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 SPECIAL PROGRAM REVIEW

P&T Comments

A. Smoking Cessation Program

Background Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the FDA-approved agents for smoking cessation. These agents include: varenicline (Chantix), bupropion SR 150 mg (Zyban), and nicotine, provided in five unique routes of administration (patch, gum, lozenge, nasal spray, and inhaler). Nicotine, via the patch, gum, and lozenge are available over-the-counter but are considered for coverage, by prescription, as part of this program.

Presently, the smoking cessation agents are not part of the TRICARE benefit, but are provided locally at most MTFs. The DoD P&T Committee has not previously reviewed the smoking cessation drugs, as they were excluded from the TRICARE benefit by statute until the signing of the 2009 Duncan Hunter NDAA. The Proposed Rule has been published in the Federal Register, comments have been received, and the rule is awaiting finalization.

The Proposed Rule would limit coverage of smoking cessation products to the MTFs and TRICARE Mail Order Pharmacy points of service (POS), and to select beneficiary groups. The Proposed Rule allows two quit attempts, defined as 120-day periods, to be available annually to eligible beneficiaries. Medication coverage for a third attempt may be offered with prior authorization.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (15 for, 0 opposed, 0 abstained, 0 absent) to accept the following clinical effectiveness conclusions:

- Varenicline (Chantix), bupropion SR, and nicotine replacement therapy (NRT) are efficacious versus placebo for improving long-term smoking abstinence. There is additive efficacy when the smoking cessation drugs are combined with behavioral therapy.
- For combination therapy, nicotine patch plus gum or nasal spray is the most efficacious smoking cessation therapy. Use of the nasal spray is limited by poor tolerability.
- Varenicline (Chantix) is the most efficacious monotherapy for smoking cessation.
- Safety concerns exist for varenicline (Chantix). Although the available data has limitations in study design and shows conflicting results, overall there appears to be an association between varenicline and adverse neuropsychiatric events to include behavioral changes, agitation, suicide/suicidal ideation, and depression.
- Caution should be exercised if varenicline is prescribed to patients with active psychiatric comorbidities.
- Varenicline has shown efficacy in patients with cardiovascular (CV) disease and chronic obstructive pulmonary disease. There is conflicting data as to whether varenicline is associated with a higher risk of adverse CV events, including non-fatal myocardial infarction, need for coronary revascularization, hospitalization for angina, and peripheral vascular disease. However, the benefits of smoking cessation with varenicline are felt to outweigh the risks in patients with pre-existing, stable CV disease.
- Varenicline is more efficacious in terms of abstinence at 52 weeks than bupropion SR. Bupropion SR is more efficacious than the NRT patch. There is additive efficacy if bupropion SR is added on to NRT (either gum or patch). However, the combination is no better than bupropion monotherapy if the bupropion is initiated first.
- When varenicline is compared to bupropion SR in randomized, controlled trials, the most commonly reported adverse events (AEs) are nausea (29%), insomnia (14%), abnormal dreams (13%), and headache (13%). The most common AEs with bupropion include insomnia (21%), nausea (7%), and dry mouth (10%).
- Bupropion carries a black box warning for changes in behavior, depressed mood, hostility, and suicidal ideation.
- All smoking cessation drugs show poor rates of compliance in both effectiveness and efficacy trials. Patient preference for a particular medication modality will determine compliance. Long-term abstinence may occur in cases of incomplete compliance. The typical long-term abstainer will make four or more serious quit attempts before finding success.

- Local MTFs remain at liberty to design their own smoking cessation program, defining which elements will be included in that program.

B. Smoking Cessation Program—Relative Cost-Effectiveness and Conclusion

Cost-minimization analyses (CMAs) and cost-effectiveness analyses (CEAs) were used to compare the different treatment options for smoking cessation, as efficacy and safety differences between the agents were noted in the clinical review. Budget impact analysis (BIA) was also performed to compare several program scenarios. The P&T Committee concluded (15 for, 0 against, 0 abstained, 0 absent) the following:

- CMA results showed that nicotine patch and gum were the least costly products among available NRTs, and bupropion SR was the least costly non-NRT option.
- CEA results demonstrated that, in adult patients who smoke more than 10 cigarettes a day, combination therapy (nicotine patch plus gum) was the most cost-effective treatment for tobacco dependence offering the greatest improvement in rates of long-term smoking abstinence. Although less cost-effective than combination therapy, varenicline was recognized as a cost-effective option when evaluating abstinence rates with monotherapy.
- BIA results showed that inclusion of bupropion SR, varenicline, and nicotine (as patch, gum, lozenge, nasal spray, and inhaler) in the TRICARE Smoking Cessation Program was the most favorable scenario for the Military Health System (MHS).

C. Smoking Cessation Program—Coverage Recommendation

The P&T Committee recommended (13 for, 1 opposed, 1 abstained, 0 absent) varenicline (Chantix), bupropion SR 150 mg, and nicotine (as patch, gum, lozenge, nasal spray, and inhaler) be covered agents in the TRICARE Smoking Cessation Program, contingent on signing of the Final Rule. No smoking cessation drugs were recommended to be excluded from the program.

D. Varenicline (Chantix)—Prior Authorization (PA) Recommendation

The P&T Committee rejected (6 in favor of prior authorization for varenicline, 8 opposed, 1 abstained, 0 absent) the proposal that PA criteria should apply to varenicline (Chantix). PA criteria for varenicline were proposed for safety concerns, primarily neuropsychiatric AEs. While the Committee recognized the potential for safety concerns with varenicline, they also concluded that a PA was not required to ensure safe prescribing with the medication because the risks with varenicline are understood by prescribing providers and can be successfully managed without PA criteria.

E. Smoking Cessation Program—Covered Beneficiary Criteria and PA for 3rd Quit Attempt

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) the following coverage criteria should apply to all seven smoking cessation products [varenicline (Chantix), buproprion SR 150 mg, nicotine gum, patch, lozenge, nasal spray, and inhaler], consistent with the requirements in the Proposed Rule, and contingent on signing of the Final Rule. Coverage not approved for patients under the age of 18 or for Medicare-eligible beneficiaries. Coverage for a 3rd quit attempt within one year may be pre-approved if the provider has verified that the patient would benefit from a 3rd quit attempt.

F. Smoking Cessation Program—UF and PA Implementation Period

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in the MTF and mail order POS, contingent on signing of the Final Rule.

III. UF SPECIAL PROGRAM REVIEW

BAP Comments

A. Smoking Cessation Program—Coverage Recommendation

The P&T Committee recommended varenicline (Chantix), bupropion SR 150 mg, and nicotine (as patch, gum, lozenge, nasal spray, and inhaler) be covered agents in the TRICARE Smoking Cessation Program, contingent on signing of the Final Rule. No smoking cessation drugs were recommended to be excluded from the program.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Varenicline (Chantix)—PA Recommendation

The P&T Committee rejected the proposal that PA criteria should apply to varenicline (Chantix). PA criteria for varenicline were proposed for safety concerns, primarily neuropsychiatric AEs. While the Committee recognized the potential for safety concerns with varenicline, they also concluded that a PA was not required to ensure safe prescribing with the medication because the risks with

varenicline are understood by prescribing providers and can be successfully managed without PA criteria.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

C. Smoking Cessation Program—Covered Beneficiary Criteria and PA for 3rd Quit Attempt

The P&T Committee recommended the following coverage criteria should apply to all seven smoking cessation products [varenicline (Chantix), buproprion SR 150 mg, nicotine gum, patch, lozenge, nasal spray, and inhaler], consistent with the requirements in the Proposed Rule, and contingent on signing of the Final Rule. Coverage not approved for patients under the age of 18 or for Medicare-eligible beneficiaries. Coverage for a 3rd quit attempt within one year may be pre-approved if the provider has verified that the patient would benefit from a 3rd quit attempt.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

D. Smoking Cessation Program—UF and PA Implementation Period

The P&T Committee recommended an effective date of the first Wednesday after a 60-day implementation period in the MTF and mail order POS, contingent on signing of the Final Rule.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

IV. UF CLASS REVIEWS—NEWER SEDATIVE HYPNOTICS DRUGS

P&T Comments

A. Newer Sedative Hypnotics Drugs

Background Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the Newer Sedative Hypnotics (SED-1s), which are used for treating insomnia. The SED-1s class is comprised of the following: zolpidem immediate-release (IR) (Ambien; generics), zolpidem extended-release (CR) (Ambien CR; generics), zolpidem oral spray (Zolpimist), zolpidem sublingual (SL) (Edluar), eszopiclone (Lunesta), zaleplon (Sonata; generics), ramelteon (Rozerem), and doxepin (Silenor).

A step therapy/prior authorization (PA) requirement has been in effect for the SED-1s class since August 2007, requiring that new SED-1s users try the preferred agent, zolpidem IR, before TRICARE® will cover the other agents in this drug class.

Zolpidem oral spray (Zolpimist) is not covered by TRICARE because the manufacturer is not included on a Master Agreement with the Veterans Administration and does not participate in the drug discount program required by 38 United States Code 8126.

Relative Clinical Effectiveness— The P&T Committee agreed (15 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions:

- The SED-1s all improve sleep latency (onset) compared to placebo. Sleep maintenance is improved with zolpidem IR, zolpidem CR, eszopiclone, and doxepin.
- Based on an indirect comparison, there do not appear to be clinically relevant differences between zolpidem CR and eszopiclone in terms of objective sleep measures.
- Doxepin improves insomnia by improving sleep maintenance; no comparative data exists with other drugs in the class.
- Zolpidem oral spray does not have comparative clinical trials with other SED-1s. FDA approval was granted based on the data originally submitted with Ambien. Zolpimist may pose additional risk for abuse given its dosage form.
- A recently published trial (Kripke, 2012) documented an increased risk of death with insomnia drugs. The interpretation of the results is hampered by several limitations in study design. No further recommendations regarding sedative hypnotic drug prescribing can be made at this time.
- The potential for abuse/misuse exists with the newer sedative hypnotics, with the exception of ramelteon and doxepin.

- The Pharmacy Outcomes Research Team (PORT) presented the results of several analyses assessing the outcomes of step therapy over the last four years. There was a decline in the number of step therapy rejections over time and an increase in utilization of the preferred product, zolpidem IR, suggesting that prescribers were aware of the step therapy requirement. The step therapy requirement did not move market share away from the military treatment facilities (MTFs), as 26% of the zolpidem IR prescriptions originated from civilian providers.

B. SED-1s—Relative Cost-Effectiveness Analysis and Conclusion

Pharmacoeconomic analyses were performed for the SED-1s class. The P&T Committee concluded (15 for, 0 against, 0 abstained, 0 absent) zolpidem IR was the least costly agent, followed by zaleplon, zolpidem CR, eszopiclone (Lunesta), doxepin (Silenor), zolpidem SL (Edluar), and ramelteon (Rozerem). BIA results showed minimal differences between scenarios, but the projected budgetary impact in the Military Health System (MHS) did vary depending on market movement of zolpidem CR when designated step-preferred versus non-step-preferred, rate of price decline of generic zolpidem CR, and market migration of generic drugs versus branded products.

C. SED-1s—UF Recommendation

The P&T Committee recommended (12 for, 1 opposed, 2 abstained, 0 absent) the following:

- zolpidem IR and zaleplon be designated formulary on the UF and step-preferred. This recommendation incorporates step therapy, which requires a trial of zolpidem IR or zaleplon (step-preferred drugs) in new users before use of another SED-1s drug;
- zolpidem CR, doxepin (Silenor), and eszopiclone (Lunesta) be designated formulary on the UF and non-step-preferred;
- ramelteon (Rozerem) and zolpidem SL (Edluar) remain NF and non-step-preferred (behind the step);
- zolpidem oral spray: Zolpimist is not covered at any POS, due to the manufacturer's lack of participation in the Federal Supply Schedule/Veterans Health Care Act pricing program.

D. SED-1s—PA Criteria

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

1. Automated PA criteria: The patient has received a prescription for zolpidem IR or zaleplon at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2. Manual (paper) PA criteria, if automated criteria are not met: The patient has had an inadequate response to, been unable to tolerate due to adverse effects, or has contraindications to zolpidem IR or zaleplon (e.g., hypersensitivity, aberrant behaviors, or intolerable rebound insomnia).

E. SED-1s—UF and PA Implementation Plan

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

V. UF CLASS REVIEWS—SED-1s

BAP Comments

A. SED-1s—UF Recommendation

The P&T Committee recommended the following:

- zolpidem IR and zaleplon be designated formulary on the UF and step-preferred. This recommendation incorporates step therapy, which requires a trial of zolpidem IR or zaleplon (step-preferred drugs) in new users before use of another SED-1s drug;
- zolpidem CR, doxepin (Silenor), and eszopiclone (Lunesta) be designated formulary on the UF and non-step-preferred;
- ramelteon (Rozerem) and zolpidem SL (Edluar) remain NF and non-step-preferred (behind the step);
- zolpidem oral spray: Zolpimist is not covered at any point of service (POS), due to the manufacturer's lack of participation in the Federal Supply Schedule/Veterans Health Care Act pricing program.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

B. SED-1s—PA Criteria

The P&T Committee recommended the following PA criteria should apply to the SED-1s class. Coverage would be approved if the patient met any of the following criteria:

1. Automated PA criteria: The patient has received a prescription for zolpidem IR or zaleplon at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2. Manual (paper) PA criteria, if automated criteria are not met: The patient has had an inadequate response to, been unable to tolerate due to adverse effects, or has contraindications to zolpidem IR or zaleplon (e.g., hypersensitivity, aberrant behaviors, or intolerable rebound insomnia).

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

C. SED-1s—UF and PA Implementation Plan

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

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

VI. RECENTLY APPROVED U.S. FDA AGENTS

P&T Comments

A. Gabapentin enacarbil (Gralise) and gabapentin (Gralise)

Relative Clinical Effectiveness—Gabapentin enacarbil (Horizant) and gabapentin (Gralise) are once-daily formulations of gabapentin (Neurontin, generics). At the time of the May 2012 meeting, Horizant was FDA-approved for treating restless leg syndrome (RLS), but was undergoing FDA review for post-herpetic neuralgia.

The Depression/Non-opioid Pain Syndrome Drug Class was reviewed for UF status at the November 2011 DoD P&T Committee meeting. Gabapentin (Neurontin, generics) is currently on the BCF. Step therapy/PA requires a trial of generic gabapentin prior to pregabalin (Lyrica) in new users.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) for both Horizant and Gralise, although the two drugs are dosed once daily versus multiple daily dosing required with generic gabapentin, there is no evidence to suggest either drug has a compelling clinical advantage over the other drugs for non-opioid pain syndromes included on the UF. Dosing conversion guidelines between Horizant, Gralise, and generic gabapentin are not available and these agents are not interchangeable due to differing pharmacokinetic properties. Gralise requires a large tablet burden to reach recommended dosing. Both drugs may cause significant somnolence and sedation, and Horizant carries a warning for adversely impairing driving ability.

B. Gabapentin enacarbil (Gralise) and gabapentin (Gralise)—Relative Cost-Effectiveness and Relative Cost-Effectiveness Conclusion

A pharmacoeconomic analysis was performed. The weighted average cost per day at all three POS was evaluated for gabapentin enacarbil (Horizant) and gabapentin (Gralise) in relation to the other drugs for non-opioid pain syndromes. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 0 absent) that Horizant and Gralise were not cost-effective when compared to other non-opioid pain syndrome agents included on the UF.

C. Gabapentin enacarbil (Gralise) and gabapentin (Gralise)—UF Recommendation

The P&T Committee, recommended (15 for, 0 opposed, 0 abstained, 0 absent) gabapentin enacarbil (Horizant) and gabapentin (Gralise) be designated NF due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

D. Gabapentin enacarbil (Gralise) and gabapentin (Gralise)—PA Criteria

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) that both gabapentin enacarbil (Horizant) and gabapentin (Gralise) 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 POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

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

a) The patient has a contraindication to gabapentin or the formulary non-opioid pain syndrome agents, which is not expected to occur with Horizant or Gralise.

b) The patient has experienced AEs with gabapentin or the formulary non-opioid pain syndrome agents, which is not expected to occur with Horizant or Gralise.

E. Gabapentin enacarbil (Gralise) and gabapentin (Gralise)—UF Implementation Plan

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 30-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision.

VII. RECENTLY APPROVED U.S. FDA AGENTS

BAP Comments

A. Gabapentin enacarbil (Gralise) and gabapentin (Gralise)—UF Recommendation

The P&T Committee, recommended gabapentin enacarbil (Horizant) and gabapentin (Gralise) be designated NF due to the lack of compelling clinical advantages and cost disadvantages compared to the UF products.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Gabapentin enacarbil (Gralise) and gabapentin (Gralise)—PA Criteria

The P&T Committee recommended that both gabapentin enacarbil (Horizant) and gabapentin (Gralise) 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 POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

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

   a) The patient has a contraindication to gabapentin or the formulary non-opioid pain syndrome agents, which is not expected to occur with Horizant or Gralise.

   b) The patient has experienced AEs with gabapentin or the formulary non-opioid pain syndrome agents, which is not expected to occur with Horizant or Gralise.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

C. Gabapentin enacarbil (Gralise) and gabapentin (Gralise)—UF Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday after a 30-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by this UF decision.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions: