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 or Tier 4/not covered status, prior authorization (PA), pre-authorizations, and the effective date for a drug's change from formulary to non-formulary (NF) or Tier 4 status are received from the Beneficiary Advisory Panel (BAP), which must be reviewed by the Director before making a final decision.

II. UF CLASS REVIEWS—PHOSPHODIESTERASE-5 (PDE-5) INHIBITORS

P&T Comments

A. PDE-5 Inhibitors – Relative Clinical Effectiveness Conclusion

Background—The P&T Committee evaluated the relative clinical effectiveness of the PDE-5 inhibitors, which include avanafil (Stendra), sildenafil (Viagra), tadalafil (Cialis), vardenafil oral disintegrating tablet (ODT) (Staxyn), and vardenafil tablets (Levitra). Generic formulations are marketed for all the products, except for Stendra. All the PDE-5 inhibitors are indicated to treat erectile dysfunction (ED) on an as needed basis. Tadalafil is the only PDE-5 inhibitor approved for daily use in addition to as needed use, and is approved for treating benign prostatic hyperplasia (BPH).

The class was most recently reviewed in November 2011. Sildenafil is currently UF and step-preferred, with the remaining PDE-5 inhibitors designated as NF and non-step-preferred. PA is not required for men over the age of 40 years for ED; however PA is required in men younger than 40 years for ED, for men of all ages for the Food and Drug Administration (FDA) approved indication of BPH, and for off-label uses (post-prostatectomy and Raynaud's phenomena). Use of the PDE-5 inhibitors for pulmonary arterial hypertension (PAH) is not a focus of this review.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

ED

- There were no major updates to the November 2011 conclusion that there is a high degree of therapeutic interchangeability for the PDE-5 inhibitors for treating ED.
- The 2018 American Urological Association (AUA) guidelines support PDE-5 inhibitors as first-line therapy for ED and state there are no major differences in efficacy between the drugs.

- Two recent network meta-analyses also support that there are no significant differences in efficacy between the PDE-5 inhibitors for ED. Sildenafil was associated with the highest efficacy compared to placebo, but head-to-head comparisons between the individual PDE-5 inhibitors have not been studied. (Chen 2015, Corona 2016).
- Based on meta-analysis findings, vardenafil is associated with the highest reporting of adverse events followed by sildenafil and tadalafil. (Chen 2015)

BPH

- A 2018 Cochrane review evaluated the effects of the PDE-5 inhibitors compared to placebo, and the alpha-blockers and 5-alpha reductase inhibitors on urinary symptoms of BPH. When compared to the alpha-blockers, the PDE-5 inhibitors probably provide similar improvement in urinary symptoms, based on moderate-quality evidence.

Off-label uses

- Post-prostatectomy: A Cochrane review in 2018 supports PDE-5 inhibitor use to preserve erectile function post-prostatectomy, but did not provide conclusive evidence of a preferred agent or dosing regimen (i.e., daily vs. on-demand). The authors acknowledge that tadalafil is the only PDE-5 inhibitor indicated for daily use and the most studied agent for daily dosing.
- Raynaud's phenomenon: There are no guidelines for treating this condition. According to the 2017 European Society of Vascular Medicine consensus statement, no specific agent is recommended, but sildenafil and tadalafil are the most studied PDE-5 inhibitors.

Individual PDE-5 characteristics

- Sildenafil (Viagra) was the first PDE-5 marketed and has a long history of use. It has the highest Military Health System (MHS) utilization of all the PDE-5 inhibitors. Generic formulations of sildenafil were launched in December 2017, and there are at least nine generic manufacturers available as of November 2019.
- Tadalafil (Cialis) advantages include its indication for BPH in addition to ED, approval for daily dosing and on-demand dosing, and a long half-life of 17 hours. Multiple generic formulations of tadalafil are marketed (17 as of November 2019).
- Vardenafil is available in both a film-coated tablet (Levitra) and orally dissolving tablet (ODT), (Staxyn). The ODT only provides a convenience to the patient. Disadvantages of vardenafil include low MHS utilization, and limited generic availability.
- Avanafil (Stendra) was the fourth PDE-5 to enter the market. Although it has the fastest onset of action of 15 minutes, this has not translated into increased efficacy over the other PDE-5 inhibitors. There is limited published data with avanafil, compared to the other products. One meta-analysis reported a statistically significant lower number of adverse events compared to the other

PDE-5 inhibitors (Corona 2016); however, this has not correlated with increased efficacy or a lower discontinuation rate. Generic formulations are not expected before 2023.

- Input from MHS providers support Tier 4 status for multiple PDE-5 inhibitors, as long as both a short-acting and long-acting product is available.

B. PDE-5 Inhibitors—Relative Cost-Effectiveness Analysis and Conclusion

Cost-minimization analysis (CMA) and budget impact analysis (BIA) were performed to evaluate the PDE-5s. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

- CMA results showed that generic sildenafil and tadalafil were the most cost effective PDE-5 inhibitors, followed by vardenafil tablet (Levitra, generics), vardenafil ODT (Staxyn, generics), and avanafil (Stendra), which were substantially less cost effective.
- BIA was performed to evaluate the potential impact of designating selected PDE-5 inhibitors as formulary, NF, or Tier 4 on the UF. The BIA results showed that designating generic sildenafil as UF and step-preferred, generic tadalafil as UF and non-step-preferred, with vardenafil ODT (Staxyn, generics), vardenafil tablet (Levitra, generics), avanafil (Stendra), and branded Viagra and branded Cialis as Tier 4 demonstrated significant cost avoidance for the MHS.

C. PDE-5 Inhibitors—UF/Tier 4/Not Covered Recommendation

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

- UF and step-preferred
  - sildenafil (generic Viagra only)
- UF and non-step-preferred
  - tadalafil (generic Cialis only)
- NF – none
- This recommendation includes step therapy in new users, which requires a trial of generic sildenafil before generic tadalafil.
- Tier 4/Not Covered
  - avanafil (Stendra, generics)
  - vardenafil ODT (Staxyn, generics)
  - vardenafil tablets (Levitra, generics)
  - Brand Viagra
  - Brand Cialis

When considering the PDE-5 candidates for Tier 4/Not Covered status, the P&T Committee considered the information outlined in the interim rule, Section 702(b)(10) of the NDAA 2018

published on December 11, 2018, and found at: https://www.federalregister.gov/documents/2018/12/11/2018-26562/tricare-pharmacy-benefits-program-reforms.

For the five PDE-5 inhibitors recommended for Tier 4/Not Covered status, the P&T Committee concluded they provide very little to no additional clinical effectiveness relative to the other PDE-5 inhibitors. Overall, the P&T Committee felt that the needs of TRICARE beneficiaries could be met by the formulary PDE-5 inhibitors, generic sildenafil, and generic tadalafil.

D. PDE-5 Inhibitors—Manual Prior Authorization (PA) Criteria

Automated step therapy requirements currently apply to the class for ED, requiring a trial of sildenafil (Viagra) first. The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) removing the automation, and requiring manual PA criteria for generic sildenafil and generic tadalafil. The manual PA will continue to require a trial of generic sildenafil prior to generic tadalafil for ED in new users. The age edit for males 40 years and older will continue to apply. PA will continue to be required for ED in males younger than age 40 years and for the off-label uses.

The PA criteria are as follows in bold and strikethrough:

1. Generic sildenafil tablets

Automated and Manual PA criteria apply to all new users of generic sildenafil. Note that brand Viagra is not covered by TRICARE.

Automated PA Criteria: Coverage is approved for treatment of ED if the patient is a male aged 40 years or older.

Manual PA Criteria: Coverage is approved if the following criteria are met:

- Patient is older than 18 years of age
- Patient is less than 40 years of age and is being treated for ED of organic or mixed organic/psychogenic origin OR
- Patient is less than 40 years of age and is being treated for drug-induced ED where the causative drug cannot be altered or discontinued OR

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

- Use of generic sildenafil for preservation/restoration of ED after prostatectomy. PA expires after one year. OR
- Use of generic sildenafil for Raynaud's Phenomenon OR
- ~~**Use of sildenafil for pulmonary arterial hypertension (PAH)**~~

Other non-FDA-approved uses are not approved, including use for females for the treatment of sexual dysfunction.
PA does not expire except as noted above following prostatectomy.

2. Generic tadalafil tablets

Manual PA criteria apply to all new users of generic tadalafil. Note that brand Cialis is not covered by TRICARE.

Automated PA Criteria: Coverage approved for treatment of ED if the patient is a male aged 40 years or older:

- Patient is older than 18 years of age
- Patient has tried generic sildenafil and has had an inadequate response or was unable to tolerate treatment due to adverse effects
  OR
- Treatment with generic sildenafil is contraindicated. OR
- Patient is less than 40 years of age and is being treated for ED of organic or mixed organic/psychogenic origin. The patient must try generic sildenafil first and is unable to use generic sildenafil due to reasons stated above (inadequate response or adverse events.) OR
- Patient is less than 40 years of age and is being treated for drug-induced ED where the causative drug cannot be altered or discontinued. The patient must try generic sildenafil first and is unable to use generic sildenafil due to reasons stated above (inadequate response or adverse events.) OR
- Use of generic tadalafil 2.5 mg or 5 mg for patients with BPH or BPH with ED meeting PA criteria requiring use of an alpha blocker [tamsulosin (Flomax) or alfuzosin (Uroxatral)] first unless there is a contraindication, inadequate response, or intolerable adverse effects with the alpha blocker

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

- Patient requires generic tadalafil for preservation/restoration of erectile function after prostatectomy. PA expires 1-years post-surgery.
- Use of generic tadalafil for Raynaud's Phenomenon OR
- ~~**Use of tadalafil for pulmonary arterial hypertension (PAH)**~~

Other non-FDA-approved uses are not approved, including use for females for the treatment of sexual dysfunction.

PA does not expire except as noted above following prostatectomy.

E. PDE-5 Inhibitors—UF/Tier 4/Not Covered and PA Implementation Plan

The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) 1) An effective date of the first Wednesday 120 days after signing of the P&T minutes at all points of service, and 2) DHA send letters to beneficiaries who are affected by the Tier 4/Not Covered recommendations at 30 and 60 days prior to implementation.

III. UF CLASS REVIEWS—PHOSPHODIESTERASE-5 (PDE-5) INHIBITORS

BAP Comments

A. PDE-5 Inhibitors—UF/Tier 4/Not Covered Recommendation

The P&T Committee recommended the formulary status for the PDE-5 Inhibitors as discussed above.

- UF and step-preferred
  - sildenafil (generic Viagra only)
- UF and non-step-preferred
  - tadalafil (generic Cialis only)
- NF – none
- Tier 4/Not Covered
  - avanafil (Stendra, generics)
  - vardenafil OTC (Staxyn, generics)
  - vardenafil tablets (Levitra, generics)
  - brand Viagra
  - brand Cialis

BAP Comment: ☐ Concur ☐ Non-concur

B. PDE-5 Inhibitors—Manual PA Criteria

The P&T Committee recommended removing the automation, and requiring manual PA criteria for generic sildenafil and generic tadalafil, as discussed previously.

BAP Comment: ☐ Concur ☐ Non-concur

C. PDE-5 Inhibitors—UF/Tier 4/Not Covered and PA Implementation Plan

The P&T Committee recommended 1) An effective date of the first Wednesday 120 days after signing of the P&T minutes at all points of service and 2) DHA send letters to beneficiaries who are affected by the Tier 4/Not Covered recommendations at 30 and 60 days prior to implementation.

BAP Comment: ☐ Concur ☐ Non-concur

IV. UF CLASS REVIEWS—RAPID-ACTING INSULINS SUBCLASS

P&T Comments

A. Rapid-Acting Insulins (RAIs)—Relative Clinical Effectiveness Analysis and Conclusion

Background—The RAIs have not been previously reviewed for formulary status. Insulin aspart (Novolog) has been BCF since 2003, prior to implementation of the UF Rule in 2005. Insulin lispro (Humalog) and insulin glulisine (Apidra) have not been previously reviewed and have been UF "by default" since their approval. Two products were reviewed as innovators: insulin aspart plus niacinamide (Fiasp) was made NF in November 2017 and inhaled insulin (Afrezza) was made NF in February 2016; both Fiasp and Afrezza require PA.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) the following:

- There were no major updates to the P&T clinical conclusions from 2003 that showed there are no clinically relevant difference between insulin aspart (Novolog) and lispro (Humalog) in lowering hemoglobin A1c.
- Numerous clinical practice guidelines are available (e.g., American Diabetes Association, American Association of Clinical Endocrinologists, American College of Endocrinology) and none give preference to one RAI over another.
- Although there are subtle differences between RAIs with regard to pharmacokinetic profiles in terms of onset and duration of action, clinical efficacy appears similar between the products.
- Insulin aspart (Novolog) is the current BCF RAI and is approved for use in insulin pumps and in children as young as 2 years of age. Other advantages include that it is available in all dosage forms (pen, vials, and cartridges), and has the majority of the market share in the MHS (>60%).
- Insulin lispro (Humalog) advantages include a long history of use in the MHS, approval for insulin pumps and in pediatric patients down to age 3 years, and availability in all dosage forms (pen, vials, and cartridges). Humalog is second in utilization in the MHS (30%).
- Insulin glulisine (Apidra) was the third FDA-approved RAI. It may be used in insulin pumps and in pediatric patients down to 4 years. Disadvantages of Apidra compared to insulin aspart or lispro include a greater susceptibility to precipitation and catheter occlusions during continuous subcutaneous insulin

infusion (CSII), and the association with significantly elevated hypoglycemia rates. It has very low utilization in the MHS (<1%).

- Fiasp is a new formulation of insulin aspart that contains niacinamide, a form of vitamin B3. Although Fiasp has a faster onset of action, the change in pharmacokinetic profile did not show a clinically significant difference in A1c or post-prandial blood glucose compared to Novolog. Fiasp recently gained FDA approval for use in pumps, but is not approved in pediatrics and has similar adverse effects to Novolog with slightly higher rates of hypoglycemia, upper respiratory infections, and nasopharyngitis.
- Admelog is a new formulation of insulin lispro that did not show a clinically significant difference in A1c or post-prandial blood glucose versus the active comparator Humalog. It is approved for use in pumps and in pediatrics down to age 3 years.
- Afrezza is the only inhaled insulin. Although it is approved for use in adults, it lacks pediatric labeling, has very low utilization in the MHS, and is the only RAI with a black box warning regarding bronchospasm in patients with asthma or chronic obstructive pulmonary disease (COPD). Despite the unique drug delivery system, Afrezza has numerous limitations including contraindications and warnings. As with all the RAIs, Afrezza requires concomitant basal insulin injections, which negates a potential advantage in patients with needle phobia. Overall, Afrezza offers no clinically compelling advantage over other RAIs.
- With regard to adverse events, there was no new data to change the 2003 conclusion that there is no evidence of a difference in the number, type, or severity of adverse reactions between insulin aspart or lispro.
- In a retrospective claims analysis comparing insulin aspart and lispro, there were no significant differences in the percentage of patients experiencing a hypoglycemic event or new or worsening diabetes complications. Additionally, there were no significant differences in emergency department visits between any of the products or device (e.g., vial, pen, and cartridge) comparisons.
- With regard to special populations, two systematic reviews found that RAIs were safe in pregnancy, pediatric patients, and in patients with diabetic ketoacidosis (DKA). No preferences were given regarding use of one RAI over another.
- With regard to devices, the RAI pens are the most widely used dosage form in the MHS, followed by vials, then cartridges.
- Overall, with the exception of inhaled insulin (Afrezza), there is a high degree of interchangeability among the RAIs.

B. RAIs—Relative Cost-Effectiveness Analysis and Conclusion

CMA and BIA were performed to evaluate the RAIs. The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) the following:

- CMA results for the RAIs showed the following products ranked from most cost effective to least cost effective as follows: insulin aspart (Novolog), insulin lispro

(Humalog and authorized generic insulin lispro), insulin lispro (Admelog), insulin glulisine (Apidra), insulin aspart with niacinamide (Fiasp), and inhaled insulin (Afrezza), respectively.

- BIA was performed to evaluate the potential impact of designating selected insulins as formulary, NF or Tier 4 on the UF. BIA results showed that designated insulin aspart (Novolog) and insulin lispro (Humalog and authorized generic insulin generic lispro) as UF and step-preferred, and insulin lispro (Admelog), insulin glulisine (Apidra), insulin aspart with niacinamide (Fiasp), and inhaled insulin (Afrezza) as NF and non-step-preferred demonstrated the most cost avoidance for the MHS.

C. RAIs—UF/Tier 4/Not Covered Recommendation

1. The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) the following:

    - UF and step-preferred
        - insulin aspart (Novolog)
        - insulin lispro (Humalog and authorized generic insulin lispro)
    - NF and non-step-preferred:
        - insulin lispro (Admelog)
        - insulin glulisine (Apidra)
        - inhaled insulin (Afrezza)

    - This recommendation includes step therapy (automated PA), which requires a trial of insulin aspart (Novolog) and insulin lispro (Humalog or authorized generic lispro) prior to use of the NF, non-step-preferred RAIs in all new and current users.

2. The P&T Committee recommended (9 for, 7 opposed, 0 abstained, 1 absent) the following:

    - Tier 4/Not Covered
        - insulin aspart plus niacinamide (Fiasp)

    The P&T Committee concluded that Fiasp provides very little to no additional clinical effectiveness relative to the other RAIs. Overall, the P&T Committee felt that the needs of TRICARE beneficiaries can be met by the other RAIs. The formulary alternatives include Novolog, Humalog, and authorized generic insulin lispro.

D. RAIs—Automated PA (Step Therapy) and Manual PA Criteria

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) automated PA and manual PA criteria for all new and current users of the non-step-preferred RAIs, insulin lispro (Admelog) and insulin glulisine (Apidra). A trial of Novolog and either Humalog or authorized generic insulin lispro will be required first, unless the patient is

using an insulin pump/CSII and is stabilized on Admelog or Apidra, or if they have tried and failed the step-preferred insulins.

Existing manual PA criteria apply to inhaled insulin (Afrezza). The P&T Committee recommend updating the manual PA criteria requiring the patient to have tried and failed Novolog and Humalog or authorized generic insulin lispro in all new and current users. Note that Afrezza will not be included in the automated step therapy criteria.

The PA criteria are as follows, with the changes highlighted in bold and strikethrough:

1. **Inhaled insulin (Afrezza)**

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

   Coverage is approved if all the criteria are met for non-smoking patients with either:

   Type 1 Diabetes Mellitus (diagnosed)

   - **Patient has tried and failed (defined as a failure to achieve hemoglobin Alc < 7% in 90 days) with insulin aspart (Novolog)**
   - **Patient has tried and failed (defined as a failure to achieve hemoglobin Alc ≤ 7 % in 90 days) with insulin lispro (Humalog or authorized generic insulin lispro (Humalog or authorized generic insulin lispro)**
   - ~~Failure to achieve hemoglobin Alc ≤ 7 % in 90 days of use of a rapid or short acting subcutaneous (SC) insulin product or clinically significant adverse effects experience 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 (FEV_1) has been performed upon initiation of therapy, with repeated FEV_1 at 6 months after initiation and repeated annually thereafter]
   - Patient does not have a contraindication of Afrezza (e.g. hypoglycemia, chronic lung disease [asthma, chronic obstructive pulmonary disease (COPD)], hypersensitivity to regular human insulin, or any Afrezza excipients)

   Type 2 Diabetes Mellitus (diagnosed)

   - **Patient has tried and failed (defined as a failure to achieve hemoglobin Alc < 7% in 90 days) with insulin aspart (Novolog)**
   - **Patient has tried and failed (defined as a failure to achieve hemoglobin Alc ≤ 7 % in 90 days) with insulin lispro (Humalog or authorized generic insulin lispro (Humalog or authorized generic insulin lispro)**
   - ~~Failure to achieve hemoglobin Alc ≤ 7 % in 90 days of use of a rapid or short acting subcutaneous (SC) insulin product or clinically significant adverse effects experience with SC rapid or short acting insulin unexpected to occur with inhaled insulin~~

- Patient has had failure of or clinically significant adverse effect to two oral anti-diabetic agents (i.e., sulfonylurea, TZD, DPP-4 inhibitor, or **SGLT2 inhibitor**) if metformin is contraindicated
- Spirometry testing [baseline forced expiratory volume in the first second (FEV1) has been performed upon initiation of therapy, with repeated FEV1 at 6 months after initiation and repeated annually thereafter]
- Patient does not have a contraindication to Afrezza (e.g. hypoglycemia, chronic lung disease [asthma, chronic obstructive pulmonary disease (COPD)], hypersensitivity to regular human insulin, or any Afrezza excipients)

Non-FDA-approved uses are not approved.

PA does not expire.

2. Insulin glulisine (Apidra) and insulin lispro (Admelog)

Step therapy and manual PA criteria apply to all new and current users of Apidra and Admelog.

Automated PA Criteria: The patient has filled a prescription for insulin aspart (Novolog) and insulin lispro (Humalog or authorized generic lispro) at any MHS pharmacy point of service [military treatment facility (MTFs), retail network pharmacies, or mail order] during the previous 720 days.

AND

Manual PA Criteria if automated criteria are not met:
Note: Novolog, Humalog, and the authorized generic insulin lispro are DoD's preferred RAIs. If the prescription is for Novolog, Humalog, or the authorized generic insulin lispro, PA is not required.

- If automated criteria are not met, Apidra or Admelog is approved if all criteria are met:
    - Patient has diabetes AND
        - Patient has tried and failed insulin aspart (Novolog) AND
        - Patient has tried and failed insulin lispro (Humalog or authorized generic insulin lispro)
          OR
        - Patient is using an insulin pump/continuous subcutaneous insulin infusion (CSII) and is stabilized on insulin glulisine (Apidra) or insulin lispro (Admelog)

Non-FDA-approved uses are not approved

PA does not expire

E. RAIs—Removal of Authorized Generic Insulin Lispro Manual PA Criteria

The authorized generic insulin lispro entered the market in April 2019, and manual PA criteria requiring a trial of Humalog first was implemented in May 2019. The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) removing the manual PA on authorized generic lispro, as it is no longer cost advantageous.

F. RAIs—UF/Tier 4/Not Covered and PA Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday after a 150-day implementation period, and no earlier than July 1, 2020 in all points of service and, 2) DHA send letters to beneficiaries who are affected by the UF/Tier 4 and PA. Patients affected by the Tier 4 recommendation will receive letters at 90, 60, and 30 days prior to implementation.

V. UF CLASS REVIEWS—RAPID-ACTING INSULINS SUBCLASS

BAP Comments

A. RAIs—UF/Tier 4/Not Covered Recommendation

The P&T Committee recommended the following:

- UF and step-preferred
  - Novolog
  - Humalog and authorized generic insulin lispro
- NF and non-step-preferred
  - Admelog
  - Apidra
  - Afrezza
- Tier 4/Not Covered
  - Fiasp

BAP Comment: ☐ Concur ☐ Non-concur

B. RAIs—Automated (Step Therapy) Manual PA Criteria

The P&T Committee recommended automated PA and manual PA criteria for Admelog and Apidra, requiring the patient to have tried and failed Novolog and Humalog or authorized generic insulin lispro in all new and current users; and updates to the PA criteria for Afrezza as discussed previously.

BAP Comment: ☐ Concur ☐ Non-concur

C. RAIs—Removal of Authorized Generic Insulin Lispro Manual PA Criteria

The P&T Committee recommended removing the manual PA on authorized generic lispro, as it is no longer cost advantageous, as discussed previously.

BAP Comment: ☐ Concur ☐ Non-concur

D. RAIs—UF/Tier 4/Not Covered and PA Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday after a 150-day implementation period, and no earlier than July 1, 2020 in all points of service and, 2) DHA send letters to beneficiaries who are affected by the UF/Tier 4 and PA. Patients affected by the Tier 4 recommendation will receive letters at 90, 60, and 30 days prior to implementation.

BAP Comment: ☐ Concur ☐ Non-concur

VI. NEWLY APPROVED DRUGS PER 32 CFR 199.21(G)(5)

P&T Comments

A. Newly Approved Drugs per 32 CFR 199.21(g)(5)—Relative Clinical Effectiveness and Relative Cost-Effectiveness Conclusions

The P&T Committee agreed for groups 1 and 2: (16 for, 0 opposed, 0 abstained, 1 absent) with the relative clinical and cost-effectiveness analyses presented for the newly approved drugs reviewed according to 32 CFR 199.21(g)(5).

B. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF/Tier 4/Not Covered Recommendation

The P&T Committee recommended for groups 1 and 2: (16 for, 0 opposed, 0 abstained, 1 absent); and group 3: (17 for, 0 opposed, 0 abstained, 0 absent) the following:

- UF:
  - bremelanotide injection (Vyleesi) – Miscellaneous gynecological agent for Hypoactive Sexual Desire Disorder (HSDD)
  - darolutamide (Nubeqa) – Oral oncologic agent for non-metastatic castration-resistant prostate cancer (nmCRPC)
  - entrectinib (Rozlytrek) – Oral oncologic agent for lung cancer
  - fedratinib (Inrebic) – Oral oncologic agent for myelofibrosis
  - glucagon injection (Gvoke Hypopen and Pre-filled Syringe) – Binders-Chelators-Antidotes-Overdose Agent for severe hypoglycemia
  - glucagon nasal spray (Baqsimi) – Binders-Chelators-Antidotes-Overdose Agent for severe hypoglycemia
  - lamivudine/tenofovir disoproxil fumarate (Temixys) – Antiretroviral combination for human immunodeficiency virus (HIV)
  - midazolam nasal spray (Nayzilam) – Anticonvulsants-antimania agent for seizures
  - pexidartinib (Turalio) – Oral oncologic agent for tenosynovial giant cell tumors
  - segesterone acetate/ethinyl estradiol vaginal ring (Annovera) – Miscellaneous contraceptive agent
  - selinexor (Xpovio) – Oral oncologic agent for relapsing remitting multiple myeloma
  - semaglutide oral tablet (Rybelsus) – Oral glucagon-like peptide-1 receptor agonist for type 2 diabetes mellitus in adults
- NF:
  - amlodipine oral suspension (Katerzia) – Calcium channel blocking agent in an oral suspension for hypertension
  - duloxetine extended-release (Drizalma Sprinkle) – Antidepressants and non-opioid pain syndrome, serotonin-norepinephrine reuptake inhibitors (SNRIs)
  - istradefylline (Nourianz) – Parkinson's agent for off episodes
  - lefamulin (Xenleta) – Antibiotic for community acquired bacterial pneumonia (CABP)
  - pitolisant (Wakix) – Sleep disorders: wakefulness promoting agent for narcolepsy
  - tiopronin ER (Thiola EC) – Miscellaneous urinary agent for cystinuria
  - upadacitinib (Rinvoq) – Targeted Immunomodulatory Biologic (TIB) for rheumatoid arthritis

- Tier 4 (Not Covered):
    - formoterol/aclidinium (Duaklir Pressair) inhaler– Pulmonary-2 Agent for Chronic Obstructive Pulmonary Disease (COPD)
        - Duaklir Pressair was recommended for Tier 4 status as it has little to no additional clinical effectiveness relative to similar long-acting muscarinic antagonist/long-acting beta agonist (LAMA/LABA) combination drugs; and the needs of TRICARE beneficiaries are met by alternative agents.
            - Formulary LAMA/LABA alternatives to Duaklir Pressair are umeclidinium/vilanterol (Anoro Ellipta), tiotropium/olodaterol (Stiolto Respimat), glycopyrrolate/indacaterol (Utibron Neohaler), glycopyrrolate/formoterol (Bevespi Aerosphere).
    - sumatriptan nasal (Tosymra) – Migraine agents, Triptans
        - Tosymra was recommended for Tier 4 status as it has little to no additional clinical effectiveness relative to similar nasal triptan migraine agents; and the needs of TRICARE beneficiaries are met by alternative agents.
            - Formulary alternatives to sumatriptan nasal (Tosymra) are sumatriptan nasal spray (Imitrex, generics); zolmitriptan nasal spray (Zomig); sumatriptan nasal powder (Onzetra Xsail).
    - tegaserod (Zelnorm) – Gastrointestinal-2 agent for constipation-predominant irritable bowel syndrome (IBS-C)
        - Zelnorm was recommended for Tier 4 status as it has no clinical benefit relative to other agents approved for IBS-C and has significant safety concerns relative to other IBS-C drugs including cardiovascular and suicidality risks; and the needs of TRICARE beneficiaries are met by alternative agents.
            - Formulary alternatives to Zelnorm include linaclotide (Linzess), plecanatide (Trulance), and lubiprostone (Amitiza).

C. Newly Approved Drugs per 32 CFR 199.21(g)(5)—PA Criteria

The P&T Committee recommended for groups 1 and 2: (16 for, 0 opposed, 0 abstained, 1 absent); and group 3: (17 for, 0 opposed, 0 abstained, 0 absent) the following:

- Applying manual PA criteria to new and current users of Drizalma Sprinkle, Nourianz, Rybelsus, Vyleesi, and Wakix.
- Applying manual PA criteria to new users of Inrebic, Nubeqa, Rozlytrek, Thiola EC, Turalio, and Xpovio.
- Targeted Immunomodulatory Biologic (TIBs): Applying the same manual PA criteria in new users of Rinvoq that is currently in place for the other non-step-preferred TIBs. Patients must first try adalimumab (Humira). Additionally, for Rinvoq a trial of tofacitinib (Xeljanz) or baricitinib (Olumiant) is required if the patient cannot be treated with Humira.

Full PA Criteria for the Newly Approved Drugs per 32 CFR 199.21(g)(5)

1. **bremelanotide injection (Vyleesi)**
   Manual PA criteria applies to all new and current users of Vyleesi.

   Manual PA Criteria: Vyleesi is approved if all criteria are met:
   - Patient is ≥ 18 years
   - Patient is a premenopausal woman with a documented diagnosis of acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty
   - Decreased sexual desire is NOT caused by:
     - Co-existing medical or psychiatric condition
     - Problems with the relationship
     - Effects of a medication or drug substance
   - Patient has been informed that other treatment options, such as cognitive-behavior therapy, sexual therapy, or couples therapy, may provide benefit without the risk of side effects
   - Patient does not have uncontrolled hypertension or known cardiovascular disease
   - Patient has been counseled on the risks of focal hyperpigmentation (skin discoloration) and severe nausea
   - Patient agrees to use effective contraception while taking Vyleesi

   Non-FDA-approved are not approved.
   PA expires in 3 months.

   Renewal PA criteria: Coverage will be approved indefinitely for continuation of therapy if the patient has had documented improvement in symptoms without serious side effects.

2. **darolutamide (Nubeqa)**
   Manual PA is required for all new users of Nubeqa.

   Manual PA Criteria: Nubeqa is approved if all criteria are met:
   - Note that Xtandi is the Department of Defense's preferred 2nd-Generation Antiandrogen Agent. The patient is required to try Xtandi first. OR
   - Patient has a contraindication or has had an inadequate response or adverse reaction to Xtandi that is not expected to occur with Nubeqa AND
   - Patient is ≥ 18 years AND
   - Drug is prescribed by or in consultation with an oncologist or urologist AND
   - Patient has diagnosis of non-metastatic castration-resistant prostate cancer (nmCRPC) AND

- The patient has had a negative CT scan of abdomen/pelvis and/or negative bone scan AND
- Prostate-specific antigen doubling time (PSADT) is ≤ 10 months
  OR
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis: _____.
- Patient must be receiving a gonadotropin-releasing hormone (GnRH) analog concomitantly OR have had a bilateral orchiectomy

Other Non-FDA-approved uses are not approved.

PA expires in 1 year.

Renewal criteria: Nubeqa is approved for 1 year for continuation therapy if all criteria are met:

- The patient continues to be metastases-free
- The patient has not progressed onto subsequent therapy (such as abiraterone)

3. Duloxetine delayed-release capsules (Drizalma Sprinkle)

PA does not apply to patients 12 years of age and younger (age edit)

PA criteria applies to all new and current users of Drizalma Sprinkle

Manual PA Criteria: Drizalma Sprinkle is approved if the provider explains why the patent requires duloxetine sprinkle capsules and cannot take alternatives.

Non-FDA-approved uses are not approved.

PA expires in 1 year.

Renewal PA criteria: No renewal allowed. A new prescription will require submission of a new PA.

4. Entrectinib (Rozlytrek)

Manual PA criteria apply to all new users of Rozlytrek.

Manual PA Criteria: Rozlytrek will be approved if all criteria are met:

- Patient is ≥ 12 years
- Drug is prescribed by or in consultation with an oncologist
- Patient has a diagnoses of either:
  - ROS1(+) Metastatic NSCLC or

- The patient has a solid tumor that meets all three of the following criteria:
    - Has a neurotrophic tropomyosin receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, and
    - Is metastatic OR where surgical resection is likely to result in severe morbidity, and
    - Has no satisfactory alternative treatments OR that has progressed following such treatment(s)
- The patient has had a recent evaluation of his/her left ventricle including ejection fraction
- The patient does not have decompensated congestive heart failure (CHF)
- The patient has had a recent uric acid level
- The provider is aware and has informed the patient of the risk of CHF development and exacerbation, myocarditis, neurotoxicity, fracture risk, hepatotoxicity, hyperuricemia, QT-prolongation, permanent visual impairment, and embryo-fetal toxicity
- Female patients will not breastfeed during treatment and for 1 week after cessation of treatment
- All patients (females AND males) of reproductive potential will use highly effective contraception during treatment and for at least 5 weeks or 3 months after cessation of treatment for females and males, respectively.
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis: _____.

Other non-FDA-approved uses are not approved.

PA does not expire.

5. fedratinib (Inrebic)

Manual PA is required for all new users of Inrebic.

Manual PA Criteria: Inrebic is approved if all criteria are met:

- Patient is ≥ 18 years
- Drug is prescribed by or in consultation with a hematologist/oncologist
- Inrebic will be used for intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis
- Provider acknowledges that serious and fatal encephalopathy including Wernicke's encephalopathy has occurred in patients treated with Inrebic. If

thiamine deficiency is expected or confirmed, Inrebic should be discontinued immediately and the patient should receive emergent parenteral thiamine.

- The patient does not have vitamin B1 deficiency.
- The following labs will be assessed prior to starting fedratinib and periodically while the patient is taking Inrebic: thiamine (Vitamin B1), complete blood count (CBC) with platelets, serum creatinine and blood, urea nitrogen (BUN), hepatic panel and amylase and lipase
- Nutritional status will be assessed prior to starting Inrebic and periodically while the patient is taking fedratinib
- If the patient is female, she is not pregnant or planning to become pregnant.
- Female patients will not breastfeed during treatment and for at least 1 month after discontinuation.
- Females of reproductive potential will use effective contraception during treatment and for at least 1 month after discontinuation.
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis: _____.

Other non-FDA-approved uses are not approved.

PA does not expire.

6. istradefylline (Nourianz)

Manual PA is required for all new and current users of Nourianz.

Manual PA Criteria: Nourianz approved if all criteria are met:

- Patient is ≥ 18 years
- Patient has a diagnosis of Parkinson's disease
- Drug is prescribed by or in consultation with a neurologist
- Patient continues to experience wearing off periods, despite optimizing (e.g., increasing dose and daily frequency) carbidopa/levodopa therapy
- Patient is currently taking and will continue taking carbidopa-levodopa therapy
- Patient must try and fail an adequate trial of at least two drugs from any of the three classes:
  - Dopamine Agonist: pramipexole, ropinirole, rotigotine
  - MAO-B: rasagiline, selegiline
  - COMT: tolcapone, entacapone

Non-FDA-approved uses are NOT approved, including restless legs syndrome.

PA does not expire.

7. pexidartinib (Turalio)

Manual PA is required for all new users of Turalio.

Manual PA Criteria: Turalio is approved if all criteria are met:

- Patient is ≥ 18
- Drug is prescribed by or in consultation with an oncologist
- Patient has symptomatic tenosynovial giant cell tumor associated with severe morbidity or functional limitations, is not amenable to improvement with surgery, and has not progressed on Turalio.
- Patient will be monitored for hepatotoxicity
- Prescriber is certified with Risk Evaluation and Mitigation Strategy (REMS) program
- Patient is enrolled in REMS program
- If the patient is female, she is not pregnant or planning to become pregnant.
- Female patients will not breastfeed.
- All patients (females AND males) of reproductive potential will use effective contraception during treatment and for 1 month after discontinuation in females and 1 week after discontinuation in males with female partners.
- The diagnosis IS NOT listed above but IS cited in the NCCN guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis: _____.

Other non-FDA-approved uses are not approved.

PA does not expire.

8. pitolisant (Wakix)

Manual PA is required for all new and current users of Wakix.

Manual PA Criteria: Wakix is approved if ALL criteria are met:

- Patient is ≥ 18 years
- Patient has a documented diagnosis of excessive daytime sleepiness associated with narcolepsy
- Narcolepsy was diagnosed by polysomnography or mean sleep latency time (MSLT) objective testing
- Drug is prescribed by a neurologist, psychiatrist, or sleep medicine specialist
- Patient is not concurrently taking any of the following:

- Modafinil, armodafinil, or stimulant-based therapy, such as amphetamine or methylphenidate
- Patient must have tried and failed and had an inadequate response to modafinil
- Patient must have tried and failed and had an inadequate response to armodafinil
- Patient must have tried and failed and had an inadequate response to stimulant-based therapy (amphetamine or methylphenidate)
- Patient does not have a history of severe hepatic impairment
- Other causes of sleepiness have been ruled out or treated, including but not limited to obstructive sleep apnea

Non-FDA-approved uses are not approved (including but not limited to fibromyalgia, insomnia, excessive sleepiness not associated with narcolepsy, cataplexy, obstructive sleep apnea, major depression, Attention Deficit Hyperactivity Disorder (ADHD), or shift work disorder).

Not approved for use in children, adolescents, or pregnant patients

PA expires in 1 year.

Renewal PA criteria: No renewal allowed. A new prescription will require submission of a new PA.

9. selinexor (Xpovio)

Manual PA applies to new users of Xpovio.

Manual PA Criteria: Xpovio is approved if all criteria are met:

- Age ≥ 18
- Drug is prescribed by or in consultation with an oncologist
- Xpovio will be used in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody
- Patient will be monitored for cytopenias including anemia, neutropenia, and thrombocytopenia
- Patient will be monitored for electrolyte disturbances including hyponatremia and hypokalemia
- Patient will be monitored for infection including upper respiratory infection and pneumonia
- Patients will be monitored for dizziness and altered mental status

- If the patient is female, she is not pregnant or planning to become pregnant.
- Female patients will not breastfeed.
- All patients (females AND males) of reproductive potential will use effective contraception during treatment and for at least 1 week after discontinuation.
- The diagnosis IS NOT listed above but IS cited in the NCCN guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis: _____.

Other non-FDA-approved uses are not approved.

PA does not expire.

10. semaglutide oral tablet (Rybelsus)

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

Manual PA Criteria: Rybelsus is approved if all criteria are met:

- Patient is ≥ 18
- Patient has a documented diagnosis of type 2 diabetes
- Patient has tried and had an inadequate response to metformin, or has a contraindication to metformin
- Patient must be able to adhere to the administration requirements (take on an empty stomach with no more than 4 oz. of water at least 30 min before the first meal of the day)
- Patient does not have a history of pancreatitis
- Patient does not have a personal or family history of medullary thyroid carcinoma (MTC)
- Patient does not have multiple endocrine neoplasia syndrome type 2 (MEN2)
- Patient and provider acknowledge that Rybelsus has not been shown to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease

Not approved for use in children or pregnant patients.

Non-FDA approved uses are not approved including weight loss (obesity) or type 1 diabetes mellitus.

PA does not expire.

11. tiopronin immediate-release (Thiola)/tiopronin delayed-release tablets (Thiola EC)

Note that PA criteria were also recommended for the original Thiola immediate release preparation.

Manual PA Criteria: Thiola or Thiola EC is approved if all criteria are met:

- Patient is ≥ 9 years
- Drug is prescribed by or in consultation with a nephrologist or urologist
- Patient has a documented diagnosis of severe homozygous cystinuria
- Patient/provider provides laboratory evidence of elevated urinary cystine concentration (> 250 mg/L) as demonstrated by a 24-hour urine test
- Patient has tried and failed treatment with all of the following conservative treatment measures:
  - High fluid intake ≥ 3 L/day
  - Urinary alkalization with potassium citrate or potassium bicarbonate
  - Diet modification with restricted protein and sodium consumption

Non-FDA-approved uses are not approved.

PA does not expire.

12. upadacitinib (Rinvoq)

Note that Humira is the DoD's preferred targeted biologic agent for rheumatoid arthritis.

Manual PA criteria applies to all new users of Rinvoq

Manual PA Criteria: Rinvoq is approved if all criteria are met:

- Patient is ≥ 18
- Patient has diagnosis of active rheumatoid arthritis
- Patient has had an inadequate response or an intolerance to methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs)
- Patient has had an inadequate response to Humira OR
- Patient has experienced an adverse reaction to Humira that is not expected to occur with the requested agent OR
- Patient has a contraindication to Humira AND
- Patient has had an inadequate response to Xeljanz or Olumiant OR
- Patient has experienced an adverse reaction to Xeljanz or Olumiant that is not expected to occur with the requested agent OR
- Patient has a contraindication to Xeljanz or Olumiant that does not apply to Rinvoq AND
- Patient has no evidence of active tuberculosis (TB) infection

- Patient has no history of venous thromboembolic (VTE) disease
- Patient has no evidence of neutropenia (ANC <1000)
- Patient has no evidence of lymphocytopenia (ALC <500)
- Patient has no evidence of anemia (Hgb < 8)
- Patient is not taking Rinvoq concomitantly with other TIBs agents except for Otezla and other potent immunosuppressants (e.g., azathioprine, cyclosporine).

Non-FDA-approved uses are not approved.

PA does not expire.

D. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF and PA Implementation Plan

The P&T Committee recommended groups 1 and 2: 16 for, 0 opposed, 0 abstained, 1 absent); and group 3: 17 for, 0 opposed, 0 abstained, 0 absent) the following:

- **New Drugs Recommended for UF or NF Status:** An effective date upon the first Wednesday two weeks after signing of the minutes in all points of service.
- **New Drugs Recommended for Tier 4 Status Duaklir Pressair, Tosymra, Zenorm:** 1) An effective date of the first Wednesday after a 120-day implementation period at all points of service, and 2) DHA send letters to beneficiaries who are affected by the Tier 4/Not Covered recommendation at 30 days and 60 days prior to implementation.

VII. NEWLY APPROVED DRUGS PER 32 CFR 199.21(G)(5)

BAP Comments

A. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF Recommendation

The P&T Committee recommended the formulary status for the new drugs as stated previously.

- UF:
  - Vyleesi
  - Nubeqa
  - Rozlytrek
  - Inrebic
  - Gvoke Hypopen and Pre-filled Syringe
  - Baqsimi
  - Temixys
  - Nayzilam
  - Turalio
  - Annovera
  - Xpovio

- Rybelsus
- Thiola EC

- NF:
  - Katerzia
  - Drizalma Sprinkle
  - Nourianz
  - Xenleta
  - Wakix
  - Rinvoq

- Tier 4/Not Covered
  - Duaklir Pressair
  - Tosymra
  - Zelnorm

BAP Comment: ☐ Concur ☐ Non-concur

B. Newly Approved Drugs per 32 CFR 199.21(g)(5)—PA Criteria

The P&T Committee recommended the PA criteria for the new drugs as stated previously.

BAP Comment: ☐ Concur ☐ Non-concur

C. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF and PA Implementation Plan

- **New Drugs Recommended for UF or NF Status:** An effective date upon the first Wednesday two weeks after signing of the minutes in all points of service
- **New Drugs Recommended for Tier 4 Status Duaklir Pressair, Tosymra, and Zelorm:** 1) An effective date of the first Wednesday after 120-day implementation

period at all points of service, and 2) DHA send letters to beneficiaries who are affected by the Tier 4/Not Covered recommendation at 30 days and 60 days prior to implementation

BAP Comment: ☐ Concur ☐ Non-concur

VIII. UTILIZATION MANAGEMENT—NEW MANUAL PA CRITERIA

P&T Comments

A. New PA Criteria—Newly Approved Drugs Not Subject to 32 CFR 199.21(g)(5)

New manual PA criteria were recommended by the P&T Committee due to a variety of reasons. The new manual PAs outlined below will apply to new users for the Parkinson's drug Neupro and the oncology drugs Venclexta and Zydelig, and to new and current users for the skeletal muscle relaxant chlorzoxazone, and the topical anesthetic cream.

1. Skeletal Muscle Relaxants and Combinations—Chlorzoxazone 375 mg and 750 mg (Lorzone, generics)

Chlorzoxazone 375 mg and 750 mg are new strengths approved via the Abbreviated New Drug Application (ANDA) pathway and thus do not qualify for review by the DoD P&T Committee under the innovator program. Chlorzoxazone 500 mg is a scored tablet and produced by several manufacturers. Skeletal muscle relaxants are not considered first-line therapy for musculoskeletal conditions. Cost-effective generic formulations of chlorzoxazone 500 mg and multiple comparable muscle relaxants (e.g., cyclobenzaprine, methocarbamol) are available on the UF without PA required. PA criteria also apply to the chlorzoxazone 250 mg strength, from the November 2018 meeting.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for chlorzoxazone 375 mg and 750 mg (Lorzone, generics) in new and current users, due to significant cost differences compared with splitting the 500 mg tablets or using other generic muscle relaxants.

Manual PA Criteria: Coverage for chlorzoxazone 375 mg and 750 will be approved if all criteria are met:

- The provider explains why the patient requires chlorzoxazone 375 mg or 750 mg and why the patient cannot take chlorzoxazone 500 mg tablet (blank write-in).
  _____

Non-FDA-approved uses are NOT approved.
PA does not expire.

2. Anesthetic Agents: Local—Lidocaine-Tetracaine 7%-7% topical cream (Pliaglis, generics)

This combination topical anesthetic cream is an authorized generic of Pliaglis and is approved for use prior to superficial dermatological procedures, including dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal. Prior to 2018, this product was restricted to use in the clinic setting by health care professionals. However, the "Not for Home Use" restriction was removed, as the manufacturer submitted a study supporting patient self-use. Numerous cost-effective topical anesthetics (e.g., lidocaine 4% cream, lidocaine 5% cream/ointment, and lidocaine-prilocaine 2.5%-2.5% cream) are available that a patient could apply prior to a procedure.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for new users and current users over the age of 12 years, due to the availability of several cost-effective alternatives.

Manual PA Criteria: Coverage for lidocaine-tetracaine 7%-7% topical cream is approved if all criteria are met:

- The provider acknowledges that there are multiple formulary topical local anesthetics are available for DoD beneficiaries without a PA including lidocaine 4% cream, lidocaine 5% cream or ointment, and lidocaine-prilocaine 2.5%-2.5% cream
- Drug is prescribed by or in consultation with a dermatologist or surgeon
- Not approved for use in back or joint pain
- Not approved for use in compounding
- Not approved for use as local anesthetic associated with cosmetic procedures including but not limited to dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal
- The provider must document the clinical rationale of why patient cannot take any of the formulary topical local anesthetics

Non-FDA-approved uses are NOT approved.

New PA required per prescription fill.

3. Parkinson's Agents: rotigotine (Neupro) patch

The P&T Committee has not previously reviewed the Parkinson's disease drug class. Rotigotine (Neupro) patch was marketed in 2012, and was designated as UF prior to the establishment of the Innovator Rule in August 2015. Although rotigotine is the only

non-oral dopamine agonist, Parkinson's disease guidelines do not give a preference for any one agent over another. Cost effective generic formulations of oral pramipexole and ropinorole are available.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for new users, requiring use of an oral dopamine agonist first, unless the patient has swallowing difficulties.

Manual PA Criteria: Coverage for Neupro patch is approved if all criteria are met:

- Age ≥ 18 years
- Patient has a diagnosis of:
  - Parkinson's disease OR
  - Moderate to severe primary restless legs syndrome
- Patient cannot swallow tablets due to a documented medical condition (i.e. dysphagia, oral candidiasis, systemic sclerosis, etc.) and not due to convenience OR
- Patient has tried and failed or has a contraindication to other dopamine agonist oral therapy:
  - pramipexole (Mirapex) OR ropinorole (Requip)

Non-FDA-approved uses are NOT approved.

Prior authorization does not expire.

4. Oral Oncologic Agents: venetoclax (Venclexta) and idelalisib (Zydelig)

PA criteria have not previously been required for the chronic lymphocytic leukemia (CLL) drugs, Venclexta and Zydelig. However, PA criteria is in place for several other oncological drugs used to treat CLL.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for these two products in new users in order to ensure prescribing in accordance with FDA-approved indications or National Comprehensive Cancer Network (NCCN) Guideline-endorsed off-label indications.

a) Venetoclax (Venclexta)

- Age ≥ 18 years
- Drug is prescribed by or in consultation with a hematologist or oncologist
- Venclexta will be used in one of the following contexts:
  - Frontline therapy for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) without del(17p)/TP53 mutation
    - Patient fits one of the following categories:
      - Frail patient with significant comorbidity (not able to tolerate purine analogues)

                - Patient ≥ 65 years old with significant comorbidity
                - Patient < 65 years old
            - Will be combined with obinutuzumab (Gazyva) infusion
        - Relapsed/refractory therapy for CLL/SLL without del(17p)/TP53 mutation
            - Patient fits one of the following categories:
                - Frail patient with significant comorbidity (not able to tolerate purine analogues)
                - Patient ≥ 65 years old with significant comorbidity
                - Patient < 65 years old
        - Frontline or relapsed/refractory therapy for CLL/SLL with del(17p)/TP53 mutation
        - Patient has newly diagnosed acute myeloid leukemia (AML) and is a candidate for intensive remission induction therapy and meets the following criteria:
            - Age ≥ 60 years old
            - Unfavorable-risk cytogenetics (exclusive of AML with myelodysplasia-related changes)
        - Patient is ≥ 60 years old and has newly diagnosed AML and is not a candidate for intensive remission induction therapy
        - Patient is ≥ 60 years old and completed lower-intensity induction therapy for AML with a response
        - Patient has relapsed refractory AML
- Will titrate to therapeutic dose in consideration of tumor lysis syndrome (TLS)
- Will not be concomitantly used at initiation or during ramp-up with a strong CYP3A inhibitor
- Will prophylax and monitor for tumor lysis syndrome (TLS) (based on tumor burden-defined risk)
- Will monitor for neutropenia
- Will monitor for signs and symptoms of infection
- Will not administer live attenuated vaccines prior to, during, or after treatment with Venclexta until B-cell recovery occurs.
- If the patient is female, she is not pregnant or planning to become pregnant
- Female patients will not breastfeed
- Male patients have been informed of risk of infertility
- Female patients of reproductive potential will use effective contraception during treatment and for at least 30 days after discontinuation
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis: _____

Non-FDA approved uses are NOT approved.

Prior Authorization does not expire.

b) Idelalisib (Zydelig)

- Age ≥ 18 years
- Drug is prescribed by or in consultation with a hematologist or oncologist
- Zydelig will be used in one of the following indications:
  - Relapsed/refractory therapy for CLL/SLL without del(17p)/TP53 mutation
    - Patient fits one of the following categories:
      - Frail patient with significant comorbidity (not able to tolerate purine analogues)
      - Patient ≥ 65 years old with significant comorbidity
      - Patient < 65 years old
  - Relapsed/refractory therapy for CLL/SLL with del(17p)/TP53 mutation
  - Relapsed/refractory follicular lymphoma AND:
    - Patient has completed ≥ 2 prior therapies OR
    - Patient has completed 1 prior therapy and relapsed ≤ 2 years
  - Relapsed/refractory marginal zone lymphoma after 2 prior therapies
- Provider has reviewed the REMS program including the letter to healthcare providers and the fact sheet and has shared the medication guide and patient safety information card with the patient
- Will monitor for hepatotoxicity, colitis, intestinal perforation, pneumonitis, infection, neutropenia, and Steven Johnson Syndrome/toxic epidermal necrolysis
- Will monitor for cytomegalovirus reactivation
- Will prophylax for *pneumocystis jiroveci* pneumonia
- If the patient is female, she is not pregnant or planning to become pregnant
- Female patients will not breastfeed
- Female patients of reproductive potential will use effective contraception during treatment and for at least 30 days after discontinuation
- Male patients of reproductive potential will use effective contraception during treatment and for at least 3 months after discontinuation
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis: _____

Non-FDA approved uses are NOT approved.

Prior Authorization does not expire.

B. New PA Criteria—PA Implementation

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) the new PAs for chlorzoxazone 375 mg and 750 mg (Lorzone, generics) and lidocaine-tetracaine 7%-7% become effective the first Wednesday 90-days after the signing of the minutes. DHA will send letters to beneficiaries affected by the new PA requirements for chlorzoxazone and lidocaine-tetracaine 7%-7%, topical cream as new and current users will be subject to the PA.

IX. UTILIZATION MANAGEMENT—NEW MANUAL PA CRITERIA

BAP Comments

A. New PA Criteria

The P&T Committee recommended new manual PA criteria for the drugs discussed above.

BAP Comment: □ Concur □ Non-concur

B. New PA Criteria—PA Implementation Plan

The P&T Committee recommended the new PA criteria for the drugs discussed above become effective 90 days after the signing of the minutes, and that DHA send letters to the patients affected by the new PA requirements for chlorzoxazone and lidocaine-tetracaine 7%-7%, topical cream as new and current users will be subject to the PA.

BAP Comment: □ Concur □ Non-concur

X. UTILIZATION MANAGEMENT—UPDATED MANUAL PA CRITERIA

P&T Comments

A. Updated PA Criteria

Updates to the manual PA criteria and step therapy criteria for several drugs were recommended due to a variety of reasons, including expanded FDA indications, new NCCN guideline recommendations, clinical trial data, and standardization with existing PAs for the drug class, changes due to FDA safety announcements and boxed warnings, and age indications. The updated PAs and step therapy criteria outlined below will apply to new users.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) to implement the PA criteria for Cimzia originally recommended at the May 2019 P&T Committee meeting (the Humira step requirement). The Committee also recommended the updates to the manual PA criteria for Symbicort and Dulera, Xeljanz, Xeljanz XR, Olumiant, Zytiga, and Doptelet.

The updates are as follows:

Updated Criteria for reasons other than new FDA indications, NCCN Guideline Updates, or Age Ranges

1. **Pulmonary-1 Agent: Combinations: budesonide/formoterol Symbicort AND mometasone/formoterol (Dulera)**—Manual PA criteria for Symbicort and Dulera were originally recommended in February 2014, requiring a trial of fluticasone/salmeterol (Advair) first. Recently the Global Initiative for Asthma (GINA) 2019 evidence-based strategy was updated, and states that combination low-dose inhaled corticosteroid (ICS)-formoterol used as needed is now the preferred reliever ("rescue use") for asthma control and reducing exacerbations in adults and adolescents 12 years and older with mild asthma. Short-acting beta agonists (SABAs) are now listed as an "other reliever option" and are no longer the preferred rescue treatment in adults and adolescents with mild asthma. This new approach was based on two studies that used a combination budesonide-formoterol inhaler (SYGMA 1 and SYGMA2, New England Journal of Medicine May 2018).

   Limitations to this recommendation include that the two supporting studies were industry funded, and used an active comparator (terbutaline Turbuhaler) that is not available in the U.S. Additionally, the budesonide-formoterol inhaler evaluated in the trials was a dry powder inhaler, while the commercially available U.S. product is a pressurized metered-dose inhaler (Symbicort), and the study design was changed from superiority trial to a non-inferiority trial. The study results also show that this method is not as effective at decreasing asthma symptoms.

   Provider feedback further support the use of ICS-formoterol combination for rescue use. Manual PA criteria for both Symbicort and Dulera were updated to allow use in patients with mild asthma who require rescue therapy with an ICS-formoterol combination, without requiring a trial of Advair first.

2. **Target Immunomodulatory Biologics (TIBs): certolizumab (Cimzia))**—Manual PA criteria for Cimzia were most recently reviewed at the May 2019 P&T Committee meeting after Cimzia was granted FDA-approval for adults with non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation. The Cimzia and Humira PA criteria were updated to allow for the indication of nr-axSpA but still require the use of adalimumab (Humira)

prior to use of Cimzia. This recommendation was based on the Assessment of Spondylo Arthritis International Society (ASAS)/European League against Rheumatism (EULAR) guidelines and clinical trial data.

The implementation of the Humira step requirement was delayed in light of new information that was not available at the May 2019 P&T meeting. The fact that the manufacturer for Humira sought FDA-approval for this indication and was denied in 2009-2013 had not been presented to the Committee in May 2019. The new information presented at this meeting included the FDA's review of both Cimzia and Humira for nr-axSpA, the high degree of difficulty of actually diagnosing this disease, and provider feedback. The P&T Committee recommended maintaining the requirement for Humira prior to Cimzia for nr-axSpA after evaluating the new information. The Cimzia PA criteria from the May 2019 P&T Committee meeting requiring use of Humira first in patients with nr-axSpA will now be implemented.

3. **TIBs: Janus Kinase (JAK) inhibitors tofacitinib (Xeljanz, Xeljanz XR) and baricitinib (Olumiant)—**The FDA has issued several safety alerts for Xeljanz and Xeljanz XR for pulmonary embolism and death with certain doses, most recently in July 2019. The Xeljanz/Xeljanz XR PA criteria were updated to ensure the provider is aware of the July 2019 FDA safety announcement and boxed warning, and to ensure patients do not have a history of thromboembolic disease.

   Olumiant PA criteria were recommended in August 2018, and suggested using Xeljanz prior to Olumiant, since at that time Xeljanz did not contain a boxed warning for thrombosis. This comment will be removed from the Olumiant PA, as Xeljanz/Xeljanz XR now have the warning mentioned above.

   For Xeljanz/Xeljanz XR and Olumiant, additional requirements for absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) monitoring were also added, consistent with the package inserts. The PAs will also allow concomitant use with Otezla, if the provider includes supporting literature for combination use.

4. **Oncological Agents: Prostate Cancer CYP-17 Inhibitors: abiraterone acetate (Zytiga, generics)—**Manual PA criteria for Zytiga were recommended when the CYP-17 Inhibitor subclass was reviewed at the February 2019 P&T Committee meeting. Step therapy requiring a trial of abiraterone acetate micronized (Yonsa) first was required. Furthermore, an additional step required Zytiga generic 250 mg prior to Zytiga brand 500 mg, as the 500 mg branded formulation did not have generic equivalents and provide no clinical benefit at a significantly higher price per day.

   As of October 2019, the blended monthly cost of generic abiraterone acetate 250 mg is now comparable to the step-preferred Yonsa formulation. The step

requiring Yonsa before Zytiga generic 250 mg will be removed. The abiraterone acetate (Zytiga) brand 500 mg PA form will still require use of Yonsa or the 250 mg generics first.

5. **Hematological Agents: Platelets: avatrombopag (Doptelet)—**Manual PA criteria for Doptelet were first recommended in August 2018 for thrombocytopenia associated with chronic liver disease in patients who are scheduled to undergo a procedure with at least a moderate bleeding risk. Manual PA criteria were later updated in February 2019 to require a trial of Mulpleta, which has the same indication as Doptelet for pre procedure use, has less complex dosing and was less expensive, first. There has been a significant price reduction in Doptelet and manual PA criteria were updated to remove the requirement that Mulpleta be used ahead of Doptelet in thrombocytopenia associated with chronic liver disease.

New FDA-Approved Indications, NCCN Guideline Updates, or Age Ranges
The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) updates to the manual PA criteria for Taltz, Stelara, Erleada, Xtandi, Corlanor, Harvoni, Sovaldi, Ofev, Esbriet, Calquence, Copiktra, Imbruvica, Vitrakvi, and Revlimid.

1. **TIBs: ixekizumab (Taltz)—**For plaque psoriasis, Taltz currently requires a trial of adalimumab (Humira), secukinumab (Cosentyx) and ustekinumab (Stelara). Taltz is now approved for treating active ankylosing spondylitis (AS) in adult patients, and the new indication was added to the criteria. Note that for AS, a trial of adalimumab (Humira) and secukinumab (Cosentyx) are required first; however a trial of ustekinumab (Stelara) is not required as it is not FDA-approved for use in AS.

2. **TIBs: ustekinumab (Stelara)—**Manual PA criteria were updated to reflect a new FDA-approved indication for adults with moderately to severely active ulcerative colitis (UC). The requirement to try Humira prior to Stelara for this indication still applies.

3. **Cardiovascular Agents Miscellaneous—ivabradine (Corlanor)—**Manual PA criteria for Corlanor were updated to reflect a new pediatric indication for treating stable symptomatic heart failure due to dilated cardiomyopathy in pediatric patients ≥ 6 months and older, who are in sinus rhythm with an elevated heart rate.

4. **Hepatitis C Agents: Direct Acting Agents: ledipasvir/sofosbuvir (Harvoni) AND sofosbuvir (Sovaldi)—**Updates were made to the PA criteria for Harvoni and authorized generics of Harvoni to allow use for adult and pediatric patients ≥ 3 years of age with chronic hepatitis C virus (HCV) genotype 1, 4, 5, or 6 infection, without cirrhosis or with compensated cirrhosis. Other recent indications were also added to the form, including genotype 1 infection with decompensated cirrhosis, in combination with ribavirin; and genotype 1 or 4 infection in liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with ribavirin. Manual PA criteria for Sovaldi were updated to reflect a new FDA-approved indication for adults and pediatric patients 3 years of age or older for treatment of chronic HCV genotype 2 or 3 infection, without cirrhosis or with compensated cirrhosis.

5. **Pulmonary-1 Agents: Idiopathic Pulmonary Fibrosis (IPF): nintedanib (Ofev) and pirfenidone (Esbriet)—**The IPF drugs were reviewed for formulary status in May 2017 and step therapy requires a trial of pirfenidone (Esbriet) prior to Ofev. Ofev recently gained an indication to slow the rate of decline in pulmonary function for a rare condition, systemic sclerosis-associated interstitial lung disease (SSc-ILD). Esbriet lacks the indication for SSc-ILD, so it is not required before Ofev in this condition. The new SSc-ILD indication was added to the Ofev PA. The renewal criteria from the May 2017 class review were also updated for clarification for both Ofev and Esbriet.

6. **Oncological Agents: Prostate Cancer 2nd-Generation Antiandrogens: apalutamide (Erleada) and enzalutamide (Xtandi)—**Manual PA criteria were updated to reflect the new FDA-approved indication and NCCN guideline update for treatment of metastatic, castration-sensitive prostate cancer (mCSPC). For Erleada, renewal criteria were removed since it is now indicated for use in metastatic disease.

7. **Oncologic Agents: acalabrutinib (Calquence), duvelisib (Copiktra), ibrutinib (Imbruvica), larotrectinib (Vitrakvi) capsules and oral solution, lenalidomide (Revlimid)—**Updates to the manual PA criteria for these oncologic agents reflects more detailed safety information, including standardized embryo-fetal toxicity information. New FDA-approved indications or NCCN guideline-supported indications were also updated as summarized below. A synopsis of the changes submitted are summarized below:

    - acalabrutinib (Calquence)—Allow use for NCCN CLL and small lymphocytic lymphoma (SLL) guideline updates for relapsed or refractory disease
    - duvelisib (Copiktra)—Allow use in refractory marginal zone lymphoma
    - ibrutinib (Imbruvica)—Allow use for mantle cell lymphoma maintenance therapy
    - larotrectinib (Vitrakvi)—Allow first-line use for neurotropic tropomyosin receptor kinase (NTRK) gene fusion positive non-small cell lung cancer (NSCLC)
    - lenalidomide (Revlimid)—Allow use for marginal zone lymphoma

B. Updated PA Criteria—Implementation Plan

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) the following implementation periods:

- Updates to the current PA criteria for abiraterone acetate 250 mg in new users will become effective the first Wednesday 30-days after the signing of the minutes.

- Updates to the current PA criteria for Xeljanz, Xeljanz XR, Olumiant, Taltz, Stelara, Erleada, Xtandi, Vitrakvi capsule and solution, Calquence, Copiktra, Imbruvica, Revlimid, Doptelet, Ofev, Esbriet, Symbicort, Dulera, Harvoni, Sovaldi, and Corlanor in new users become effective the first Wednesday 60-days after the signing of the minutes.

XI. UTILIZATION MANAGEMENT—UPDATED MANUAL PA CRITERIA

BAP Comments

A. Updated Manual PA Criteria

The P&T Committee recommended updates to the manual PA criteria for the drugs discussed above.

BAP Comment: □ Concur □ Non-concur

B. Updated Manual PA Criteria—PA Implementation Plan

The P&T Committee recommended the updates to the PA criteria for Zytiga and generics become effective 30 days after the signing of the minutes, and that the PA criteria for the remainder of the drugs discussed previous become effective 60 days after the signing of the minutes.

BAP Comment: □ Concur □ Non-concur

XII. INFORMATIONAL ITEM—SUMMARY OF RECOMMENDATIONS AND BENEFICIARY IMPACT AUGUST 2019

Table of Implementation Status of UF Recommendations/Decisions Summary

DoD PEC	UF Drugs	NF Drugs	Tier 4/Not	Implement	Notes and Unique
Phosphodiesterase-5 Inhibitors	*UF and Step-preferred* ▪ sildenafil generic only *UF and non-step-preferred* ▪ tadalafil generic only	▪ None	▪ avanafil (Stendra) ▪ vardenafil OTC (Staxyn and generics) ▪ vardenafil tablet (Levitra and generics) ▪ brand Viagra ▪ brand Cialis	Pending signing of the minutes / 120 days	▪ Manual PA criteria applies to both sildenafil and generic tadalafil ▪ Trial of sildenafil still required before tadalafil ▪ Men over 40 years do not require a PA <u>Unique Users Affected (Tier 4 candidates)</u> Mail – 6,016 MTF – 3,744 Retail – 433 Total – 10,193
Rapid-Acting Insulins	*UF and step-preferred* ▪ insulin aspart (Novolog) ▪ insulin lispro (Humalog and authorized generic insulin lispro)	*NF and non-step-preferred* ▪ insulin lispro (Apidra) ▪ insulin glulisine (Afrezza) ▪ inhaled insulin (Afrezza)	▪ insulin aspart plus niacinamide (Fiasp)	Pending signing of the minutes / 150 days and no earlier than July 1 2020	▪ All new and current users of Admelog and Apidra must try Novolog and Humalog ▪ Changes also made to the Afrezza PA <u>Unique Users Affected (Tier 4 candidate Fiasp)</u> Mail: 122 MTF: 44 Retail: 17 Total: 183

Drugs with New Prior Authorization Criteria—Unique Utilizers Affected

Drug	MTF	Mail	Retail	Total
Chlorzoxazone 375 mg (Lorzone, generics)	2	21	61	84
Chlorzoxazone 750 mg (Lorzone, generics)	24	86	233	340
Anesthetic Agents: Local—Lidocaine-Tetracaine 7%-7% topical cream (Pliaglis, generics)	0	0	1,616	1,616