DEPARTMENT OF DEFENSE

PHARMACY AND THERAPEUTICS COMMITTEE
MINUTES AND RECOMMENDATIONS

May 2015

I. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on May 13 and 14, 2015, at the Defense Health Agency (DHA) Formulary Management Branch, Fort Sam Houston, Texas.

II. ATTENDANCE

The attendance roster is listed in Appendix A.

A. Review Minutes of Last Meetings

1. **Approval of February Minutes**—Lt. Gen. Douglas J. Robb, DO, MPH, Director, DHA, approved the minutes from the February 2015 DoD P&T Committee meeting on May 5, 2015.

2. **Correction to the February 2015 Minutes**

   a) Compound Prescriptions—On May 8, 2015, Dr. Jonathan Woodson, Assistant Secretary of Defense for Health Affairs, signed the Decision Paper on Implementing ESI Commercial Reject List and Prior Authorization for all Compound Medication Prescriptions. As of May 1, 2015, Express Scripts will screen all TRICARE compound drug claims to ensure each ingredient is safe, effective and covered by TRICARE. Prescribers/beneficiaries may request prior authorization for compound claims that do not pass the initial screen, and file an appeal using the regular TRICARE appeal process if prior authorization is not granted.

   Adopting the ESI "commercial reject list" would protect access to legitimate compound medications while further restricting those attempting to exploit the system. Implementation of the ESI commercial reject list will occur as soon as operationally possible.

III. REQUIREMENTS

All clinical and cost evaluations for new drugs and full drug class reviews included, but were not limited to, the requirements stated in 32 Code of Federal Regulations 199.21(e)(1). All Uniform Formulary (UF) and Basic Core Formulary (BCF) recommendations considered the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors. Medical necessity (MN) criteria were based on the

clinical and cost evaluations, and the conditions for establishing MN for a nonformulary (NF) medication.

IV. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

A. Newer Sedative Hypnotics (SED-1s): Suvorexant (Belsomra)

Background—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.

Relative Clinical Effectiveness Conclusion—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).

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.

1. ***COMMITTEE ACTION: 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.
2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) MN criteria for suvorexant (Belsomra). See Appendix B for the full criteria.

3. ***COMMITTEE ACTION: PA CRITERIA***—Existing automated PA criteria (step therapy) for the SED-1s requires a trial of immediate release 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). All new users of suvorexant will undergo the PA process. See Appendix C for the full criteria.

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—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. Based on the P&T Committee's recommendation, the effective date is October 21, 2015.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Multiple Sclerosis (MS) Drug: Peginterferon Beta-1a (Plegridy)

Background—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.

Relative Clinical Effectiveness Conclusion—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.

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.

1. ***COMMITTEE ACTION: 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.

2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) MN criteria for peginterferon beta-1a (Plegridy). See Appendix B for the full criteria.

3. ***COMMITTEE ACTION: UF IMPLEMENTATION PERIOD***—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. Based on the P&T Committee's recommendation, the effective date is October 21, 2015.

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

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

Background—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.

Relative Clinical Effectiveness Conclusion—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.

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.

1. ***COMMITTEE ACTION: 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.
2. ***COMMITTEE ACTION: MN CRITERIA***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) MN criteria for doxylamine succinate and pyridoxine hydrochloride (Diclegis). See Appendix B for the full criteria.
3. ***COMMITTEE ACTION: 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 current PA criteria for doxylamine succinate and pyridoxine hydrochloride (Diclegis). See Appendix C for the full criteria.

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***—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. Based on the P&T Committee's recommendation, the effective date is October 21, 2015.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

V. UF DRUG CLASS REVIEWS

A. Hepatitis C Virus (HCV) Drugs: Direct Acting Antivirals (DAAs)

Background—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.

Relative Clinical Effectiveness Conclusion—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.

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.

1. ***COMMITTEE ACTION: 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

2. ***COMMITTEE ACTION: EXTENDED CORE FORMULARY (ECF)***
   As the recommended AASLD/IDSA treatment guidelines are continually updated and changing, the P&T Committee recommended (16 for, 0

opposed, 1 abstained, 1 absent) to not add an HCV DAA drug to the ECF. For the HCV class, ribavirin 200 mg capsules and peginterferon alfa-2a (Pegasys) were designated ECF in November 2012.

3. ***COMMITTEE ACTION: 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. See Appendix D for the full criteria.

4. ***COMMITTEE ACTION: UF AND PA IMPLEMENTATION PERIOD***
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.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Oral Anticoagulants

Relative Clinical Effectiveness—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)

Relative Clinical Effectiveness Conclusion—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 it 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 mortality, 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.

Overall Relative Clinical Effectiveness Conclusion: 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.

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 greater cost avoidance for the MHS compared to the current baseline formulary status.

1. ***COMMITTEE ACTION: UF RECOMMENDATIONS***—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

2. ***COMMITTEE ACTION: BCF RECOMMENDATION***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) generic warfarin remain designated with BCF status.

3. ***COMMITTEE ACTION: SECTION 716 PILOT PROGRAM FOR REFILLS OF MAINTENANCE MEDICATIONS FOR TRICARE FOR LIFE BENEFICIARIES THROUGH THE TRICARE MAIL ORDER PROGRAM***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) adding edoxaban (Savaysa) to the maintenance medication drug list, as the other TSOACs are on the program. Implementation will occur upon signing of the minutes.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VI. UTILIZATION MANAGEMENT

A. PA and MN Criteria

1. **Testosterone Replacement Therapy (TRT): Testosterone Nasal Gel (Natesto)** 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 TRT products 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).

a) ***COMMITTEE ACTION: TESTOSTERONE NASAL GEL (NATESTO) STEP THERAPY AND PA CRITERIA***—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. See Appendix C for the full criteria.

2. **Cystic Fibrosis (CF) Drugs: Ivacaftor (Kalydeco)**—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 CF transmembrane conductance regulator 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 that are mixed with either soft food or liquid every 12 hours for weight-based pediatric dosing.

   a) ***COMMITTEE ACTION: IVACAFTOR (KALYDECO) PA CRITERIA***—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. See Appendix C for the full criteria.

3. **Renin Angiotensin Antihypertensives (RAAs): Perindopril/Amlodipine (Prestalia)** 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.

   a) ***COMMITTEE ACTION: PERINDOPRIL/AMLODIPINE (PRESTALIA) PA CRITERIA***—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. See Appendix C for the full criteria.

4. **Inhaled Insulin (Afrezza)**—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. See Appendix C for the full criteria.

   a) ***COMMITTEE ACTION: INHALED INSULIN (AFREZZA) PA CRITERIA*** 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. See Appendix C for the full criteria.

5. **Self-Monitoring Blood Glucose System (SMBGS) Test Strips: ACCU-CHEK Aviva Plus Test Strips**—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.

   a) ***COMMITTEE ACTION: ACCU-CHEK AVIVA PLUS SMBGS TEST STRIPS MANUAL PA CRITERIA AND MN CRITERIA***—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 and MN criteria for patients using the ACCU-CHEK Aviva Combo meter with the ACCU-CHEK Spirit Combo pump. See Appendices B and C for full criteria.

B. QUANTITY LIMITS (QLs)—QLs were reviewed for three oral oncologic drugs. QLs already apply to products in the Oral Oncology Drug Class.

1. ***COMMITTEE ACTIONS: QLs***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) QLs for palbociclib (Ibrance), panobinostat (Farydak), lenvatinib (Lenvima), consistent with the product labeling and packaging. See Appendix E for QLs.

Director, DHA, Decision: ☑ Approved ☐ Disapproved

Approved, but modified as follows:

VII. LINE EXTENSIONS

A. Formulary Status Clarification—The P&T Committee clarified the formulary status for two product line extensions ("follow-on products") by the original manufacturers. Line extensions have the same FDA indications as the "parent" drug.

Nuvigil was reviewed for formulary placement in 2012 and designated NF at that time with a manual PA implemented. A 200 mg Nuvigil dose was approved in February 2014 and has been on the UF since its launch. Vogelxo is an AB-rated generic to Testim, which was designated NF and placed behind the TRT step in May 2013.

1. ***COMMITTEE ACTION: LINE EXTENSIONS FORMULARY STATUS CLARIFICATION***—The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent vote) clarifying the formulary status of armodafinil (Nuvigil) 200 mg and testosterone gel (Vogelxo).

    - Armodafinil (Nuvigil) 200 mg: Designated NF and subject to the same manual PA as the other marketed strengths of Nuvigil
    - Testosterone Gel (Vogelxo): Designated NF and placed behind the TRT step along with its parent drug, Testim

Director, DHA, Decision: ☒ Approved ☐ Disapproved

Approved, but modified as follows:

VIII. ADJOURNMENT

The meeting adjourned at 1020 hours on May 14, 2015. The next meeting will be in August 2015.

Appendix A—Attendance: May 2015 P&T Committee Meeting
Appendix B—Table of Medical Necessity Criteria
Appendix C—Table of Prior Authorization Criteria
Appendix D—Table of Prior Authorization Criteria for Hepatitis C Drugs
Appendix E—Table of Quantity Limits
Appendix F—Table of Implementation Status of UF Recommendations/Decisions Summary
Appendix G—Table of Abbreviations

SUBMITTED BY:

John P. Kugler, M.D., MPH
DoD P&T Committee Chair

DECISION ON RECOMMENDATIONS

Director, DHA, decisions are as annotated above.

Douglas J. Robb, DO, MPH

Lieutenant General, USAF, MC, CFS
Director

20 July 2015
Date

Appendix A—Attendance: May 2015 P&T Committee Meeting

Voting Members Present	
John Kugler, COL (Ret.), MC, USA	DoD P&T Committee Chair
CAPT Nita Sood for George Jones, PharmD, M.S.	Chief, DHA Operations Management Branch
CAPT Walter Downs, MC	Chief, DHA Formulary Management Branch (Recorder)
COL John Spain, MS	Army, Pharmacy Officer
LTC Kevin Tiller, BSC	Air Force, Pharmacy Officer Alternate
CDR Aaron Middlekauf, USCG	Coast Guard, Pharmacy Officer Alternate
CAPT Thinh Ha, MSC	Navy, Pharmacy Officer
CPT Danika Alexander, MC for MAJ John Poulin, MC	Army, Physician at Large
COL Michael Wynn, MC	Army, Family Practice Physician
Col James Jablonski, MC	Air Force, Physician at Large
LCDR Adam Deising, MC for CDR Brian King, MC	Navy, Internal Medicine Physician
LCDR Carey Welsh, MC	Navy, Pediatrics Representative
COL Jack Lewi, MC	Army, Internal Medicine Physician
CDR Shaun Carstairs, MC	Navy, Physician at Large
Lt Col William Hannah, MC	Air Force, Internal Medicine Physician
Maj Larissa Weir, MC	Air Force, OB/GYN Physician
Dr. Miguel Montalvo	TRICARE Regional Office-South, Chief of Clinical Operations Division and Medical Director
Mr. Joe Canzolino	U.S. Department of Veterans Affairs
Nonvoting Members Present	
Mr. Bryan Wheeler	Acting General Counsel, DHA
Guests	
Mr. Bill Davies via DCO	DHA Pharmacy Operations Division
LTC Kevin Ridderhoff, MS	DHA, Pharmacy Operations Division
MAJ Randall Sweeney	Defense Logistics Agency Troop Support
MAJ Richard Caballero	Defense Logistics Agency Troop Support
CDR Matthew Baker	Indian Health Service
Mr. Matthew Halbe	DHA Contract Operations Division
Ms. Patricia Legra	DHA Contract Operations Division
Capt Nina Tachikawa	Air Force, Pharmacy Officer

Appendix A—Attendance (continued)

Others Present	
LCDR Marisol Martinez, USPHS	DHA Pharmacy Operations Division
LTC Misty Carlson, MC	DHA Pharmacy Operations Division
Maj David Folmar, BSC	DHA Pharmacy Operations Division
Lt Col Ronald Khoury, MC	DHA Pharmacy Operations Division
CDR Edward Vonberg, BSC	DHA Pharmacy Operations Division
Angela Allerman, PharmD, BCPS	DHA Pharmacy Operations Division
Shana Trice, PharmD, BCPS	DHA Pharmacy Operations Division
Amy Lugo, PharmD, BCPS via DCO	DHA Pharmacy Operations Division
Teresa Anekwe, PharmD, BCPS via DCO	DHA Pharmacy Operations Division
Eugene Moore, PharmD, BCPS	DHA Pharmacy Operations Division
Brian Beck, PharmD, BCPS	DHA Pharmacy Operations Division
Dean Valibhai	DHA Pharmacy Operations Division
David Meade, PharmD, BCPS via phone	DHA Pharmacy Operations Division
Ms. Deborah Garcia	DHA Pharmacy Operations Division contractor
Mr. Kirk Stocker	DHA Pharmacy Operations Division contractor
Esmond Nwokeji, PhD	DHA Pharmacy Operations Division contractor
Daniel DeLeon	Incarnate Word Pharmacy student

Appendix B—Table of Medical Necessity Criteria

Drug / Drug Class	Medical Necessity Criteria
• Suvorexant (Belsomra) **Newer Sedative Hypnotics (SED-1s)**	• Use of the formulary agent is contraindicated **Formulary alternatives:** zolpidem IR, zaleplon, zolpidem ER (Ambien CR), eszopiclone (Lunesta), and doxepin (Silenor)
• Peginterferon beta-1a (Plegridy) **Multiple Sclerosis (MS) Drugs**	• No alternative formulary agent. Patient requires Peginterferon beta-1a and cannot be treated with Avonex or Rebif. **Formulary alternatives**: Avonex, Rebif, Copaxone, Betaseron, Extavia, and the oral agents
• Doxylamine succinate and pyridoxine hydrochloride (Diclegis) **Antiemetics/Antivertigo Agents**	• No alternative formulary agent. Patient cannot swallow two tablets separately and must take a fixed-dose combination product. **Formulary Alternatives:** over-the-counter vitamin pyridoxine, over-the-counter doxylamine, metoclopramide, ondansetron
• ACCU-CHEK Aviva Plus Test Strips **Self-Monitoring Blood Glucose (SMBGS) Test Strips**	No alternative formulary agent: • Patient uses an insulin pump and requires a specific test strip that communicates wirelessly with a specific meter: o CONTOUR NEXT strip with CONTOUR NEXT Link meter for Medtronic pump. o Nova Max strip with Nova Max Link meter for Medtronic pump. o **ACCU-CHEK Aviva Plus test strips with the ACCU-CHEK Combo meter for the ACCU-CHEK Spirit Combo pump.** o For Retail Network Only: OneTouch Ultra test strips with OneTouch Ultra Link meter for Medtronic Mini Med Paradigm insulin pump. o For Retail Network Only: OneTouch Ultra test strips with OneTouch Ping meter and using the OneTouch Ping insulin pump

Appendix C—Table of Prior Authorization (PA) Criteria

Drug / Drug Class	Prior Authorization Criteria
• Suvorexant (Belsomra) **Newer Sedative Hypnotics (SED-1s)**	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.
• Doxylamine succinate and pyridoxine hydrochloride (Diclegis) **Antiemetics/Antivertigo Agents**	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.
• Testosterone nasal gel (Natesto) **Testosterone Replacement Therapy (TRTs)**	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.

Drug / Drug Class	Prior Authorization Criteria
• Ivacaftor (Kalydeco) **Cystic Fibrosis (CF) Drugs**	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 cystic fibrosis transmembrane conductance regulator (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.
• Perindopril/amlodipine (Prestalia) **Renin Angiotensin Antihypertensives (RAAs)**	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 ACE 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
• Inhaled Insulin (Afrezza) **Insulins**	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 use 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 use 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 (TZD), or dipeptidyl peptidase-4 inhibitor (DPP-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
• ACCU-CHEK Aviva Plus test strips **Self-Monitoring Blood Glucose System Test Strips**	New and current users of the nonformulary test strips are required to try FreeStyle Lite or Precision Xtra. See November 2014 P&T Committee Meeting minutes for full class PA criteria. 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

Appendix D—Table of Prior Authorization (PA) Criteria for Hepatitis C Drugs

Prior Authorization Criteria

Sofosbuvir (Sovaldi)
Direct Acting Antiviral Subclass

- 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 ≥ 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 plus 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.

Appendix E—Table of Quantity Limits

Drug / Drug Class	Quantity Limits
• Palbociclib (Ibrance) **Oral Oncologic Drugs**	▪ Retail Network : 21 capsules per 28 days ▪ MTF and Mail Order Pharmacy: 42 capsules per 56 days
• Panobinostat (Farydak) **Oral Oncologic Drugs**	▪ Retail Network : 6 capsules per 28 days ▪ MTF and Mail Order Pharmacy: 12 capsules per 56 days
• Lenvatinib (Lenvima) **Oral Oncologic Drugs**	▪ Retail Network: 1 carton per 30 days ▪ MTF and Mail Order Pharmacy: 2 cartons per 60 days

Appendix F—Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
May 2015	**Hepatitis C Virus (HCV) Agents – Direct Acting Agents (DAAs) Subclass**	UF class review Previously reviewed Nov 2012	▪ ECF: No DAA selected ▪ Peginterferon alfa-2a (Pegasys) ▪ Ribavirin 200 mg capsules (generics); excludes Ribapak formulation	▪ Sofosbuvir (Sovaldi) ▪ Simeprevir (Olysio) ▪ Ledipasvir/Sofosbuvir (Harvoni) ▪ Paritaprevir/ritonavir/ombitasvir plus dasabuvir (Viekira Pak) ▪ Note: Victrelis will remain UF until withdrawn from the market in December 2015	▪ None	Pending singing of the minutes	▪ Manual PA required ▪ QLs also apply; 28-day supply	-
May 2015	**Oral Anticoagulants**	UF class review Previously reviewed Feb 2013	▪ Generic warfarin	▪ Apixaban (Eliquis) ▪ Dabigatran (Pradaxa) ▪ Edoxaban (Savaysa) ▪ Rivaroxaban (Xarelto)	▪ None	Pending singing of the minutes	-	-
May 2015	**Newer Sedative Hypnotics (SED-1s)**	New Drug	▪ Zolpidem immediate release (IR)	*Step preferred* ▪ Zaleplon (Sonata) *Non step-preferred* ▪ Zolpidem ER (Ambien CR) ▪ Eszopiclone (Lunesta) ▪ Doxepin (Silenor)	▪ **Suvorexant (Belsomra) May 2015** ▪ Ramelteon (Rozerem) ▪ Zolpidem SL (Edluar) ▪ Zolpidem SL (Intermezzo) ▪ Tasimelteon (Hetlioz) Feb 2015	Pending signing of the minutes / 90 days	▪ Step therapy (automated PA); requires a trial of zolpidem IR or zaleplon for all SED-1 agents except tasimelteon	▪ BCF, UF, and NF drugs are designated for the SED-1s. There are 2 step-preferred agents: zolpidem IR and zaleplon. See DoD P&T Minutes for May 2012 and Feb. 2013. ▪ See Appendix C for Manual PA criteria.

Date	DoD PEC Drug Class	Type of Action	BCF/ECF Medications MTFs must have BCF meds on formulary	UF Medications MTFs may have on formulary	Nonformulary Medications MTFs may not have on formulary	Decision Date / Implement Date	PA and QL Issues	Comments
May 2015	**Multiple Sclerosis Drugs**	New Drug	▪ Interferon beta-1b SC (Betaseron)	**Injectables** ▪ Interferon beta-1a SC (Rebif and Rebif Rebidose) ▪ Interferon beta-1a IM (Avonex) ▪ Interferon beta-1b SC (Extavia) **Orals** ▪ Dalfampridine (Ampyra) ▪ Teriflunomide (Aubagio) ▪ Glatiramer (Copaxone) ▪ Fingolimod (Gilenya) ▪ Dimethyl fumarate (Tecfidera)	▪ **PEG interferon beta-1a SC (Plegridy) May 2015**	Pending signing of the minutes / 90 days	-	-
May 2015	**Antiemetics/ Antivertigo Agents**	New Drug	Older Antiemetics (May 2006) ▪ Promethazine oral and rectal (generics)	Newer Antiemetics (Nov 2005) ▪ Granisetron tablets (generics) ▪ Ondansetron oral tablets (generics) ▪ Aprepitant (Emend) Older Antiemetics (May 2006) ▪ Dronabinol (Marinol) ▪ Meclizine (Antivert, generics) ▪ Prochloperazine (Compazine, generics) ▪ Thiethylperazine (Torecan) ▪ Trimethobenzamide (Tigan, generics) ▪ Transdermal scopolamine (Transderm Scop)	▪ **Doxylamine succinate/ pyridoxine hydrochloride (Diclegis) May 2015** Newer Antiemetics ▪ Ondansetron soluble film (Zuplenz) ▪ Dolasetron (Anzemet) ▪ Granisetron patch (Sancuso)	Pending signing of the minutes / 90 days	PA criteria recommended at Aug 2013 meeting	-

TRICARE Formulary Search tool: http://tricare.mil/pharmacyformulary

IR: immediate release
ER: extended release

Appendix G—Table of Abbreviations

AASLD/IDSA	American Association for the Study of Liver Diseases/Infectious Diseases Society of America
BCF	Basic Core Formulary
BIA	budget impact analysis
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CMA	cost minimization analysis
DAAs	direct acting antivirals
DCO	Defense Connect Online
DHA	Defense Health Agency
DoD	Department of Defense
ECF	Extended Core Formulary
ER	extended release
FDA	U.S. Food and Drug Administration
GI	gastrointestinal
HCV	hepatitis C virus
IM	intramuscular
IR	immediate release
LMWH	low-molecular weight heparin
MHS	Military Health System
MN	medical necessity
MS	multiple sclerosis
MTF	Military Treatment Facility
NF	nonformulary
NVAF	non-valvular atrial fibrillation
NVP	nausea and vomiting during pregnancy
OTC	over-the-counter
P&T	Pharmacy and Therapeutics
PA	prior authorization
PE	pulmonary embolism
POS	points of service
QLs	quantity limits
RAAs	renin angiotensin antihypertensive
SED-1s	Sedative Hypnotic-1s Drug Class
SMBGS	self-monitoring blood glucose system
SC	subcutaneous
SL	sublingual
SVR	sustained virologic response
SVR12	sustained virologic response at 12 weeks
TRT	testosterone replacement therapy
TSOACs	target-specific oral anticoagulants
UF	Uniform Formulary
VTE	venous thromboembolism