showed the most cost-effective scenario was gabapentin as step-

preferred on the UF/BCF, with pregabalin (Lyrica) designated NF and non-step-preferred; a trial of gabapentin would be required for new users of pregabalin.

Depression and Non-Opioid Pain Syndromes Analysis and duloxetine (Cymbalta) and milnacipran (Savella): CMA results specifically focused on duloxetine (Cymbalta) versus all depression and non-opioid pain syndrome drugs (Groups B and C drugs), and milnacipran (Savella) versus all non-opioid pain syndrome drugs (Group C drugs). CMA results showed that generic SSRIs, SNRIs, SARIs, NDRIs, A2RAs, SPARIs, TCAs, MAOIs, GABA analogs and cyclobenzaprine were less costly for the treatment of depression and non-opioid pain syndromes than duloxetine (Cymbalta) or milnacipran (Savella). Milnacipran (Savella) is less costly than duloxetine (Cymbalta), based on the cost per day of treatment; however, clinical evidence and FDA labeling supports the use of duloxetine in a wider range of indications than milnacipran.

BIA was used to assess the potential impact of cost scenarios where selected agents were designated formulary or NF on the UF. Cost scenarios evaluating the impact of designating agents on the BCF were also considered. BIA results showed that maintaining all depression and non-opioid pain syndrome drugs in their current BCF/UF status, maintaining duloxetine and milnacipran both as NF and non-step-preferred, was the most cost-effective scenario. Since indications for use and prior medication history beyond a 180-day lookback window cannot be determined, a trial of any other Group B or C drug was required for new users of duloxetine. Similarly, a trial of any Group C drug was required for milnacipran.

C. Depression and Non-Opioid Pain Syndrome 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:

Drugs designated with formulary status on UF:	For	Opposed	Abstain	Absent
SSRIs: citalopram fluoxetine fluvoxamine paroxetine HCl IR paroxetine HCl CR paroxetine mesylate sertraline *SNRIs:* venlafaxine IR venlafaxine ER venlafaxine ER tablets *SARIs:* nefazodone trazodone *NDRIs:* bupropion HCl IR bupropion HCl SR bupropion HCl ER *TCAs:* amitriptyline desipramine doxepin imipramine HCl imipramine pamoate nortriptyline protriptyline *A2RAs:* mirtazapine tablets mirtazapine ODT	17	0	1	0
GABA analogs: gabapentin	16	1	1	0

Drugs designated with NF status on UF:	For	Opposed	Abstain	Absent
SNRIs: desvenlafaxine (Pristiq)[1] *SARIs:* trazodone ER (Oleptro) *NDRIs:* bupropion HBr (Aplenzin)	17	0	1	0
SNRIs: duloxetine (Cymbalta)[2] milnacipran (Savella)[3] *GABA analogs:* pregabalin (Lyrica)[4] *SPARIs:* vilazodone (Viibryd)	16	1	1	0

Drugs approved to move from NF status to Formulary status on UF, once cost-effective generic formulations become available:	For	Opposed	Abstain	Absent
escitalopram (Lexapro) fluoxetine in special packaging (Sarafem) fluoxetine weekly (Prozac weekly)	17	0	1	0

[1] Desvenlafaxine (Pristiq) is nonformulary and non-step-preferred. All new users of Pristiq are required to try venlafaxine. *See* Prior Authorization Criteria, below.

[2] Duloxetine (Cymbalta) is nonformulary and non-step-preferred. All new users of Cymbalta are required to try an antidepressant [Group B drug—SSRI, SNRI (except milnacipran), TCA, mirtazapine, bupropion, SARI, or MAOI] or non-opioid pain syndrome agent [Group C drug—SNRI including milnacipran, TCA, cyclobenzaprine, gabapentin or pregabalin]. *See* Prior Authorization Criteria, below.

[3] Milnacipran (Savella) is nonformulary and non-step-preferred. All new users of Savella are required to try a non-opioid pain syndrome agent [Group C drug—SNRI including milnacipran, TCA, cyclobenzaprine, gabapentin or pregabalin]. *See* Prior Authorization Criteria, below.

[4] Pregabalin (Lyrica) is nonformulary and non-step-preferred. All new users of Lyrica are required to try gabapentin. *See* Prior Authorization Criteria, below.

D. Desvenlafaxine (Pristiq)—Prior Authorization (PA) Criteria

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) that desvenlafaxine (Pristiq) be designated step non-preferred, requiring a trial of venlafaxine in new users. Coverage would be approved if the patient met any of the following step therapy/PA criteria:

1. Automated PA criteria:
    a) The patient has filled a prescription for any venlafaxine product at any MHS pharmacy point of service [Military Treatment Facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.
2. Manual (paper) PA criteria, if automated criteria are not met: PA criteria will be developed from existing MN criteria. The existing MN criteria are as follows:

    a) The patient requires treatment with an SNRI due to failure of another formulary depression agent or has experienced adverse events from the other formulary antidepressant.
    b) The patient has a contraindication to venlafaxine or failed therapy with venlafaxine, which is not expected to occur with desvenlafaxine (Pristiq).
    c) The patient has experienced adverse events with venlafaxine which is not expected to occur with desvenlafaxine (Pristiq).
    d) The patient has previously responded to desvenlafaxine (Pristiq) and changing to a formulary depression agent would incur unacceptable risk.

E. Pregabalin (Lyrica)—PA Criteria

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) that pregabalin (Lyrica) be designated non-step-preferred, requiring a trial of gabapentin in new users. Coverage would be approved if the patient met any of the following step therapy/PA criteria:

1. Automated PA criteria:
    a) The patient has filled a prescription for gabapentin 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: PA criteria will be developed from existing MN criteria. The existing MN criteria are as follows:

a) The patient has failed therapy with gabapentin or the formulary non-opioid pain syndrome agents.

b) The patient has a contraindication to gabapentin or the formulary non-opioid pain syndrome agents which is not expected to occur with pregabalin (Lyrica).

c) The patient has experienced adverse events with gabapentin or the formulary non-opioid pain syndrome agents, which is not expected to occur with pregabalin (Lyrica).

d) The patient has previously responded to pregabalin (Lyrica).and changing to a formulary non-opioid pain syndrome agent would incur unacceptable risk.

F. Duloxetine (Cymbalta)—PA Criteria

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) that duloxetine (Cymbalta) be designated non-step-preferred, requiring a trial of any antidepressant [Group B drug—SSRI, SNRI (except milnacipran), TCA, mirtazapine, bupropion, SARI, or MAOI] or non-opioid pain syndrome agent [Group C drug—SNRI including milnacipran, TCA, cyclobenzaprine, gabapentin or pregabalin] in new users. Coverage would be approved if the patient met any of the following step therapy/PA criteria:

1. Automated PA criteria:
    a) The patient has filled a prescription for any antidepressant (Group B) or non-opioid pain medicine (Group C) 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: PA will be developed from existing MN criteria. The existing MN criteria are as follows:

    a) The patient has failed therapy with failed therapy with the formulary depression/non-opioid pain syndrome agents, which is not expected to occur with duloxetine (Cymbalta).

    b) The patient has a contraindication to the formulary depression/non-opioid pain syndrome agents which is not expected to occur with duloxetine (Cymbalta).

    c) The patient has experienced adverse events with the formulary depression/non-opioid pain syndrome agents, which is not expected to occur with duloxetine (Cymbalta).

d) The patient has previously responded to duloxetine (Cymbalta).and changing to a formulary depression/non-opioid pain syndrome agent would incur unacceptable risk.

G. Milnacipran (Savella)—PA Criteria

P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) that milnacipran (Savella) be designated non-step-preferred requiring a trial of any non-opioid pain syndrome agent [Group C drug—SNRI, including milnacipran, TCA, cyclobenzaprine, gabapentin or pregabalin] in new users. Coverage would be approved if the patient met any of the following criteria: Automated PA criteria:

1. Automated PA criteria:
    a) The patient has filled a prescription for any non-opioid pain syndrome agent (Group C) 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: PA criteria will be developed from existing MN criteria. The existing MN criteria are as follows:

    a) Use of the formulary non-opioid pain syndrome agents is contraindicated.
    b) The patient has experienced adverse effects from the formulary non-opioid pain syndrome agents.
    c) Use of the formulary non-opioid pain syndrome agents has resulted in therapeutic failure.
    d) The patient has previously responded to milnacipran (Savella) and changing to a formulary non-opioid pain syndrome agent would incur unacceptable risk.

H. Depression and Non-Opioid Pain Syndrome Agents—UF Implementation Plan

P&T Committee recommended (17 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, and 2) TMA send a letter to beneficiaries affected by this UF decision.

III. UF CLASS REVIEWS—DEPRESSION AND NON-OPIOID PAIN SYNDROME AGENTS

BAP Comments

A. Depression and Non-Opioid Pain Syndrome 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:

Drugs designated with formulary status on UI	For	Opposed	Abstain	Absent
SSRIs: citalopram fluoxetine fluvoxamine paroxetine HCl IR paroxetine HCl CR paroxetine mesylate sertraline *SNRIs:* venlafaxine IR venlafaxine ER venlafaxine ER tablets *SARIs:* nefazodone trazodone *NDRIs:* bupropion HCl IR bupropion HCl SR bupropion HCl ER *TCAs:* amitriptyline desipramine doxepin imipramine HCl imipramine pamoate nortriptyline protriptyline *A2RAs:* mirtazapine tablets mirtazapine ODT	17	0	1	0
GABA analogs: gabapentin	16	1	1	0

Drugs designated with NF status on UF:	**For**	**Opposed**	**Abstain**	**Absent**
SNRIs: desvenlafaxine (Pristiq)[1] *SARIs:* trazodone ER (Oleptro) *NDRIs:* bupropion HBr (Aplenzin)	17	0	1	0
SNRIs: duloxetine (Cymbalta)[2] milnacipran (Savella)[3] *GABA analogs:* pregabalin (Lyrica)[4] *SPARIs:* vilazodone (Viibryd)	16	1	1	0

Drugs approved to move from NF status to Formulary status on UF, once cost-effective generic formulations become available:				
	For	**Opposed**	**Abstain**	**Absent**
escitalopram (Lexapro) fluoxetine in special packaging (Sarafem) fluoxetine weekly (Prozac weekly)	17	0	1	0

[1] Desvenlafaxine (Pristiq) is nonformulary and non-step-preferred. All new users of Pristiq are required to try venlafaxine. *See* Prior Authorization Criteria, below.

[2] Duloxetine (Cymbalta) is nonformulary and non-step-preferred. All new users of Cymbalta are required to try an antidepressant [Group B drug—SSRI, SNRI (except milnacipran), TCA, mirtazapine, bupropion, SARI, or MAOI] or non-opioid pain syndrome agent [Group C drug—SNRI including milnacipran, TCA, cyclobenzaprine, gabapentin or pregabalin]. *See* Prior Authorization Criteria, below.

[3] Milnacipran (Savella) is nonformulary and non-step-preferred. All new users of Savella are required to try a non-opioid pain syndrome agent [Group C drug—SNRI including

milnacipran, TCA, cyclobenzaprine, gabapentin or pregabalin]. *See* Prior Authorization Criteria, below.

[4] Pregabalin (Lyrica) is nonformulary and non-step-preferred. All new users of Lyrica are required to try gabapentin. *See* Prior Authorization Criteria, below.

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

B. Desvenlafaxine (Pristiq)—Prior Authorization (PA) Criteria

The P&T Committee recommended that desvenlafaxine (Pristiq) be designated step non-preferred, requiring a trial of venlafaxine in new users. Coverage would be approved if the patient met any of the following step therapy/PA criteria:

1. Automated PA criteria:
    a) The patient has filled a prescription for any venlafaxine product at any MHS pharmacy point of service [Military Treatment Facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.
2. Manual (paper) PA criteria, if automated criteria are not met: PA criteria will be developed from existing MN criteria. The existing MN criteria are as follows:

    a) The patient requires treatment with an SNRI due to failure of another formulary depression agent or has experienced adverse events from the other formulary antidepressant.
    b) The patient has a contraindication to venlafaxine or failed therapy with venlafaxine, which is not expected to occur with desvenlafaxine (Pristiq).
    c) The patient has experienced adverse events with venlafaxine which is not expected to occur with desvenlafaxine (Pristiq).
    d) The patient has previously responded to desvenlafaxine (Pristiq) and changing to a formulary depression agent would incur unacceptable risk

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

C. Pregabalin (Lyrica)—PA Criteria

P&T Committee recommended that pregabalin (Lyrica) be designated non-step-preferred, requiring a trial of gabapentin in new users. Coverage would be approved if the patient met any of the following step therapy/PA criteria:

1. Automated PA criteria:
    a) The patient has filled a prescription for gabapentin 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: PA criteria will be developed from existing MN criteria. The existing MN criteria are as follows:
    a) The patient has failed therapy with gabapentin or the formulary non-opioid pain syndrome agents.
    b) The patient has a contraindication to gabapentin or the formulary non-opioid pain syndrome agents which is not expected to occur with pregabalin (Lyrica).
    c) The patient has experienced adverse events with gabapentin or the formulary non-opioid pain syndrome agents, which is not expected to occur with pregabalin (Lyrica).
    d) The patient has previously responded to pregabalin (Lyrica).and changing to a formulary non-opioid pain syndrome agent would incur unacceptable risk.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

D. Duloxetine (Cymbalta)—PA Criteria

The P&T Committee recommended that duloxetine (Cymbalta) be designated non-step-preferred, requiring a trial of any antidepressant [Group B drug—SSRI, SNRI (except milnacipran), TCA, mirtazapine, bupropion, SARI, or MAOI] or non-opioid pain syndrome agent [Group C drug—SNRI including milnacipran, TCA, cyclobenzaprine, gabapentin or pregabalin] in new users. Coverage would be approved if the patient met any of the following step therapy/PA criteria:

1. Automated PA criteria:
    a) The patient has filled a prescription for any antidepressant (Group B) or non-opioid pain medicine (Group C) 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: PA will be developed from existing MN criteria. The existing MN criteria are as follows:
    a) The patient has failed therapy with failed therapy with the formulary depression/non-opioid pain syndrome agents, which is not expected to occur with duloxetine (Cymbalta).
    b) The patient has a contraindication to the formulary depression/non-opioid pain syndrome agents which is not expected to occur with duloxetine (Cymbalta).
    c) The patient has experienced adverse events with the formulary depression/non-opioid pain syndrome agents, which is not expected to occur with duloxetine (Cymbalta).
    d) The patient has previously responded to duloxetine (Cymbalta).and changing to a formulary depression/non-opioid pain syndrome agent would incur unacceptable risk.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

E. Milnacipran (Savella)—PA Criteria

P&T Committee recommended that milnacipran (Savella) be designated non-step-preferred requiring a trial of any non-opioid pain syndrome agent [Group C drug— SNRI, including milnacipran, TCA, cyclobenzaprine, gabapentin or pregabalin] in new users. Coverage would be approved if the patient met any of the following criteria: Automated PA criteria:

1. Automated PA criteria:
    a) The patient has filled a prescription for any non-opioid pain syndrome agent (Group C) 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: PA criteria will be developed from existing MN criteria. The existing MN criteria are as follows:

    a) Use of the formulary non-opioid pain syndrome agents is contraindicated.
    b) The patient has experienced adverse effects from the formulary non-opioid pain syndrome agents.
    c) Use of the formulary non-opioid pain syndrome agents has resulted in therapeutic failure.
    d) The patient has previously responded to milnacipran (Savella) and changing to a formulary non-opioid pain syndrome agent would incur unacceptable risk.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

F. Depression and Non-Opioid Pain Syndrome Agents—UF Implementation Plan

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—SHORT-ACTING BETA AGONISTS (SABAs)

P&T Comments

A. SABAs

Relative Clinical Effectiveness—The P&T Committee evaluated the clinical effectiveness of the inhaled Short-Acting Beta Agonists (SABAs). There are three SABA products marketed in the United States, which are formulated as pressurized metered dose inhalers (MDIs) or solutions for inhalation: albuterol (a racemic mixture), levalbuterol (the (R)-enantiomer form of albuterol), and pirbuterol. The SABA inhaled solutions include albuterol (Accuneb, generics; various concentrations), and levalbuterol (Xopenex).

Hydrofluoroalkane (HFA) replaced chlorofluorocarbon (CFC) as the propellant in albuterol MDIs in December 2008. The SABA MDI formulations include albuterol HFA (Ventolin HFA, Proventil HFA, ProAir), levalbuterol HFA (Xopenex), and pirbuterol (Maxair). Pirbuterol (Maxair) is the sole remaining CFC MDI on the market, and will be discontinued in December 2013. The three albuterol HFA products are not considered therapeutically interchangeable by the FDA.

The SABA drug class was previously reviewed for UF placement in November 2008. In fiscal year 2011, over $43M was spent on the SABAs at all three points of service in the MHS.

Information regarding the safety, effectiveness, and clinical outcomes of the SABAs was considered by the Committee. The clinical effectiveness review for the SABAs was limited to the outpatient setting; emergency department use was evaluated only when pertinent.

Relative Clinical Effectiveness Conclusion—The P&T Committee voted (18 for, 0 against, 0 abstained, 0 absent) to accept the following clinical effectiveness conclusions:

1. In terms of efficacy/clinical effectiveness, there is little evidence to suggest there are clinically relevant differences between the SABAs for their FDA-approved indications. There is no new significant information to change the clinical effectiveness conclusion from the November 2008 UF review.
    - Evidence-based guidelines from the VA/DoD Clinical Practice Group (updated 2009), Global Initiative for Asthma, National Heart, Lung and Blood Institute/National Asthma Education & Prevention Program, and Global Initiative for Chronic Obstructive Lung Disease do not list a preference for one SABA over another for treating asthma, exercise-induced bronchospasm (EIB) or chronic obstructive pulmonary disease (COPD).
    - For asthma, all the SABAs are more efficacious than placebo at improving the change in forced expiratory volume in one second ≥ 12% from baseline, whether administered via MDI or inhalational solution.
    - There are no head-to-head studies comparing albuterol MDI with levalbuterol (Xopenex) MDI in adults or children.
    - For adults with asthma, there is little evidence to suggest there are clinically relevant differences between albuterol and levalbuterol when administered via the nebulized route in either the outpatient or emergency department settings—in terms of number of puffs of rescue medication used daily or from hospitalization admission rates.
    - For children with asthma, there are conflicting and inconclusive results as to whether there are efficacy differences between albuterol and levalbuterol inhalation solution when administered in the outpatient setting or emergency department.
    - EIB—Placebo-controlled trials with albuterol administered via MDI 15 to 30 minutes before exercise reported statistically significant results in terms of preventing exercise-related symptoms compared to placebo. Although levalbuterol MDI (Xopenex) is not currently approved by the FDA for EIB, the results of placebo-controlled phase III trials do not suggest that the effect of levalbuterol at preventing EIB symptoms would differ from albuterol.
    - COPD—There is insufficient evidence to compare the SABAs when used in COPD.
2. With regards to safety/tolerability, the following conclusions were made:
    - SABAs are associated with similar systemic adverse effects. A systematic review found no clinically relevant differences in discontinuation rates due to changes in heart rate, blood pressure,

palpitations, nervousness, anxiety, tremor, hyperglycemia or hypokalemia between albuterol and levalbuterol inhalation solution.

- In the outpatient setting, in adults and children, the incidence of the withdrawal rates due to AEs and overall AE rates were similar between albuterol and levalbuterol inhaled solutions. However, in children there is insufficient evidence from the outpatient studies to determine whether there are clinically relevant differences in the incidence of tachycardia, as conflicting results were reported.
- There is insufficient data with the SABA MDI formulations to assess safety differences between albuterol and levalbuterol.

3. With regards to differences between the SABAs in terms of other factors, the following conclusions were made:
    - Special populations—The P&T Committee recognized that the FDA-approved pediatric age ranges differ between the products.
    - HFA formulations—There are only minor differences between the HFA formulations of albuterol and levalbuterol, including presence of a dose counter (Ventolin HFA is the only product with a dose counter), requirements for priming, storage conditions, and excipients (Ventolin HFA is the only SABA that does not contain alcohol). However, per FDA ruling, the HFA albuterol agents are not interchangeable.
    - Delivery devices—The Ventolin MDI is not compatible with the Lever Haler spacer, but is compatible with all other spacer devices.

B. SABAs—Relative Cost-Effectiveness

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the SABAs Drug Class. Based on the clinical findings regarding efficacy, safety, tolerability, and clinical outcomes with SABAs, cost-minimization analyses (CMAs) were performed to compare the metered-dose inhalers (MDIs) and inhalation solutions. Additionally, a BIA was performed to compare competing formulary scenarios for the MDIs. 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 with the SABAs MDIs showed albuterol HFA (Ventolin HFA, Proventil HFA, ProAir HFA) inhalers are most cost-effective. While levalbuterol (Xopenex) is comparable to albuterol HFA with regards to cost, pirbuterol (Maxair) is not cost-effective relative to the other MDIs in the class. BIA results indicated that pirbuterol (Maxair) MDI designated with NF status on the UF was the most cost-effective scenario for the MHS. When the inhalation solutions were

compared, albuterol (generic; 2.5 mg/3mL concentration) was the most cost-effective inhalation solution.

Relative Cost-Effectiveness Conclusion—Based on the results of the economic analysis and other clinical and cost considerations, the P&T Committee concluded (17 for, 0 opposed, 1 abstained, 0 absent) that the most cost-effective scenario designated albuterol HFA (Ventolin HFA, Proventil HFA, ProAir HFA), levalbuterol HFA (Xopenex HFA), albuterol inhalation solution (Accuneb, generics), and levalbuterol inhalation solution (Xopenex) with formulary status on the UF and pirbuterol CFC (Maxair) inhaler with NF status on the UF.

C. SABAs—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 (17 for, 0 opposed, 1 abstained, 0 absent) albuterol HFA (Ventolin HFA, Proventil HFA, ProAir HFA), levalbuterol HFA (Xopenex HFA), albuterol inhlation solution (Accuneb, generics), and levalbuterol inhalation solution (Xopenex) remain formulary on the UF. The P&T Committee recommended that pirbuterol CFC inhaler (Maxair) be designated NF on the UF.

D. SABAs—UF Implementation Plan

Given no change in formulary status for all agents in the SABA class, the P&T Committee's recommendation reflects status quo and an implementation date is not applicable.

V. UF CLASS REVIEWS—SABAs

BAP Comments

A. SABAs—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 albuterol HFA (Ventolin HFA, Proventil HFA, ProAir HFA), levalbuterol HFA (Xopenex HFA), albuterol inhlation solution (Accuneb, generics), and levalbuterol inhalation solution (Xopenex) remain formulary on the UF. The P&T Committee recommended that pirbuterol CFC inhaler (Maxair) be designated NF on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. SABAs—UF Implementation Plan

Given no change in formulary status for all agents in the SABA class, the P&T Committee's recommendation reflects status quo and an implementation date is not applicable.

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

The P&T Committee evaluated the cost-effectiveness analysis for the PDE-5 inhibitors for ED at an interim meeting held on December 15, 2011. Please refer to the August 2011 P&T Committee minutes for the relative clinical effectiveness review and conclusions.

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

Relative Cost Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the PDE-5 inhibitors sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra, Staxyn) for erectile dysfunction. Based on clinical findings regarding efficacy, safety, tolerability, other relevant factors, and clinical

outcomes with these agents, CMAs were performed to compare individual agents. BIAs were also performed to compare competing formulary scenarios.

During this drug class evaluation, the DoD joined the VA in a joint national contracting effort. Sildenafil (Viagra) was selected as the winner of the VA/DoD national contract. To comply with the terms of the joint national contract, all scenarios considered in this review included sildenafil (Viagra) as a UF and BCF agent with all other agents designated NF.

Relative Cost Effectiveness Conclusion—Based on the results of the economic analysis and other clinical and cost considerations, the P&T Committee concluded (11 for, 0 opposed, 0 abstained, 0 absent) the following for the PDE-5 inhibitors:

- CMA results showed that sildenafil (Viagra) was the most cost-effective agent across all three points of service.

- BIA was used to compare the potential impact of discontinuing the current step therapy program (which requires a trial of vardenafil for new users with prescriptions for sildenafil or tadalafil) with scenarios where step therapy was maintained, but sildenafil (Viagra) replaced vardenafil as the step-preferred agent. Additional formulary scenarios evaluating the impact of implementing new retail restrictions were also considered. BIA results showed that, among currently available formulary options, the most cost-effective scenario placed sildenafil (Viagra) on the BCF and as the step-preferred product on the UF, with vardenafil (Levitra, Staxyn) and tadalafil (Cialis) designated NF and non-step preferred. Sensitivity analysis results supported the above conclusion.

- The P&T Committee discussed a potential program designed to strongly encourage the use of mail order instead of retail, for appropriate medications. The P&T Committee concluded that the PDE-5s would be well-suited to such a program clinically and including this drug class in such a program, if it becomes available, would most likely generate additional cost avoidance.

C. PDE-5 Inhibitors for ED—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 (11 for, 0 opposed, 0 abstained, 0 absent):

1. Sildenafil (Viagra 25 mg, 50 mg, and 100 mg) be designated with formulary status on the UF.

2. Tadalafil (Cialis 2.5 mg, 5 mg, 10 mg, and 20 mg) and vardenafil (Levitra 2.5 mg, 5 mg, 10 mg, and 20 mg; Staxyn 10 mg) be designated NF on the UF, based on cost-effectiveness.

D. PDE-5 Inhibitors for ED—UF Implementation Plan

The P&T Committee recommended (11 for, 0 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service, and 2) TMA send a letter to beneficiaries affected by this UF decision.

E. PDE-5 Inhibitors for ED—Step Therapy and PA Criteria

The P&T Committee recommended (11 for, 0 opposed, 0 abstained, 0 absent) that step therapy apply to the PDE-5 inhibitors for the treatment of ED. For all new users of PDE-5 inhibitors, the following criteria apply:

1. Automated Criteria:
   Coverage approved for treatment of ED if:
   a) The patient has received a prescription for sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra and Staxyn) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days, AND
   b) The patient is a male aged 40 years or older.

2. Manual Criteria:
   Coverage approved if:
   a) Patient has tried sildenafil (Viagra) and has had an inadequate response or was unable to tolerate treatment due to adverse effects.
   b) Treatment with sildenafil (Viagra) is contraindicated.
   c) Patient is less than 40 years of age and is being treated for ED of organic or mixed organic/psychogenic origin. [Must try sildenafil (Viagra) first or indicate inability to due to reasons stated above in 2) (a) or 2) (b)].
   d) Patient is less than 40 years of age and is being treated for drug-induced ED where the causative drug cannot be altered or discontinued. [Must try sildenafil (Viagra) first or indicate inability to due to reasons stated above in 2) (a) or 2) (b)].

Coverage approved for the following non-ED uses requiring daily therapy:

a) Use of tadalafil (Cialis or Adcirca) for Pulmonary Arterial Hypertension (PAH)

b) Use of any PDE-5 inhibitor for preservation/restoration of erectile function after prostatectomy

c) Use of any PDE-5 inhibitor for Raynaud's Phenomenon

d) Use of Cialis 5 mg for treatment of benign prostatic hyperplasia (BPH)

F. PDE-5 Inhibitors for ED—PA Implementation Plan

The P&T Committee voted (11 for, 0 opposed, 0 abstained, 0 absent) to recommend the PA implementation plan be timed to coincide with that established for the UF decision for tadalafil and vardenafil.

G. PDE-5 Inhibitors for BPH – Cialis PA

The PDE-5 inhibitor tadalafil (Cialis) 5 mg received FDA approval in October 2011 for treatment of BPH and ED with BPH. All PDE-5 inhibitors are currently subject to prior authorization, step therapy, quantity limits, and MN criteria. Prior authorization and step therapy also apply to the alpha-1 blockers used for BPH.

The DoD P&T Committee reviewed the clinical efficacy of tadalafil for BPH. Although the efficacy of tadalafil and the alpha-1 blockers for BPH cannot be directly compared, alpha-1 blockers provide relief of BPH urinary symptoms to a greater extent than PDE-5 inhibitors, based on changes from baseline in the International Prostate Symptom Scale reported in clinical trials. The P&T Committee also recommended that when used for BPH, new users of tadalafil would be required to try a preferred alpha-1 blocker first.

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) in addition to the existing PDE-5 inhibitors automated and manual PA criteria, the following PA criteria should also apply to the tadalafil when used for BPH.

1. Manual PA criteria:
    a) Patient is being treated for benign prostatic hyperplasia (BPH) and the dosing regimen prescribed is tadalafil 5 mg once daily AND
        (1) The patient has tried tamsulosin or alfuzosin and had an inadequate response;
        OR

(2) The patient has tried tamsulosin or alfuzosin and was unable to tolerate them due to adverse effects;

OR

(3) Treatment with tamsulosin or alfuzosin is contraindicated.

(4) Prior authorization for the BPH indication will expire after 1 year from input date.

H. PDE-5 Inhibitors for BPH – Cialis PA – PA Implementation Plan

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

VII. UF CLASS REVIEWS—PDE-5 INHIBITORS FOR ED

BAP Comments

A. PDE-5 Inhibitors for ED—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:

1. Sildenafil (Viagra 25 mg, 50 mg, and 100 mg) be designated with formulary status on the UF.

2. Tadalafil (Cialis 2.5 mg, 5 mg, 10 mg, and 20 mg) and vardenafil (Levitra 2.5 mg, 5 mg, 10 mg, and 20 mg; Staxyn 10 mg) be designated NF on the UF, based on cost-effectiveness.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. PDE-5 Inhibitors for ED—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:

C. PDE-5 Inhibitors for ED—Step Therapy and PA Criteria

The P&T Committee recommended that step therapy apply to the PDE-5 inhibitors for the treatment of ED. For all new users of PDE-5 inhibitors, the following criteria apply:

1. Automated Criteria:
   Coverage approved for treatment of ED if:
   a) The patient has received a prescription for sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra and Staxyn) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days, AND
   b) The patient is a male aged 40 years or older.

2. Manual Criteria:
   Coverage approved if:
   a) Patient has tried sildenafil (Viagra) and has had an inadequate response or was unable to tolerate treatment due to adverse effects.
   b) Treatment with sildenafil (Viagra) is contraindicated.
   c) Patient is less than 40 years of age and is being treated for ED of organic or mixed organic/psychogenic origin. [Must try sildenafil (Viagra) first or indicate inability to due to reasons stated above in 2) (a) or 2) (b)].

d) Patient is less than 40 years of age and is being treated for drug-induced ED where the causative drug cannot be altered or discontinued. [Must try sildenafil (Viagra) first or indicate inability to due to reasons stated above in 2) (a) or 2) (b)].

Coverage approved for the following non-ED uses requiring daily therapy:

a) Use of tadalafil (Cialis or Adcirca) for Pulmonary Arterial Hypertension (PAH)

b) Use of any PDE-5 inhibitor for preservation/restoration of erectile function after prostatectomy

c) Use of any PDE-5 inhibitor for Raynaud's Phenomenon

d) Use of Cialis 5 mg for treatment of benign prostatic hyperplasia (BPH)

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

D. PDE-5 Inhibitors for ED—PA Implementation Plan

The P&T Committee voted to recommend the PA implementation plan be timed to coincide with that established for the UF decision for tadalafil and vardenafil.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

E. PDE-5 Inhibitors for BPH – Cialis PA

The PDE-5 inhibitor tadalafil (Cialis) 5 mg received FDA approval in October 2011 for treatment of BPH and ED with BPH. All PDE-5 inhibitors are currently subject to prior authorization, step therapy, quantity limits, and MN criteria. Prior authorization and step therapy also apply to the alpha-1 blockers used for BPH.

The DoD P&T Committee reviewed the clinical efficacy of tadalafil for BPH. Although the efficacy of tadalafil and the alpha-1 blockers for BPH cannot be directly compared, alpha-1 blockers provide relief of BPH urinary symptoms to a greater extent than PDE-5 inhibitors, based on changes from baseline in the International Prostate Symptom Scale reported in clinical trials. The P&T Committee also recommended that when used for BPH, new users of tadalafil would be required to try a preferred alpha-1 blocker first.

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) in addition to the existing PDE-5 inhibitors automated and manual PA criteria, the following PA criteria should also apply to the tadalafil when used for BPH.

2. Manual PA criteria:
    b) Patient is being treated for benign prostatic hyperplasia (BPH) and the dosing regimen prescribed is tadalafil 5 mg once daily AND
        (5) The patient has tried tamsulosin or alfuzosin and had an inadequate response;
        OR
        (6) The patient has tried tamsulosin or alfuzosin and was unable to tolerate them due to adverse effects;
        OR
        (7) Treatment with tamsulosin or alfuzosin is contraindicated.
        (8) Prior authorization for the BPH indication will expire after 1 year from input date.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

F. **PDE-5 Inhibitors for BPH – Cialis PA – PA Implementation Plan**

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

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

VIII. RECENTLY APPROVED U.S. FDA AGENTS—OSTEOPOROSIS DRUGS

P&T Comments

A. Risedronate Delayed Release (Atelvia)—Relative Clinical Effectiveness

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of a newly approved bisphosphonate, risedronate delayed release (DR) tablets (Atelvia). It is only approved for the treatment of postmenopausal osteoporosis. Risedronate is also available in an immediate release (IR) formulation, under the trade name Actonel, which has other FDA indications in addition to postmenopausal osteoporosis. Generic formulations of risedronate IR are expected in 2012. The osteoporosis drug class, which includes the bisphosphonates, was reviewed for UF placement in June 2008.

Atelvia was developed to allow coadministration with food, and it is administered immediately after breakfast. Other oral bisphosphonates (alendronate, ibandronate, risedronate IR) require administration with water 30–60 minutes in the morning prior to breakfast. Clinical trials with Atelvia have only evaluated changes in bone mineral density; there are no studies assessing Atelvia's affect on outcomes of fracture prevention.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) risedronate DR (Atelvia) offers some convenience to the patients in terms of administration schedule, but there are no studies assessing patient compliance, and it has limited clinical trial data and safety information compared to risedronate IR (Actonel). Alternative treatments are available for patients who cannot comply with the administration schedule of the other oral bisphosphonates.

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. Risedronate Delayed Release (Atelvia)—Relative Cost-Effectiveness

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—Cost-minimization analysis (CMA) was performed. Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) Atelvia was more costly when compared to other bisphosphonates on the UF.

C. Risedronate Delayed Release (Atelvia)—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 (17 for, 0 opposed, 1 abstained, 0 absent) risedronate DR (Atelvia) be designated NF.

D. Risedronate Delayed Release (Atelvia)—Implementation Plan

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 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—OSTEOPOROSIS DRUGS

BAP Comments

A. Risedronate Delayed Release (Atelvia)—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 risedronate DR (Atelvia) be designated NF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Risedronate Delayed Release (Atelvia)—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. UTILIZATION MANAGEMENT

P&T Comments

A. Abatacept (Orencia)—PA

A subcutaneous injection of abatacept (Orencia) has been marketed. Orencia will be reviewed as a new FDA-approved drug in the Targeted Immunomodulatory Biologics (TIBs) Drug Class at an upcoming DoD P&T Committee meeting. PA requirements apply to the other TIBs in the UF. The P&T Committee agreed that the following PA criteria should apply to Orencia, consistent with the FDA-approved labeling and PA requirements for the other TIBs.

1. Coverage would be approved for the treatment of adult patients with moderate to severely active rheumatoid arthritis.
2. Coverage would not be provided for concomitant use with adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), infliximab (Remicade), golimumab (Simponi), or rituximab (Rituxan).

The P&T Committee recommended (15 for, 0 against, 1 abstain, 2 absent) approving the PA criteria outlined above.

XI. UTILIZATION MANAGEMENT

BAP Comments

A. Abatacept (Orencia)—PA

A subcutaneous injection of abatacept (Orencia) has been marketed. Orencia will be reviewed as a new FDA-approved drug in the Targeted Immunomodulatory Biologics (TIBs) Drug Class at an upcoming DoD P&T Committee meeting. PA requirements apply to the other TIBs in the UF. The P&T Committee agreed that the following PA criteria should apply to Orencia, consistent with the FDA-approved labeling and PA requirements for the other TIBs.

1. Coverage would be approved for the treatment of adult patients with moderate to severely active rheumatoid arthritis.
2. Coverage would not be provided for concomitant use with adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), infliximab (Remicade), golimumab (Simponi), or rituximab (Rituxan).

The P&T Committee recommended approving the PA criteria outlined above.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions: