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. RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS—NEWER SEDATIVE HYPNOTICS (SED-1s)

P&T Comments

A. SED-1s: Suvorexant (Belsomra)—Relative Clinical Effectiveness and Conclusion

Suvorexant (Belsomra) is a first-in-class orexin receptor antagonist indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or maintenance. Its mechanism of action antagonizes orexin receptors, which turns off the wakefulness signal in the brain.

- There are no head-to-head studies with suvorexant and other sedative hypnotic drugs.
- Suvorexant reduced the time to sleep onset by approximately 10 minutes and increased the total sleep time by approximately 30 minutes compared to placebo.
- The 5 mg dose has not been studied in clinical trials and is meant for patients with drug interaction concerns.
- Suvorexant is generally well tolerated. The most common adverse effects include next-day somnolence, headache, and fatigue.
- Somnolence was more common in the non-elderly treatment group, was mild to moderate, and occurred earlier in the course of therapy.
- Similar to other agents in the class, suvorexant is a controlled substance (Schedule IV), has several drug interactions, and carries the same warnings regarding sleep-related behaviors.

The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) despite its unique mechanism of action, suvorexant (Belsomra) offers no clinically compelling advantages over the existing newer sedative hypnotic agents on the UF. Other SED-1

drugs on the UF also have the same FDA-approved indications as suvorexant (Belsomra).

B. SED-1s: Suvorexant (Belsomra)—Relative Cost-Effectiveness Analysis and Conclusion

Cost minimization analysis (CMA) was performed to evaluate suvorexant (Belsomra) with other agents on the UF used in the treatment of insomnia. The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) that suvorexant was not cost effective.

C. SED-1s: Suvorexant (Belsomra)—UF Recommendation

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) suvorexant (Belsomra) be designated NF, due to the lack of compelling clinical advantages and cost disadvantage compared to the existing sedative hypnotics on the UF.

D. SED-1s: Suvorexant (Belsomra)—Prior Authorization (PA) Criteria

Existing automated PA criteria (step therapy) for the SED-1s require a trial of immediate release (IR) zolpidem or zaleplon. The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) that the existing automated PA criteria for the SED-1s apply to suvorexant (Belsomra).

The full PA criteria are as follows:

A trial of generic zolpidem IR or zaleplon is required for new users of Belsomra.

Automated PA: The patient has filled a prescription for zolpidem IR or zaleplon at any Military Health System pharmacy point of service (Military Treatment Facility, retail network pharmacies, or mail order) during the previous 180 days.

Manual PA Criteria: The patient has an inadequate response to, been unable to tolerate due to adverse effects, or has a contraindication to zolpidem IR or zaleplon.

E. SED-1s: Suvorexant (Belsomra)—UF and PA Implementation Plan

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all points of service (POS); and, 2) DHA send a letter to beneficiaries affected by the UF decision.

III. RECENTLY APPROVED U.S. FDA AGENTS—SED-1s

BAP Comments

A. SED-1s: Suvorexant (Belsomra)—UF Recommendation

The P&T Committee's recommendation for suvorexant (Belsomra) is listed above. This section is reserved for BAP discussion and comments.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

B. SED-1s: Suvorexant (Belsomra)—PA Criteria

The P&T Committee's recommendation for suvorexant (Belsomra) is listed above. This section is reserved for BAP discussion and comments.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

C. SED-1s: Suvorexant (Belsomra)—UF and PA Implementation Plan

The P&T Committee's recommendations for suvorexant (Belsomra) are listed above. This section is reserved for BAP discussion and comments.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

IV. RECENTLY APPROVED U.S. FDA AGENTS—MULTIPLE SCLEROSIS (MS) DRUGS

P&T Comments

A. MS Drugs: Peginterferon Beta-1a (Plegridy)—Relative Clinical Effectiveness and Conclusion

Peginterferon beta-1a (Plegridy) is a new pegylated interferon that is dosed every two weeks and administered subcutaneously. It is a disease-modifying agent approved for

patients with relapsing forms of MS. There are no head-to-head trials comparing Plegridy with oral or injectable drugs for MS.

- Compared to interferon beta-1a (Avonex), Plegridy offers the advantage of less frequent dosing (every 2 weeks instead of once weekly dosing) and subcutaneous administration, instead of intramuscular (IM) dosing. However, Avonex is now available in an autoinjector, which can ease IM administration.
- Plegridy's safety profile is similar to that of established interferons on the market, but it has a higher incidence of injection-site reactions than Avonex or placebo.
- While Plegridy offers the patient the convenience of every two-weeks administration, there is no data in patients who have received long-term prior treatment with another beta interferon or an oral agent.

The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) that the place in therapy for peginterferon beta-1a (Plegridy) is limited because the oral MS agents and the other disease-modifying drugs for MS, including Avonex, are on the UF and available to patients. Peginterferon beta-1a (Plegridy) should be reserved for those patients who are not able to tolerate the currently available oral medications or injectables for MS.

B. MS Drugs: Peginterferon Beta-1a (Plegridy)—Relative Cost-Effectiveness Analysis and Conclusion

CMA was performed to evaluate peginterferon beta-1a (Plegridy) with other injectable disease-modifying agents that are used to treat MS. The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) that peginterferon beta-1a (Plegridy) was not cost effective.

C. MS Drugs: Peginterferon Beta-1a (Plegridy)—UF Recommendation

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) peginterferon beta-1a (Plegridy) be designated NF based on clinical and cost effectiveness.

D. MS Drugs: Peginterferon Beta-1a (Plegridy)—UF Implementation Plan

The P&T Committee recommended (17 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. RECENTLY APPROVED U.S. FDA AGENTS—MS DRUGS

BAP Comments

A. MS Drugs: Peginterferon Beta-1a (Plegridy)—UF Recommendation

The P&T Committee's recommendation for peginterferon beta-1a (Plegridy) is listed above. This section is reserved for BAP discussion and comments.

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

B. MS Drugs: Peginterferon Beta-1a (Plegridy)—UF Implementation Plan

The P&T Committee's recommendation for peginterferon beta-1a (Plegridy) is listed above. This section is reserved for BAP discussion and comments.

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

VI. RECENTLY APPROVED U.S. FDA AGENTS—ANTIEMETICS/ANTIVERTIGO AGENTS

P&T Comments

A. Antiemetics/Antivertigo Agents: Doxylamine Succinate and Pyridoxine Hydrochloride (Diclegis)—Relative Clinical Effectiveness and Conclusion

Diclegis is a delayed-release product containing doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, or vitamin B6. Diclegis is indicated for treatment of nausea and vomiting during pregnancy (NVP) in women who do not respond to conservative therapies.

- The individual components of Diclegis are available over-the-counter (OTC) in inexpensive formulations of the sleep aid Unisom and vitamin B6.
- The components of Diclegis were previously available in a formulation known as Bendectin, which was approved in 1956. Bendectin was voluntarily removed from the market in 1983 due to litigation concerns. The FDA New Drug Application for Diclegis references the data for Bendectin. Since the market withdrawal of Bendectin, OTC doxylamine and vitamin B6 continue to be available and are frequently used for NVP.

- Current treatment guidelines from the American College of Obstetrics and Gynecology state vitamin B6 or use of doxylamine with vitamin B6 are safe and effective, and are the recommended first-line treatments for NVP. Other treatments, including acupressure and ginger, other antihistamines, and ondansetron are also recommended.
- In the 15-day small clinical trial used to obtain FDA approval, Diclegis showed a statistically significant benefit over placebo in emesis but the clinical difference was small.
- A 2013 Cochrane review found that there was limited evidence to support use of vitamin B6, antihistamines, and other antiemetics for mild to moderate nausea and vomiting during pregnancy. However, there are no significant head-to-head trials available to compare the agents currently used for NVP.
- No studies have suggested a definitive link between fetal malformations and the drugs typically used for treating NVP, including Diclegis, the equivalent OTC components, or the other commonly used antiemetics.

The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) the combination prescription product of doxylamine succinate and pyridoxine hydrochloride (Diclegis) offers no clinically compelling advantages when compared to the individual OTC components or other antiemetic available on the UF.

B. Antiemetics/Antivertigo Agents: Doxylamine Succinate and Pyridoxine Hydrochloride (Diclegis)—Relative Cost-Effectiveness Analysis and Conclusion

CMA was performed. The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) Diclegis is more costly than the individual OTC components and the formulary agents used in the treatment of nausea and vomiting during pregnancy.

C. Antiemetics/Antivertigo Agents: Doxylamine Succinate and Pyridoxine Hydrochloride (Diclegis)—UF Recommendation

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) doxylamine succinate and pyridoxine hydrochloride (Diclegis) be designated NF due to the lack of compelling clinical advantages, aside from its pregnancy Category A rating, and its cost disadvantage when compared to the individual OTC components and the formulary agents available to treat NVP.

D. Antiemetics/Antivertigo Agents: Doxylamine Succinate and Pyridoxine Hydrochloride (Diclegis)—PA Criteria

Manual PA criteria were recommended at the February 2013 DoD P&T Committee meeting and implemented in August 2013 for doxylamine succinate and pyridoxine hydrochloride (Diclegis), requiring a trial of nonpharmacologic interventions and OTC pyridoxine, and consideration of alternate antiemetics. The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) maintaining the PA criteria for

doxylamine succinate and pyridoxine hydrochloride (Diclegis).

The full PA criteria are as follows:

> All new users of Diclegis are required to try a nonpharmacologic method for management of nausea and vomiting during pregnancy AND over-the-counter pyridoxine before receiving doxylamine succinate and pyridoxine hydrochloride (Diclegis).
>
> Manual PA Criteria—Doxylamine succinate and pyridoxine hydrochloride (Diclegis) is approved if:
>
> - The patient has not had relief of symptoms after trying a nonpharmacologic method to manage nausea and vomiting during pregnancy,
>
> **AND**
>
> - The patient has not had relief of symptoms after trying over-the-counter pyridoxine for management of nausea and vomiting during pregnancy.
>
> - Providers are encouraged to consider an alternate antiemetic (e.g., ondansetron) prior to prescribing doxylamine succinate and pyridoxine hydrochloride (Diclegis).
>
> Prior Authorization will expire after 9 months.

E. Antiemetics/Antivertigo Agents: Doxylamine Succinate and Pyridoxine Hydrochloride (Diclegis)—UF and PA Implementation Plan

The P&T Committee recommended (17 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. RECENTLY APPROVED U.S. FDA AGENTS—ANTIEMETICS/ANTIVERTIGO AGENTS

BAP Comments

A. Antiemetics/Antivertigo Agents: Doxylamine Succinate and Pyridoxine Hydrochloride (Diclegis)—UF Recommendation

The P&T Committee's recommendation for doxylamine succinate and pyridoxine hydrochloride (Diclegis) is listed above. This section is reserved for BAP discussion and comments.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

B. Antiemetics/Antivertigo Agents: Doxylamine Succinate and Pyridoxine Hydrochloride (Diclegis)—PA Criteria

The P&T Committee's recommendation for doxylamine succinate and pyridoxine hydrochloride (Diclegis) is listed above. This section is reserved for BAP discussion and comments.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

C. Antiemetics/Antivertigo Agents: Doxylamine Succinate and Pyridoxine Hydrochloride (Diclegis)—UF and PA Implementation Plan

The P&T Committee's recommendations for doxylamine succinate and pyridoxine hydrochloride (Diclegis) are listed above. This section is reserved for BAP discussion and comments.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

VIII. UF CLASS REVIEWS—HEPATITIS C VIRUS (HCV) DRUGS: DIRECT ACTING ANTIVIRALS (DAAs)

P&T Comments

A. HCV Drugs: DAAs—Relative Clinical Effectiveness and Conclusion

Simeprevir (Olysio), sofosbuvir (Sovaldi), ledipasvir/sofosbuvir (Harvoni), and ombitasvir/paritaprevir/ritonavir/dasabuvir co-packaged tablets (Viekira Pak) are DAAs with FDA indications for the treatment of genotype 1 chronic HCV in adults. Additionally, sofosbuvir is indicated for the treatment of adults with genotypes 2, 3, and

4 chronic HCV. Boceprevir (Victrelis) is a first generation DAA and is no longer the standard of care; market withdrawal is expected in December 2015.

Due to the rapidly evolving HCV field, use of the DAAs outside of their FDA-labeled indications is not uncommon. The American Association for the Study of Liver Diseases/ Infectious Diseases Society of America (AASLD/IDSA) updated the HCV treatment guidelines on April 8, 2015. The AASLD/IDSA HCV treatment guidelines recommend all-oral, (interferon-free) options whenever feasible for patients with HCV. Harvoni and Viekira Pak are now prominently featured in the guidelines as recommended regimens for patients with genotype 1 and 4 chronic HCV. Sovaldi in combination with Olysio is also a recommended regimen in patients with genotype 1 HCV. Sovaldi with ribavirin is recommended for patients with non-genotype 1 chronic HCV, in most situations. Consult the guidelines for the most up-to-date recommendations at: www.HCVguidelines.org.

The P&T Committee concluded (17 for, 0 against, 0 abstained, 1 absent) the following:

- There are no studies directly comparing Harvoni, Sovaldi in combination with Olysio, or Viekira Pak. In general, when making indirect comparisons across similar patient populations, efficacy (assessed as sustained virologic response at 12 weeks (SVR12), the primary endpoint) appears similar among these products.
- In general, the rate of SVR12 across clinical trials in patients with genotype 1 chronic HCV treated with any DAA except Victrelis is > 90%. With Harvoni and Viekira Pak, SVR12 rates are > 95% in most instances.
- Harvoni and Viekira Pak represent all-oral (interferon-free) therapies that have demonstrated high rates of clinical cure (SVR12) in large populations across Phase III clinical trials.
- Sovaldi, when used with Olysio, represents an all-oral option for patients with genotype 1 chronic HCV; however, data are limited to one small Phase IIa study.
- Harvoni is the only one of these three regimens (Harvoni, Sovaldi with Olysio, and Viekira Pak) that has been studied in previous HCV protease inhibitor treatment failures.
- Viekira Pak with ribavirin was evaluated in HCV genotype 1 patients with liver transplant and patients co-infected with HIV. There is a potential for significant drug-drug interactions with Viekira Pak.
- Sovaldi remains as an important therapy that allows for interferon-free options in patients with genotypes 2 or 3 chronic HCV.
- In the absence of head-to-head trials, HCV treatment should be based on current AASLD/IDSA treatment guideline recommendations, individual patient characteristics, likelihood of adherence, and patient preferences, as well as cost.

B. HCV Drugs: DAAs—Relative Cost-Effectiveness Analysis and Conclusion

A cost-effectiveness analysis (CEA) and Budget Impact Analysis (BIA) were performed to evaluate the HCV drugs. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 1 absent) the following:

- CEA results showed that all DAA agents were within a range considered cost-effective to the MHS.
- BIA was performed to evaluate the potential impact of designating selected agents as step-preferred, formulary, or NF on the UF. BIA results showed that designating all agents UF, with no step-therapy, demonstrated significant cost avoidance for the MHS.

C. HCV Drugs: DAAs—UF Recommendation

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

- UF:
  - Ledipasvir/sofosbuvir (Harvoni)
  - Paritaprevir/ritonavir/ombitasvir + dasabuvir (Viekira Pak)
  - Sofosbuvir (Sovaldi)
  - Simeprevir (Olysio)
  - Boceprevir (Victrelis), until market withdrawal in December 2015
- NF: None

D. HCV Drugs: DAAs—Sofosbuvir (Sovaldi) PA Criteria

Manual PA criteria for the individual DAAs were recommended previously. The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) minor revisions to the Sovaldi manual PA criteria to include the table of the recommended treatments for each HCV genotype and duration of therapy.

The full PA criteria are as follows:

Sofosbuvir (Sovaldi)

- New users of sofosbuvir are required to undergo the PA process.
- Current users are not affected by PA; they can continue therapy uninterrupted.
- Consult the AASLD/IDSA HCV guidelines (www.hcvguidelines.org) for the most up-to-date and comprehensive treatment for HCV. Unique patient populations are also addressed and treatment recommendations may differ from those for the general population.

Manual PA Criteria:

- Age $\geq$ 18
- Has laboratory evidence of chronic HCV infection
- Has laboratory evidence of HCV genotype 1, 2, 3, or 4 HCV infection
  - State the HCV genotype and HCV RNA viral load on the PA form
- Sofosbuvir (Sovaldi) is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician

- Sofosbuvir (Sovaldi) is not prescribed as monotherapy

Treatment Regimens and Duration of Therapy

- Treatment and duration of therapy are approved for one of the following regimens outlined below, based on HCV genotype or unique population.
- Prior authorization will expire after 12 to 24 weeks, based on the treatment regimen selected.

Table of Recommended Treatment Regimens and Duration of Therapy for Sofosbuvir (Sovaldi)

HCV genotype	Treatment	Duration
Genotype 1	SOFOSBUVIR + peginterferon alfa + ribavirin	12 weeks
	SIMEPREVIR 150 mg once daily + SOFOSBUVIR 400 mg once daily (treatment naïve or experienced* without cirrhosis)	12 weeks
	SIMEPREVIR 150 mg once daily + SOFOSBUVIR 400 mg once daily (treatment naïve or experienced* with cirrhosis)	24 weeks
Genotype 2	SOFOSBUVIR + ribavirin	12 weeks
	SOFOSBUVIR + ribavirin (cirrhotic or treatment experienced)	16 weeks
Genotype 3	SOFOSBUVIR + ribavirin	24 weeks
	SOFOSBUVIR + peginterferon alfa + ribavirin (cirrhotic or treatment experienced)	12 weeks
Genotype 4, 5, 6	SOFOSBUVIR + peginterferon alfa + ribavirin	12 weeks
Hepatocellular carcinoma awaiting transplant	SOFOSBUVIR + ribavirin	up to 48 weeks or at transplant
*Treatment-experienced patients who have failed treatment with peginterferon alfa + ribavirin but not a HCV protease inhibitor		

Regimen other than those listed above: Explain the rationale for treatment and duration of therapy. Consult the AASLD/IDSA HCV guidelines for new updates and guidelines.

E. HCV Drugs: DAAs—UF and PA Implementation Plan

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) the UF and PA implementation become effective upon signing of the minutes in all POS.

IX. UF CLASS REVIEWS—HCV DRUGS: DAAs

BAP Comments

A. HCV Drugs: DAAs—UF Recommendation

The P&T Committee's recommendation for the HCV DAAs is listed above. This section is reserved for BAP discussion and comments.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

B. HCV Drugs: DAAs—Sofosbuvir (Sovaldi) PA Criteria

The P&T Committee's recommendation for the HCV DAA drug sofosbuvir (Sovaldi) is listed above. This section is reserved for BAP discussion and comments.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

C. HCV Drugs: DAAs—UF and PA Implementation Plan

The P&T Committee's recommendations for the HCV DAAs are listed above. This section is reserved for BAP discussion and comments.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

X. UF CLASS REVIEWS—ORAL ANTICOAGULANTS

P&T Comments

A. Oral Anticoagulants—Relative Clinical Effectiveness and Conclusion

The P&T Committee evaluated the relative clinical effectiveness of the oral anticoagulant drugs, which is comprised of the following:

- **Target-Specific Oral Anticoagulants (TSOACs)**: apixaban (Eliquis), dabigatran (Pradaxa), edoxaban (Savaysa), and rivaroxaban (Xarelto)
- **Vitamin K Antagonists**: warfarin (Coumadin, generic)

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) the following conclusions:

- **Non-valvular Atrial Fibrillation (NVAF):**
    - In NVAF, dabigatran and apixaban were superior to not optimally controlled warfarin, while edoxaban and rivaroxaban were non-inferior.
    - Intracranial bleeding was lower with all four TSOACs compared with warfarin in the major trials used to obtain FDA approval for apixaban, dabigatran, edoxaban, and rivaroxaban.
    - Edoxaban advantages include once daily dosing and an overall lower rate of bleeding versus warfarin. Disadvantages include a higher rate of gastrointestinal (GI) bleeding, and a higher risk of stroke in patients with normal renal function (creatinine clearance greater than 95 mL/min).
    - Dabigatran was the only TSOAC to show superior ischemic stroke reduction, but has a higher incidence of GI bleeding than warfarin, causes dyspepsia, and is highly dependent on renal clearance.
    - Rivaroxaban advantages include once daily dosing, but it has an increased incidence of GI bleeding and major bleeding compared to warfarin. The patient population studied with rivaroxaban had more comorbidities than the other three TSOACs.
    - Apixaban had significantly less major bleeding than warfarin, and was the only TSOAC to show a reduction in morbidity, but the confidence interval approached one. The point estimates and confidence intervals for all the TSOACs are similar for mortality.
- **Venous Thromboembolism (VTE)**
    - For acute VTE, no overlap with low-molecular weight heparin (LMWH) is required with apixaban or rivaroxaban. All four TSOACs were non-inferior to LMWH and/or warfarin for the composite endpoint of recurrent VTE, nonfatal pulmonary embolism (PE), or death.
    - Apixaban and rivaroxaban had significantly less major bleeding than LMWH and/or warfarin.
- **VTE Prevention following Orthopedic Surgery (Hip or Knee Replacement)**
    - The TSOACs offer a convenience to patients in that LMWH injections are not required.
    - Rivaroxaban and apixaban are FDA approved, while edoxaban and dabigatran are not approved for this use.

Due to a lack of head-to-head trials, the P&T Committee concluded there is insufficient evidence to determine if one TSOAC has advantages over the others. The TSOACs have advantages of predictable anticoagulant effect, fixed dosing, fewer drug interactions, and lack of laboratory monitoring and dietary restrictions, compared to warfarin. However, overall warfarin remains a viable therapy option due to its large number of FDA-approved indications, long history of use, preferred choice for patients with severe renal

dysfunction, and availability of an antidote.

B. Oral Anticoagulants—Relative Cost-Effectiveness Analysis and Conclusion

CMA, CEA, and BIA were performed to evaluate the oral anticoagulants. The P&T Committee concluded (17 for, 0 opposed, 1 abstained, 0 absent) the following:

- CMA and CEA results showed generic warfarin was the most cost-effective oral anticoagulant, followed by all branded TSOACs (apixaban, dabigatran, edoxaban and rivaroxaban).
- BIA was performed to evaluate the potential impact of designating selected TSOACs with formulary or NF status on the UF. BIA results showed that modeled scenarios where generic warfarin is BCF, with all other branded TSOACs designated as formulary on the UF, demonstrated lower cost avoidance for the MHS compared to the current baseline formulary status.

C. Oral Anticoagulants—UF Recommendation

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) the following:

- UF:
  - Warfarin (Coumadin; generic)
  - Apixaban (Eliquis)
  - Dabigatran (Pradaxa)
  - Edoxaban (Savaysa)
  - Rivaroxaban (Xarelto)
- NF: None

XI. UF CLASS REVIEWS—ORAL ANTICOAGULANTS

BAP Comments

A. Oral Anticoagulants—UF Recommendation

The P&T Committee's recommendation for the Oral Anticoagulants is listed above. This section is reserved for BAP discussion and comments.

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

XII. UTILIZATION MANAGEMENT—TESTOSTERONE REPLACEMENT THERAPY (TRT)

P&T Comments

A. TRT: Testosterone Nasal Gel (Natesto)—PA Criteria

Natesto is a new formulation of testosterone that is administered intranasally. It is dosed as one pump actuation per nostril, three times daily, six to eight hours apart. The TRTs were reviewed by the P&T Committee in August 2012 and automated PA (step therapy) and manual PA criteria were recommended for the class (implemented March 2013).

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) step therapy and manual PA criteria for testosterone nasal gel (Natesto), consistent with the rest of the class and its FDA-approved indication.

The full PA criteria are as follows:

PA criteria apply to all new and current users of Natesto.

Automated PA Criteria: The patient has filled a prescription for transdermal 2% gel pump (Fortesta) at any Military Health System pharmacy point of service (Military Treatment Facilities, retail network pharmacies, or mail order) during the previous 180 days

AND

Manual PA Criteria: If automated criteria are not met, coverage is approved for Natesto if:

- Contraindications exist to Fortesta (hypersensitivity to a component)
- Inadequate response to Fortesta (minimum of 90 days **AND** failed to achieve testosterone levels above 400 ng/dL **AND** denied improvement in symptoms)
- Clinically significant adverse reactions to Fortesta not expected with Natesto

AND

Coverage approved for male patients aged 17 years or older with:

- A diagnosis of hypogonadism evidenced by 2 or more morning testosterone levels in the presence of symptoms usually associated with hypogonadism

Coverage for use in women or in adolescent males under the age of 17 is not approved and will be considered upon appeal only.

XIII. UTILIZATION MANAGEMENT—TRT

BAP Comments

A. TRT: Testosterone Nasal Gel (Natesto)—PA Criteria

The P&T Committee's recommendation for Natesto is listed above.

This section is reserved for BAP discussion and comments.

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

XIV. UTILIZATION MANAGEMENT—CYSTIC FIBROSIS (CF) DRUGS

P&T Comments

A. CF: Ivacaftor (Kalydeco)—PA Criteria

Ivacaftor (Kalydeco) is indicated for the treatment of CF. PA criteria were recommended at the February 2012 meeting, updated in May 2014 and December 2014 to reflect the FDA-approved indication for various mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. In March 2015, the FDA-approved indication was further expanded to include pediatric patients aged 2 years and older. Along with this expanded indication, a new dosage form was launched in the form of oral granules to be mixed with either soft food or liquid every 12 hours for weight-based pediatric dosing.

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) updated manual PA criteria for Kalydeco to include the expanded FDA-approved indication.

The full PA criteria are as follows:

Manual PA criteria apply to all new and current users of Ivacaftor (Kalydeco).

- Coverage will be approved for the treatment of CF patients aged 2 years and older who have a G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or for R117H mutation in the CFTR gene, detected by an FDA-approved test.

- Coverage is not approved for patients who are homozygous for the F508del mutation in the CFTR gene.

XV. UTILIZATION MANAGEMENT—CF DRUGS

BAP Comments

A. CF: Ivacaftor (Kalydeco)—PA Criteria

The P&T Committee's recommendation for ivacaftor (Kalydeco) is listed above.

This section is reserved for BAP discussion and comments.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

XVI. UTILIZATION MANAGEMENT—RENIN ANGIOTENSIN ANTIHYPERTENSIVES (RAAs)

P&T Comments

A. RAAs: Perindopril/Amlodipine (Prestalia)—PA Criteria

The FDA recently approved the combination product perindopril and amlodipine (Prestalia). It is indicated for the treatment of hypertension as monotherapy or as initial therapy in patients requiring multiple drugs to achieve their blood pressure goals. The RAAs class was reviewed in August 2010; step therapy was implemented in January 2011 and applies to all drugs in the class.

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) step therapy criteria for perindopril/amlodipine (Prestalia), consistent with the current criteria for the RAAs class.

The full PA criteria are as follows:

> PA criteria apply to all new and current users of Prestalia.
>
> Automated PA Criteria—The patient has filled a prescription for one of the preferred agents (generic angiotensin-converting enzyme inhibitors, generic losartan, losartan HCTZ, Diovan, Diovan HCT, Exforge, Exforge HCT, Micardis, Micardis HCT, or Twynsta) at any Military Health System pharmacy point of service (Military Treatment Facilities, retail network pharmacies, or mail order) during the previous 180 days
>
> **AND**
>
> Manual PA Criteria—If automated criteria are not met, coverage is approved for Prestalia if:

- Contraindications exist to one step-preferred RAA agent not expected to occur with Prestalia
- Inadequate response to one step-preferred RAA agent
- Inability to tolerate due to adverse effects to one step-preferred RAA agent

XVII. UTILIZATION MANAGEMENT—RAAs

BAP Comments

A. RAAs: Perindopril/Amlodipine (Prestalia)—PA Criteria

The P&T Committee's recommendation for perindopril/amlodipine (Prestalia) is listed above.

This section is reserved for BAP discussion and comments.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

XVIII. UTILIZATION MANAGEMENT—INSULINS

P&T Comments

A. Insulins: Inhaled Insulin (Afrezza)—PA Criteria

Afrezza is rapid-acting inhaled insulin indicated to improve glycemic control in adult patients with Type 1 or Type 2 diabetes mellitus. It is available as single-use cartridges of 4, 8, and 12 units, administered via oral inhalation at the beginning of a meal. Dosing must be individualized. Manual PA criteria were recommended to ensure appropriate use of the drug in Type 1 and Type 2 diabetic patients, including failure of or inability to tolerate an adequate trial (90 days) of a rapid or short-acting subcutaneous insulin product.

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) manual PA criteria for Afrezza, consistent with the FDA-approved product labeling for use in Type 1 and Type 2 diabetic patients.

The full PA criteria are as follows:

Manual PA criteria apply to all new and current users of Afrezza.

Coverage is approved for non-smoking patients with either:

Type 1 Diabetes Mellitus (diagnosed)

- Failure to achieve hemoglobin A1C ≤ 7 % in 90 days of a rapid or short-acting subcutaneous (SC) insulin product or clinically significant adverse effects experienced with SC rapid or short-acting insulin unexpected to occur with inhaled insulin
- Afrezza is used as adjunctive treatment to current basal insulin therapy
- Spirometry testing [baseline forced expiratory volume in the first second (FEV1) upon initiation with repeated FEV1 at 6 months after initiation and repeated annually thereafter] has been performed

Type 2 Diabetes Mellitus (diagnosed)

- Failure to achieve hemoglobin A1C ≤ 7 % in 90 days of a rapid or short-acting SC insulin product or clinically significant adverse effects experienced with SC rapid or short-acting insulin unexpected to occur with inhaled insulin
- Failure of or clinically significant adverse effect to two oral anti-diabetic agents [i.e. sulfonylurea, thiazolidinedione, or dipeptidyl peptidase-4 inhibitor] if metformin is contraindicated
- Spirometry testing (baseline FEV1 upon initiation with repeated FEV1 at 6 months after initiation and repeated annually thereafter) has been performed

Contraindications to the use of Afrezza: hypoglycemia, chronic lung disease (asthma, COPD), hypersensitivity to regular human insulin, or any Afrezza excipients

XIX. UTILIZATION MANAGEMENT—INSULINS

BAP Comments

A. Insulins: Inhaled Insulin (Afrezza)—PA Criteria

The P&T Committee's recommendation for the Afrezza is listed above.

This section is reserved for BAP discussion and comments.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

XX. UTILIZATION MANAGEMENT—SELF-MONITORING BLOOD GLUCOSE SYSTEM (SMBGS) TEST STRIPS

P&T Comments

A. SMBGS Test Strips: ACCU-CHEK Aviva Plus Test Strips—PA Criteria

The SMBGS test strips were evaluated at the November 2014 P&T Committee Meeting. Step therapy and MN criteria were recommended with an implementation date of August 5, 2015. PA and MN criteria allow for use of a non-preferred, NF test strip if the patient uses an insulin pump and requires a specific test strip that communicates wirelessly with a specific meter.

The ACCU-CHEK Aviva Plus test strips are designated non-preferred and NF. However, the ACCU-CHEK Aviva Plus test strips are used in the ACCU-CHEK Combo meter, which communicates wirelessly with the ACCU-CHEK Spirit Combo insulin pump.

The P&T Committee recommended (17 for, 0 opposed, 1 abstain, 0 absent) adding the ACCU-CHEK Aviva Plus test strips to the SMBGS Test Strips PA criteria for patients using the ACCU-CHEK Aviva Combo meter with the ACCU-CHEK Spirit Combo pump.

The PA criteria are as follows:

> New and current users of the NF test strips are required to try FreeStyle Lite or Precision Xtra.
>
> Manual PA Criteria—Non-preferred test strip allowed if: patient uses an insulin pump and requires a specific test strip that communicates wirelessly with a specific meter
>
> - CONTOUR NEXT strip with CONTOUR NEXT Link meter for Medtronic pump
> - Nova Max strip with Nova Max Link meter for Medtronic pump
> - **ACCU-CHEK Aviva Plus test strip with the ACCU-CHEK Combo meter for the ACCU-CHEK Spirit Combo pump**

XXI. UTILIZATION MANAGEMENT—SMBGS TEST STRIPS

BAP Comments

A. SMBGS Test Strips: ACCU-CHEK Aviva Plus Test Strips—PA Criteria

The P&T Committee's recommendation for ACCU-CHEK Aviva Plus test strips is listed above.

This section is reserved for BAP discussion and comments.

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