

# EXECUTIVE SUMMARY

## Uniform Formulary Beneficiary Advisory Panel (BAP)

June 26, 2019

### UNIFORM FORMULARY DRUG CLASS REVIEW

#### I. UF CLASS REVIEW

##### A. PROTON PUMP INHIBITORS (PPIS) – CAPSULES AND TABLETS AND ALTERNATIVE DOSAGE FORM SUBCLASSES

###### 1. PPIs – Capsules and Tablets and Alternative Dosage Form Subclasses—UF/Tier 4/Not Covered Recommendation

The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) the following formulary recommendations for the PPIs as outlined below, based on clinical and cost-effectiveness.

When considering the PPI 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>. The interim rule allows for complete exclusion of drugs from TRICARE pharmacy benefit coverage when certain criteria are met. Tier 4 status will apply to all users of the recommended candidates.

###### Capsules and Tablets Subclass

- UF and step-preferred
  - a) omeprazole 20 mg and 40 mg capsules (Prilosec brand and generics)
  - b) pantoprazole tablets (Protonix brand and generics)
- UF and non-step-preferred
  - a) rabeprazole tablets (Aciphex brand and generics)
  - b) esomeprazole capsules (Nexium brand and generics)
- NF and non-step-preferred
  - a) lansoprazole capsules (Prevacid brand and generics)

- b) omeprazole/sodium bicarbonate capsules (Zegerid brand and generics)
- This recommendation includes step therapy, which requires a trial of Prilosec or Protonix before Nexium and Aciphex and a trial of all the UF step-preferred and non-step preferred products (Prilosec, Protonix, Aciphex, and Nexium) before Prevacid or Zegerid. See the PA section below.
- Tier 4/Not Covered
  - a) dexlansoprazole (Dexilant)—The P&T Committee concluded that Dexilant provides very little to no additional clinical effectiveness relative to the other PPIs; that the risk of use may outweigh any potential benefit including a higher discontinuation rate; and that the FDA reviewer expressed concerns regarding the benefit-to-risk profile. Overall, the P&T Committee found that the needs of TRICARE beneficiaries can be met by the other PPIs.
  - b) esomeprazole strontium—The P&T Committee concluded that esomeprazole strontium has little clinical data to support its use; has very little or no additional clinical effectiveness relative to the other PPIs and that the needs of TRICARE beneficiaries can be met by the other PPIs.

**Alternative Dosage Form Subclass**

- UF
    - a) esomeprazole (Nexium) packet for suspension
    - b) omeprazole (Prilosec) packet for suspension
    - c) pantoprazole (Protonix) packet for suspension
    - d) rabeprazole (Aciphex) Sprinkle
  - NF
    - a) lansoprazole ODT (Prevacid ODT)
    - b) omeprazole/sodium bicarbonate (Zegerid) packet for suspension
  - Note that step therapy does not apply to the PPI Alternative Dosage Forms.
- 2. PPIs – Capsules and Tablets and Alternative Dosage Form Subclasses—Manual Prior Authorization (PA) Criteria**

The PPI class currently has step therapy requirements. The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) updated PA criteria for the

PPIs. PA criteria are not required for Prilosec or Protonix. Updated manual and automated step therapy PA criteria were recommended in new users for Aciphex and Nexium, requiring a trial of either of the preferred products (Prilosec or Protonix) first. Additionally, the manual PA criteria for new users of Prevacid and Zegerid were updated to require a trial of all of the UF products (Prilosec, Protonix, Aciphex, and Nexium) first. Use of the non-preferred PPI is allowed if there is a contraindication, inadequate response, or adverse reaction to the preferred PPI.

The current PA criteria for the Alternative Dosage Forms were also updated. PA criteria are not required for the packets for oral suspension formulations of Prilosec, Nexium, or Protonix, or the Aciphex sprinkles. Manual PA criteria are recommended for Prevacid ODT and Zegerid packets for oral suspension in all new and current users older than age 18. The provider must state why the patient needs an alternative dosage form and why they cannot take all of the formulary alternative dosage forms.

The PA criteria are as follows:

- **Nexium capsules, Aciphex tablets, and generics**

Note that prior authorization is not required for omeprazole capsules or pantoprazole tablets.

Manual and Automated PA criteria apply to all new users of esomeprazole (Nexium brand and generics) and rabeprazole (Aciphex brand and generics).

Automated PA Criteria: The patient has filled an Rx for generic omeprazole OR generic pantoprazole product at any Military Treatment Facility (MTF), retail network pharmacy, or the mail order pharmacy in the previous 365 days.

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

- a) Provider acknowledges that omeprazole and pantoprazole are the DoD's preferred agents
- b) Provider acknowledges that omeprazole and pantoprazole are Uniform Formulary and do not require prior authorization
- c) The patient has a contraindication to omeprazole and pantoprazole  
OR
- d) The patient has had an inadequate response or had an adverse reaction to omeprazole  
OR

- e) The patient has had an inadequate response or had an adverse reaction to pantoprazole

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

- **Prevacid capsules and Zegerid capsules**

Manual PA and Automated PA criteria apply to all new users of lansoprazole (Prevacid brand and generics) and omeprazole/sodium bicarbonate (Zegerid brand and generics).

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

- a) Provider acknowledges that omeprazole and pantoprazole are the DoD's preferred agents
- b) Provider acknowledges that omeprazole and pantoprazole are Uniform Formulary and do not require prior authorization
- c) And the patient meets all four of the following criteria:
  - d) Has a contraindication, had an inadequate response, or had an adverse reaction to omeprazole  
  
AND
  - e) Has a contraindication, had an inadequate response, or had an adverse reaction to pantoprazole  
  
AND
  - f) Has a contraindication, had an inadequate response, or had an adverse reaction to esomeprazole  
  
AND
  - g) Has a contraindication, had an inadequate response, or had an adverse reaction to rabeprazole

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

- **Prevacid ODT and Zegerid packet for suspension**

Age edit applies: Patients 18 years and older will be subject to the PA.

Manual PA criteria apply to all new and current users of Prevacid ODT and Zegerid packet for suspension.

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

- a) Provider acknowledges that omeprazole and pantoprazole tablets and capsules are Uniform Formulary and do not require prior authorization
- b) Provider acknowledges that omeprazole, esomeprazole, and pantoprazole packets for suspension and rabeprazole sprinkles are Uniform Formulary and do not require prior authorization
- c) Provider must document patient-specific clinical rationale of why the patient cannot take ALL alternative PPI agents

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

### **3. PPIs – Capsules and Tablets and Alternative Dosage Form Subclasses—OTC Omeprazole UF Recommendation**

OTC omeprazole and omeprazole magnesium tablets and capsules have been included on the TRICARE Pharmacy benefit since the August 2015 DoD P&T Committee meeting, under provisions of 32 CFR 199.21(h)(5). The P&T Committee reviewed the cost and utilization of the OTC PPIs, including omeprazole, at the three points of service (POS). OTC omeprazole is not cost-effective compared to generic prescription formulations of omeprazole and pantoprazole. Low-cost OTC omeprazole is readily available for purchase at several venues (retail pharmacies, commissary, grocery stores, etc.).

The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) removing OTC omeprazole and omeprazole magnesium capsules and tablets from the UF, based on cost-effectiveness.

### **4. PPIs – Capsules and Tablets and Alternative Dosage Form Subclasses—UF/Tier 4/Not Covered and PA Implementation Plan**

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 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 and those affected by the removal of OTC omeprazole and omeprazole magnesium from the UF.

#### ***Summary of Physician's Perspective:***

Currently, we have over 690,000 patients on a PPI; this has decreased from a high of

880,000 patients back in 2015. The decrease is likely due to a combination of factors to include deprescribing efforts and greater awareness of the safety concerns with the class. We currently spend over \$112 million dollars yearly on the PPIs, however, this is likely to decrease due to the reduction in utilization, and also price reductions with the generic PPIs.

With the current recommendations, we are now moving generic Nexium back to formulary status, however it will be non-step-preferred. The approximately 24,000 patients on Nexium will see the reduction in copay.

One other change is that generic Aciphex stays UF, but goes from step-preferred to non-step-preferred. There are currently some supply issues with generic Aciphex. For both Nexium and Aciphex, the new step therapy criteria will only apply to new patients. We will continue to monitor the prices of generic Nexium and Aciphex and consider removing the step therapy requirements once the prices fall closer to that of generic Prilosec and Protonix.

Dexilant has been NF since May 2009, with esomeprazole strontium NF since May 2014. Both drugs have also had the step therapy and PA requirements in place.

For Dexilant, the Tier 4 status was recommended clinically due to lack of a clear clinical benefit relative to other agents, safety issues identified by the FDA, and the high discontinuation rate due to adverse reactions found in the clinical trials. A survey of DOD GI specialists also found that the majority were comfortable with Dexilant being not covered. Safety concerns and lack of data to support a clinical benefit relative to other agents for esomeprazole strontium were the basis for the Tier 4 status recommendation.

The Committee did consider having additional PPI candidates for Tier 4 status, but settled on Dexilant and esomeprazole strontium, due to the aforementioned issues with these two drugs.

The alternate dosage forms all currently have step therapy and PA requirements. The Committee is now recommending removal of PAs for the majority of the alternate dosage forms and only leaving PAs in place for the two drug which are currently NF – Zegerid packets and Prevacid ODT. The Committee did acknowledge that the alternate dosage forms are approved for special populations, such as children or for administration in NG or PEG tubes.

For Prevacid ODT and Zegerid packets, children younger than 18 years will not have to go through the PA. Although all patients older than 18 years will be subject to the new PA criteria for these two drugs, we are removing the current step therapy requirements for all alternate dosage forms, and the provider only has to document why the patient can't take the formulary PPIs.

The PPIs have been on the market for almost 30 years. There are now several safety

concerns with the drugs if they are used long-term beyond 8 weeks. The Committee did consider different options to ensure that patients are re-assessed for long-term use. However, from an operations perspective, there is no one method that would work for the entire system. For patients who are subject to the PA, this actually does allow the provider an opportunity to consider whether continued use is necessary.

The Committee also recommended removing OTC omeprazole from the formulary. As a reminder, OTC omeprazole has been available for patients with a prescription for that product specifically. This will affect about 1,000 patients (800 of the patients are at Retail). Inexpensive OTC omeprazole products are widely available – for as low as 24 cents per tablet at Costco. The affected patients would need to get a new prescription for the prescription version of omeprazole, or buy the OTC version on their own.

***Summary of Panel Questions and Comments:***

Mr. Ostrowski asks how many beneficiaries are affected by the Tier 4 decision on Dexilant and esomeprazole strontium

Dr. Khoury replies that Dexilant was reviewed last quarter. Currently there are 18,833 patients using the medication and 22 patients are using esomeprazole.

There were no further questions or comments from the Panel. The Chair called for a vote on the UF/Tier 4/Not Covered, Manual PA Criteria, OTC Omeprazole UF Recommendation and the UF/Tier 4/Not Cover and PA Implementation Plan for the Proton Pump Inhibitors.

• **PPI – UF/Tier 4/Not Covered Recommendation**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

***Director, DHA:***

 These comments were taken under consideration prior to my final decision.

• **PPI – Manual PA Criteria**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

***Director, DHA:***

 These comments were taken under consideration prior to my final decision.

- **PPI – OTC Omeprazole UF Recommendation**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

*Director, DHA:*

 These comments were taken under consideration prior to my final decision.

- **PPI – UF/Tier 4/Not Covered and PA Implementation Plan**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

*Director, DHA:*

 These comments were taken under consideration prior to my final decision.

## **II. PULMONARY ARTERIAL HYPERTENSION (PAH) AGENTS – PROSTACYCLINS, ENDOTHELIN RECEPTOR ANTAGONISTS (ERAS), AND NITRIC OXIDE DRUGS**

### **A. PAH AGENTS**

#### **1. PAH Agents – Prostacyclins, ERAs, and Nitric Oxide Drugs—UF Recommendation**

##### **Endothelin Receptor Antagonists (ERAs)**

- UF
  - a) bosentan (Tracleer)
  - b) ambrisentan (Letairis brand and generics)
  - c) macitentan (Opsumit)

##### **Prostacyclins**

- UF
  - a) treprostinil nebulized solution (Tyvaso)
  - b) iloprost nebulized solution (Ventavis)

- c) treprostinil extended-release oral tablets (Orenitram ER)
- d) selexipag (Uptravi)

### **Nitric Oxide Drugs**

- UF and step-preferred
  - a) sildenafil 20 mg tablets (Revatio brand and generics)
- UF and non-step-preferred
  - a) tadalafil 20 mg (Adcirca, Alyq, and generics)
  - b) riociguat (Adempas)
- For the nitric oxide drugs, note that this recommendation includes step therapy, which requires a trial of sildenafil 20 mg generic in all new users of Adcirca, Alyq, and tadalafil generics or Adempas.
- Note that sildenafil 10 mg/mL oral suspension is also UF, but not part of the step therapy requirements for the other nitric oxide drugs.
- Note that for all the PAH drugs, no products were recommended for NF status.

## **2. PAH Agents – Prostacyclins, ERAs, and Nitric Oxide Drugs—Manual PA Criteria**

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) new manual PA criteria in new users for the ERAs (Tracleer, Letairis, and Opsumit) and the prostacyclins (Ventavis, Tyvaso, Orenitram ER, and Uptravi). Updated step therapy and manual PA criteria were recommended in new users for Adempas and Adcirca, Alyq, and tadalafil generics requiring a trial of sildenafil 20 mg.

### **a. Letairis brand and Opsumit**

Manual PA criteria apply to new users of Letairis or Opsumit.

Manual PA Criteria: Letairis or Opsumit is approved if all criteria are met:

- Prescribed by or in consultation with a cardiologist or a pulmonologist
- Patient has documented diagnosis of WHO group 1 PAH
  - a) Patient has had a right heart catheterization (documentation required)

b) Results of the right heart catheterization confirm the diagnosis of World Health Organization (WHO) group 1 PAH

- Patient and provider are enrolled in the Letairis or Opsumit REMS program
- Patient is not pregnant
- Women of childbearing potential must use adequate contraception
- Patient has no history of liver function test (LFT) elevations on previous endothelin receptor antagonist (ERA) therapy accompanied by signs or symptoms of liver toxicity or increases in bilirubin greater than two times the upper limit of normal
- Patient does not have moderate or severe liver impairment (e.g., Child-Pugh Class B or C)

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**b. Generic ambrisentan**

Manual PA criteria apply to new and current users of generic ambrisentan.

Manual PA Criteria: Ambrisentan generics are approved if all criteria are met:

- a) The brand Letairis formulation is the preferred product over generic Letairis (ambrisentan). Although Letairis is a branded product, it will be covered at the generic formulary copayment or cost-share.
- b) The provider must document a patient-specific justification as to why the brand Letairis product cannot be used in this patient.
- c) AND the patient must meet the criteria for Letairis:
- d) Prescribed by or in consultation with a cardiologist or a pulmonologist
- e) Patient has documented diagnosis of WHO group 1 PAH
  - Patient has had a right heart catheterization (documentation required)
  - Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH
- f) Patient and provider are enrolled in the ambrisentan REMS program

- g) Patient is not pregnant
- h) Women of childbearing potential must use adequate contraception
- i) Patient has no history of liver function test (LFT) elevations on previous endothelin receptor antagonist (ERA) therapy accompanied by signs or symptoms of liver toxicity or increases in bilirubin greater than two times the upper limit of normal.
- j) Patient does not have moderate or severe liver impairment (e.g., Child-Pugh Class B or C)

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**c. Tracleer**

Manual PA criteria apply to new users of Tracleer.

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

- Prescribed by or in consultation with a cardiologist or a pulmonologist
- Patient has diagnosis of WHO group 1 or 4 (see below)
- Patient has documented diagnosis of WHO group 1 PAH
  - a) Patient has had a right heart catheterization (documentation required)
  - b) Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH OR
- Patient has documented diagnosis of Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO group 4) and the patient has tried Adempas or has a contraindication to Adempas
- Patient and provider are enrolled in the Tracleer REMS program
- Patient is not pregnant
- Women of childbearing potential must use adequate contraception
- Patient does not have baseline elevated aminotransferases greater than three times the upper limit of normal due to difficulty in monitoring for hepatotoxicity

- Patient does not have moderate or severe liver impairment (e.g., Child-Pugh Class B or C)

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**d. Ventavis and Tyvaso**

Manual PA criteria apply to new users of Ventavis or Tyvaso.

Manual PA Criteria: Ventavis or Tyvaso is approved if all criteria are met:

- Prescribed by or in consultation with a cardiologist or a pulmonologist
- Patient has documented diagnosis of WHO group 1 PAH
  - a) Patient has had a right heart catheterization (documentation required)
  - b) Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**e. Uptravi and Orenitram ER**

Manual PA criteria apply to new users of Uptravi or Orenitram ER.

Manual PA Criteria: Uptravi or Orenitram ER is approved if all criteria are met:

- Prescribed by or in consultation with a cardiologist or a pulmonologist
- Patient has documented diagnosis of WHO group 1 PAH
  - a) Patient has had a right heart catheterization (documentation required)
  - b) Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH
- Patient meets one of the following criteria
  - a) The patient has tried one oral therapy for PAH from one of the three following different categories (either alone or in combination) each for  $\geq$  60 days: one PDE-5 inhibitor (tadalafil or sildenafil), one ERA (Letairis, Opsumit, or Tracleer), or Adempas; OR

b) The patient has tried one prostacyclin therapy (oral, IV, or nebulized)

Non-FDA-approved uses are not approved.

Prior authorization does not expire.

**f. Adempas**

Manual PA criteria apply to new users of Adempas.

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

- Prescribed by or in consultation with a cardiologist or a pulmonologist
- Patient has a documented diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) WHO Group 4 PAH

OR

- Patient has documented diagnosis of WHO group 1 PAH
  - a) Patient has had a right heart catheterization (documentation required)
  - b) Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH
- Patient has had an adequate trial of sildenafil 20 mg (Revatio brand or generics) and failed or did not respond to therapy AND
- Patient has had an adequate trial of tadalafil 40 mg (Adcirca brand or generics) and failed or did not respond to therapy AND
- Patient is not receiving PDE-5 inhibitors or nitrates concomitantly

Non-FDA-approved uses are not approved.

Prior authorization does not expire.

**g. Adcirca, Alyq, and generics**

Manual PA criteria apply to new users of tadalafil 20 mg (Adcirca brand and generics) and Alyq.

Manual PA Criteria: Tadalafil 20 mg (Adcirca brand and generics) or Alyq is approved if all criteria are met:

- Prescribed by or in consultation with a cardiologist or a pulmonologist

- Patient has documented diagnosis of WHO group 1 PAH
  - a) Patient has had a right heart catheterization (documentation required)
  - b) Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH
- Patient has had an adequate trial of sildenafil 20 mg (Revatio brand and generics) and failed or did not respond to therapy and
- Patient is not receiving other PDE-5 inhibitors, nitrates, or riociguat (Adempas) concomitantly

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

### **3. PAH Agents – Prostacyclins, ERAs, and Nitric Oxide Drugs—Brand over Generic Requirement for ambrisentan (Letairis) and PA Criteria**

TRICARE Policy requires dispensing of generic products at the Retail Network and Mail Order Pharmacy. However, pricing for the branded Letairis is more cost-effective than the AB-rated generic formulations for ambrisentan, which were launched in March 2019. Therefore, branded Letairis will continue to be dispensed, and the generic will only be available with prior authorization (i.e., the reverse of the current brand to generic policy).

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) requiring brand Letairis over generic ambrisentan in all new and current users, based on cost-effectiveness. The prescriber will provide patient-specific justification as to why branded Letairis cannot be used. The Tier 1 (generic) copayment will apply to brand Letairis. The “brand over generic” requirement will be removed administratively when it is no longer cost-effective compared to the AB-rated generics.

### **4. PAH Agents – Prostacyclins, ERAs, and Nitric Oxide Drugs—Brand Letairis Copayment Change**

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) lowering the current cost-share for the endothelin receptor antagonist Letairis to the generic Tier 1 cost-share.

The authority for this recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate."

## **5. PAH Agents – Prostacyclins, ERAs, and Nitric Oxide Drugs—UF and PA Implementation Plan**

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) an effective date of the first Wednesday 90 days after the signing of the minutes in all points of service (POS).

### ***Summary of Physician's Perspective:***

This is the second time that the PAH drugs have been reviewed. No drugs are currently NF, and no drugs were recommended for NF or Tier 4 status at this review.

There are about 1,000 patients in the MHS with PAH, and yearly expenditures for these drugs (excluding sildenafil and Adcirca) are approximately \$100 million dollars.

The major changes from the previous review are that there are new PA recommendations for the prostacyclins and the ERAs; these drugs don't currently have PAs in place. The PAs are recommended to ensure that the patient has the diagnosis of PAH, and for safety; for example the ERAs require liver monitoring and are teratogenic.

A review of at least eight other health care plans showed that these drugs all are widely managed with PAs. The PAH clinical specialist we talked to also commented that providers are used to completing PA paperwork, since insurance plans routinely require PAs.

For the prostacyclins and the ERAs, only new users will be affected by the PAs; patients who are currently receiving one of these drugs won't have to go through the PA, so these patients are "grandfathered".

For the nitric oxide drugs Adempas and Adcirca, PA requirements have been in place since the first review in February 2015. One change was requiring that the nitric oxide drugs be prescribed by or in consultation with a pulmonologist or cardiologist. Both sildenafil and tadalafil were recommended to be tried before Adempas, based on the comments from the PAH specialist and cost effectiveness. Adempas has no benefits over the PDE-5 inhibitors, other than for CTEPH patients. Patients with the unique indication of CTEPH do not have to try a PDE-5 inhibitor first.

Adcirca has always had the requirement to try sildenafil first. Even though Adcirca generics have recently entered the market, they are not cost-effective compared to sildenafil. The PAH clinical specialist we spoke with did consider the PDE-5 inhibitors as therapeutically interchangeable for PAH. We will continue to monitor the price of the Adcirca generics, and update PA criteria accordingly.

The Committee did look at the clinical practice guidelines, individual clinical trials,

current utilization patterns in DoD, and also consulted with an outside PAH specialist when considering the PA criteria.

***Summary of Panel Questions and Comments:***

Dr. Peloquin requests clarification on the PA criteria for Uptravi and Orenitram. Does the patient have to try one prostacyclin therapy to meet the criteria? The PA is confusing.

Dr. Lugo responds that is one of the options. If a patient has tried one prostacyclin therapy they do meet the criteria. Basically, the patient has to try one oral therapy for PAH from one of the three categories mentioned in the background information. For example, if the patient has been on a PDE-5 or an ERA they can move to a prostacyclin. If the patient has been on an inhaled prostacyclin, they can move over to an oral prostacyclin.

There were no further questions or comments from the Panel. The Chair called for a vote on the UF Recommendation, Manual PA Criteria, Brand over Generic Requirement for Ambrisentan (Letairis) and PA Criteria, Brand Letairis Copayment change and UF and PA Implementation Plan for the Pulmonary Arterial Hypertension (PAH) Agents.

• **PAH Agents – UF Recommendation**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

***Director, DHA:***

 These comments were taken under consideration prior to my final decision.

• **PAH Agents – Manual PA Criteria**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

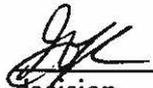
***Director, DHA:***

 These comments were taken under consideration prior to my final decision.

- **PAH Agents – Brand over Generic Requirement for ambrisentan (Letairis) and PA Criteria**

Concur: 6                  Non-Concur: 0                  Abstain: 0                  Absent: 4

*Director, DHA:*

 These comments were taken under consideration prior to my final decision.

- **PAH Agents – Brand Letairis Copayment Change**

Concur: 6                  Non-Concur: 0                  Abstain: 0                  Absent: 4

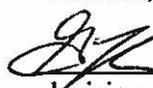
*Director, DHA:*

 These comments were taken under consideration prior to my final decision.

- **PAH Agents – UF and PA Implementation Plan**

Concur: 6                  Non-Concur: 0                  Abstain: 0                  Absent: 4

*Director, DHA:*

 These comments were taken under consideration prior to my final decision.

### III. NEWLY APPROVED DRUGS PER 32 CFR 199.21(g)(5)

#### (DR. LUGO)

#### A. Newly Approved Drugs per 32 CFR 199.21(g)(5)

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

The P&T Committee recommended (group 1: 17 for, 0 opposed, 0 abstained, 1 absent; group 2: 18 for, 0 opposed, 0 abstained, 0 absent; Tirosint-SOL: 10 for, 7 opposed, 1 abstained, 0 absent) the following:

- UF:
  - a) cladribine (Mavenclad) – Multiple Sclerosis Agents: Oral Agents

- b) epinephrine injection (Symjepi) – Respiratory Agents Miscellaneous\
- c) levodopa inhalation powder (Inbrija) – Parkinson’s Agents
- d) levothyroxine sodium oral solution (Tirosint-SOL) – Thyroid and Antithyroid Agents
- e) loteprednol etabonate 0.38% ophthalmic gel (Lotemax SM) – Anti-inflammatory Immunomodulatory Ophthalmic Agents: Ophthalmic Anti-inflammatory Agents
- f) netarsudil 0.02%/latanoprost 0.005% ophthalmic solution (Rocklatan) – Glaucoma Agents
- g) siponimod (Mayzent) – Multiple Sclerosis Agents: Oral Miscellaneous
- h) stiripentol (Diacomit) – Anticonvulsants-Antimania Agents
- i) tacrolimus oral suspension (Prograf) – Immunosuppressives
- NF:
  - a) benzhydrocodone/acetaminophen (Apadaz) – Narcotic Analgesics and Combinations
  - b) estradiol 1 mg/progesterone 100 mg capsules (Bijuva) – Gynecological Agents Miscellaneous
  - c) meloxicam ODT (Qmiiz ODT) – Pain Agents: NSAID
  - d) prucalopride (Motegrity) – Gastrointestinal-2 Agents: Chronic Idiopathic Constipation (CIC) and Irritable Bowel Syndrome Constipation-Predominant (IBS-C)

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

The P&T Committee recommended (group 1: 17 for, 0 opposed, 0 abstained, 1 absent; group 2: 18 for, 0 opposed, 0 abstained, 0 absent; Tirosint-SOL: 10 for, 7 opposed, 1 abstained, 0 absent) the following:

- Applying the same manual PA criteria for Rocklatan in new users as is currently in place for Rhopressa.

- Applying manual PA criteria to new and current users of Mavenclad, Mayzent, Motegrity, and Qmiiz ODT.
- Applying manual PA criteria to new users of Inbrija.
- Applying an automated age edit to new and current users of Tirosint-SOL and new users of Prograf solution. Patients younger than 6 years for Tirosint solution and younger than 12 years for Prograf solution will not be subject to the PA.

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

**a. cladribine (Mavenclad)**

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

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

- Prescribed by a neurologist
- Patient has a documented diagnosis of one of the following:
  - a) Relapsing-Remitting Multiple Sclerosis
  - b) Active Secondary Progressive Multiple Sclerosis
- Patient is not currently using a disease-modifying therapy (DMT)
- Patient has failed another DMT
- Mavenclad is not used in patients with:
  - a) Current malignancy
  - b) Pregnant women or breastfeeding
  - c) Men and women of reproductive potential who do not plan to use effective contraception during treatment and 6 months after the last dose
  - d) Active chronic infection (e.g., hepatitis, tuberculosis, or HIV infection)
- Monitoring for hematological and lymphocytic parameters will occur before, during, and after treatment

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**b. levodopa inhalation powder (Inbrija)**

Manual PA criteria apply to all new users.

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

- Age  $\geq$  18 years
- Patient has a diagnosis of Parkinson's disease
- Inbrija is prescribed by or in consultation with a neurologist
- Patient continues to experience wearing off periods, despite optimizing carbidopa/levodopa therapy (e.g., increasing the dose or increasing the frequency of dosing)
- Patient is currently taking and will continue taking carbidopa-levodopa therapy
- Inbrija is not being used concomitantly with, or within 2 weeks of, a non-selective monoamine oxidase (MAO) inhibitor (e.g., phenelzine, tranylcypromine, isocarboxazid, hydracarbazine)
- Patient does not have chronic underlying pulmonary disease (e.g., asthma, COPD)

Non-FDA-approved uses are not approved.

Prior authorization expires in one year.

Renewal Criteria: PA will be renewed indefinitely if the patient:

- Has had a documented reduction in motor symptoms associated with "off" periods of Parkinson's disease, and
- Is not taking an MAO inhibitor, and does not have a chronic underlying pulmonary disease (e.g., asthma, COPD).

**c. levothyroxine sodium solution (Tirosint-SOL)**

PA does not apply to patients younger than 6 years of age (age edit)

PA criteria apply to all new and current users of Tirosint-SOL 6 years of age and older.

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

- Patient is not able to chew a levothyroxine tablet

- Patient is not able to swallow a capsule or tablet
- Drug is prescribed by or in consultation with an endocrinologist

Non-FDA-approved uses are not approved.

PA expires after 12 months. No renewal allowed; must fill out a new PA.

**d. meloxicam orally disintegrating tablets (ODT) (Qmiiz ODT)**

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

Manual PA Criteria: Coverage for Qmiiz will be approved if:

- Note: Multiple formulary NSAIDs, including meloxicam oral tablets, are available for DoD beneficiaries without a PA.
- The provider must state the clinical rationale of why the patient cannot take any of the formulary NSAIDs.

Non-FDA-approved uses are not approved.

Prior authorization expires in one year.

Renewal criteria – No renewal criteria. PA will be renewed for an additional year if a new PA form is completed.

**e. netarsudil 0.02%/latanoprost 0.005% ophthalmic solution (Rocklatan)**

Manual PA criteria apply to all new users of Rocklatan.

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

- Written by an ophthalmologist or an optometrist
- Patient has had a trial of appropriate duration of 2 different formulary options from different drug classes in combination or separately and has not reached intraocular pressure (IOP) target goals
  - a) Prostaglandin analogs
  - b) Beta-blockers

- c) Alpha 2-adrenergic agonists
- d) Topical carbonic anhydrase inhibitors

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**f. prucalopride (Motegrity)**

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

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

- Patient is  $\geq 18$  years of age
- Patient has tried and failed all formulary agents including Amitiza, Linzess, and Trulance
- Patient has documented symptoms for  $\geq 3$  months
- Patient has diagnosis of chronic idiopathic constipation (CIC)
- Patient does not have a GI obstruction
- Patient has no history of suicidal ideation
- Patient has low cardiovascular risk
- Patient has documentation of failure of an increase in dietary fiber/dietary modification
- Patient has tried at least 2 standard laxative classes or has an intolerance or FDA-labeled contraindication to at least 2 standard laxative classes defined as:
  - a) osmotic laxative (e.g., lactulose, sorbitol, magnesium [Mg] citrate, Mg hydroxide, glycerin rectal suppositories)
  - b) bulk forming laxative (e.g., psyllium, oxidized cellulose, calcium polycarbophil) with fluids;
  - c) stool softener (e.g., docusate);
  - d) stimulant laxative (e.g., bisacodyl, sennosides)

- Patient is not taking any of these agents concomitantly (Amitiza, Linzess, Trulance, Symproic, Relistor, Movantik)

Non-FDA-approved uses are not approved.

Initial Expiration date: 1 year; Renewal PA (continuation): 1 year

Renewal PA Criteria: Motegrity will be approved for an additional 12 months if the following are met:

- Patient has had improvement in constipation symptoms
- Patient is not taking any of these agents concomitantly (Amitiza, Linzess, Trulance, Symproic, Relistor, Movantik)
- Patients are monitored for suicidal risk

**g. siponimod (Mayzent)**

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

Manual PA criteria: Coverage will be approved if all criteria are met:

- Prescribed by a neurologist
- A documented diagnosis of one of the following:
  - a) Clinically Isolated Syndrome
  - b) Relapsing-Remitting Multiple Sclerosis
  - c) Active Secondary Progressive Multiple Sclerosis
- Patient is not currently using another disease-modifying therapy (DMT)
- Patient has not failed an adequate course of fingolimod (Gilenya)
- All recommended Mayzent monitoring has been completed, and patient will be monitored throughout treatment as recommended in the label. Monitoring includes complete blood count (CBC), liver function tests (LFT), varicella zoster virus (VZV) antibody serology, genotyping of CYP2C9, electrocardiogram (ECG), and macular edema screening.
- In patients with CYP2C9 \*1/\*3 or \*2/\*3 maintenance dosing will be 1 mg daily
- Mayzent will not be used in patients with a CYP2C9 \*3/\*3 genotype

- Mayzent will not be used in patients with significant cardiac history, including:
  - a) Patients with a recent history (within the past 6 months) of class III/IV heart failure, myocardial infarction, unstable angina, stroke, transient ischemic attack, or decompensated heart failure requiring hospitalization
  - b) Patients with a history or presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless a functioning pacemaker is inserted

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**h. tacrolimus oral suspension (Prograf)**

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

PA criteria apply to all new users of Prograf solution 12 years of age and older.

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

- Prescribed by or in consultation with a transplant specialist AND
- Has severe dysphagia (e.g., severe esophagitis, mucositis) or is completely unable to swallow (e.g., has G-tube) OR
- Patient is < 18 years old and has difficulty swallowing tablets/capsules

Applies to new users (grandfathering allowed).  
PA does not expire.

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

The P&T Committee recommended (group 1: 17 for, 0 opposed, 0 abstained, 1 absent; group 2: 18 for, 0 opposed, 0 abstained, 0 absent) an effective date upon the first Wednesday two weeks after the signing of the minutes in all points of service.

***Summary of Physician's Perspective:***

There were a total of 13 new drugs reviewed. The decrease from the usual number of 30 drugs was likely due to the Federal government shutdown last Fall, which resulted in a lower number of year end approvals than we normally see.

For the 13 new drugs, 9 were recommended for UF status, with 4 recommended for NF status. No drugs were selected for Tier 4 status.

A total of 8 drugs were recommended for PAs. Of these 8 drugs, four were recommended to have “no grandfathering”, in that both new and current users will be affected by the PA. “No grandfathering” was recommended for the 2 MS drugs (Mavenclad and Mayzent) due to safety concerns. For Motegrity, the PA is very similar to the other chronic idiopathic constipation drugs that were reviewed in November 2018 that also affected new and current users. The NSAID Qmiiiz is just an orally dissolving formulation of meloxicam, which has been available as a generic for several years.

Two of the drugs that are marketed in oral solutions both the thyroid drug Tirosint and the anti-rejection drug Prograf, have age edits in the PA criteria so that children won't be affected by the PA.

***Summary of Panel Questions and Comments:***

Dr. Peloquin notices there was a 10-7 vote on the Tirosint and asks if more can be shared regarding the vote.

Dr. Lugo responds that it was a split vote because the committee could not decide if it should be Formulary, Non-formulary or Tier 4.

Dr. Lugo states that the committee did vote to move the Tirosint to Uniform Formulary. There was a lot of discussion on whether to add a PA, not add PA, or move Levothyroxine to Tier 4 because it has been around for a really long time. There were also questions/concerns about age criteria for the PA. The pediatric endocrinologist stated that 3-year olds can chew and swallow the tablet. Due to the concerns voiced by the committee, the age criteria was increased to 6 years old. The pediatric endocrinologist said that a 4 years old patients can chew the tablet. The PA expires annually to re-evaluate whether or not the patient can chew the tablets.

Dr. Dager has questions about the PA process for current users. Do they come off the medication or is it renewed?

Dr. Khoury responds, as of June 17, Qmiiiz, Mayzent, and Mavenclad have no current users in our system. The manual PA criteria for these three drugs impacts new and current users. The manual PA criteria also impacts new and current users for Motegrity and Tirosint. Motegrity having new and current users be impacted is a result of it being part of a class with similar recommendations. When we reviewed the class, the PA was a requirement for all new and current users. The committee followed the same approach for this decision. There were safety and clinical efficacy concerns. For instance, the patients did not maintain the drug over time. There were a lot of reasons we wanted to make sure new and current users were reassessed. Currently, 43 patients are impacted by the committee decision for the Tirosint solution. The majority are not in the 0-4 year old age group but are patients over 18

years old. We want ensure and validate that those patients need the drug.

Dr. Dager asks for clarification about the process to implement the PA operationally when patients are already on the drug.

Dr. Khoury replies that when the claim comes through they'll be faced with the prior authorization.

Ms. Buchanan asks why they are looking at UF and PA Implementation plan effective upon the first Wednesday 2 weeks after the signing.

Lugo responded that she misspoke. It's not 90 days; it 2 weeks after the signing of the minutes.

Ms. Buchanan asks if that's enough time.

Dr. Lugo answered that it is given our number of utilizers on these agents.

Dr. Khoury states it is our intent to move new drugs as appropriate off of non-formulary status as quickly as possible. Otherwise, the patient would be forced to pay the \$53 co-pay at mail for a 90-day supply or a \$54 co-pay at retail for 30-day supply. The 2-week implementation period benefits the patient because they avoid paying the higher co-pay.

Dr. Spatz brings it back to initial question regarding the vote for Tirosint. What is driving this discussion? Is it an issue with the age criteria for the PA or is it about the cost of the solution as compared to the tablets

Dr. Khoury responded that it was a very lengthy discussion and multiple providers had differences of opinion on both. Whether it should be formulary and available to patients. Whether it was needed. Dr. Lugo mentioned that the committee members were supportive of moving it to Tier 4 because they saw no clinical need for the medication. According to the endocrinologist, there were other options available to the patients. The committee also expressed concerns about who really needs the medication and methods to ensure those patients receive it. Others supported a formulary status over non-formulary to ensure patients were aware of the cost perspective from the system side. Also, the committee wanted to ensure, via the PA process, that the medication was needed. As you saw with the vote, there was no unanimity among the committee members. There were opinions on both sides.

Dr. Spatz responds, there was never a question of clinical efficacy for the drug, it was just about the cost differential between the generic and the levothyroxine which has been around since whenever as compared to this agent.

Dr. Khoury responds yes, it is the new formulation, specifically.

Dr. Piirainen looked at the PAs. It states that Non-FDA or usage not approved. Do you require prescribers to put in a diagnosis code or something to show what they will use it for?

Dr. Khoury replied that depends on the PA. It is not a requirement as a standard.

Dr. Piirainen responds it is just a statement for them to be aware but not required.

Dr. Khoury answered if there is an alternate diagnosis the patient is trying to use the drug for, the language is there for them to abide by that.

There were no further questions or comments from the Panel. The Chair called for a vote on the UF Recommendation, PA Criteria, and UF and PA Implementation plan for the Newly Approved Drugs per 32 CFR 199.21(g)(5).

- **Newly Approved Drugs per 32 CFR 199.21(g)(5) – UF Recommendation**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

*Director, DHA:*

 These comments were taken under consideration prior to my final decision.

- **Newly Approved Drugs per 32 CFR 199.21(g)(5) –PA Criteria**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

*Director, DHA:*

 These comments were taken under consideration prior to my final decision.

- **Newly Approved Drugs per 32 CFR 199.21(g)(5) – UF and PA Implementation**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

*Director, DHA:*

 These comments were taken under consideration prior to my final decision.

#### IV. UTILIZATION MANAGEMENT—NEW MANUAL PA CRITERIA

##### A. NEWLY APPROVED DRUGS NOT SUBJECT TO 32 CFR 199.21(g)(5)

###### 1. NEWLY APPROVED DRUGS NOT SUBJECT TO 32 CFR 199.21(g)(5):

**Antihistamine-1: First generation and combinations – Carbinoxamine maleate 6 mg tablets (Ryvent brand and generics) and Carbinoxamine maleate 4 mg/5 mL ER oral suspension (Karbinal ER)**

Ryvent brand and generics and Karbinal ER are new drugs 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 or new drug reviews. These ANDA-approved products contain ingredients that are currently available in generic products or were included in formulations previously removed from the market.

Carbinoxamine maleate is a first-generation antihistamine and is available in 4 mg and 6 mg generic tablets, 6 mg brand tablets (Ryvent), 4 mg/5 mL immediate release oral solution, and a 4 mg/5 mL ER suspension (Karbinal ER). Ryvent brand and generics and Karbinal ER are not cost-effective relative to the generic 4 mg tablets and 4 mg/5 mL IR oral solution. Cost-effective generic formulations of carbinoxamine 4 mg oral tablets and IR solution are available on the UF without a PA required. Low-cost OTC tablet formulations for diphenhydramine, fexofenadine, or dimenhydrinate tablets and low-cost OTC liquid formulations for diphenhydramine, fexofenadine, or loratadine are widely available.

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) manual PA criteria for Ryvent brand and generics and Karbinal ER in new and current users, due to the significant cost differences and lack of clinically compelling benefits over generic alternatives.

The manual PA criteria are as follows:

Manual PA criteria apply to all new and current users of carbinoxamine 6 mg tablets (Ryvent brand and generics) and 4 mg/5 mL ER oral suspension (Karbinal ER).

**Note:** Carbinoxamine generic IR liquid and 4 mg tablets are available without a PA; providers are encouraged to consider changing the prescription to generic IR liquid or 1 or 2 of the 4 mg tablets.

Coverage for carbinoxamine 6 mg tablets (Ryvent brand and generics) or Karbinal ER suspension will be approved if:

- This agent has been identified as having cost-effective alternatives. The provider must describe why this drug is required as opposed to available alternatives.

Non-FDA-approved uses are not approved.

Prior authorization does not expire.

- **Insulins: Rapid Acting Agents: generic insulin lispro (authorized generic for Humalog)**

An authorized generic for Humalog entered the market in April 2019. An "authorized generic" is the brand company's own product repackaged and marketed as a generic drug. An authorized generic is considered therapeutically equivalent to the name brand drug because it is the same drug. The FDA does not consider authorized generics as AB-rated generic formulations.

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) manual PA criteria for the authorized generic insulin lispro in new and current users, requiring a trial of branded Humalog, due to cost-effectiveness. The PA requirement will be removed when it is no longer cost advantageous.

The manual PA criteria are as follows:

Manual PA criteria apply to all new and current users of insulin lispro (authorized generic for Humalog). Coverage is approved if all criteria are met:

- a) Note: Brand Humalog is the preferred insulin lispro product in the DoD. If the prescription is for Humalog, prior authorization is not required.
- b) The provider must provide a patient-specific justification as to why the brand Humalog product cannot be used.

Non-FDA-approved uses are not approved.

PA does not expire.

- **Oral Oncologic Agents: niraparib (Zejula), olaparib (Lynparza), and rucaparib (Rubraca)**

PA criteria have not previously been required for the ovarian cancer drugs (PARP inhibitors). The P&T Committee reviewed three oral oncologic agents, Zejula, Lynparza, and Rubraca. PA criteria were recommended for these three products in new users, in order to assure prescribing in accordance with FDA-approved indications or a National Comprehensive Cancer Network (NCCN) Guideline-endorsed indication.

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) manual PA criteria for new users.

- a. **niraparib (Zejula)**

Manual PA criteria apply to all new users of Zejula.

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

- Zejula is prescribed by or in consultation with a hematologist/oncologist
- Patient is 18 years of age or older
- Patient has a deleterious or suspected deleterious BRCA mutation as detected by an FDA-approved test
- Zejula will be prescribed as a maintenance therapy for one of the following diagnoses:
  - a) Recurrent epithelial ovarian cancer, fallopian tube or primary peritoneal cancer
  - AND
  - b) Patient has received 2 or more lines of platinum-based chemotherapy
  - AND
  - c) Patient was in objective response (either complete or partial) to most recent treatment regimen AND
  - d) Zejula will not be combined with bevacizumab (Avastin)
  - 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, the provider must list the diagnosis.
- Female patients are not pregnant or planning to become pregnant and will take highly effective contraception while taking Zejula and for 6 months after the last dose.

Other non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**b. olaparib (Lynparza)**

Manual PA criteria apply to all new users of Lynparza.

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

- Lynparza is prescribed by or in consultation with a hematologist/oncologist

- Patient is 18 years of age or older
- Patient has a deleterious or suspected deleterious BRCA mutation as detected by an FDA-approved test
- Patient will use Lynparza as either treatment or maintenance therapy for one or more of the following diagnoses:
  - a) Recurrent or Stage IV Triple negative breast cancer OR
  - b) Recurrent or Stage IV hormone receptor (+) (ER, PR, or both) HER2 (-) breast cancer AND the patient was either:
    - Previously treated with prior endocrine therapy OR
    - The patient was not an appropriate candidate for endocrine therapy OR
  - c) Recurrent advanced ovarian cancers (either platinum-sensitive or platinum-resistant), fallopian tube or primary peritoneal cancers AND
    - Patient has received at least 3 prior lines of therapy
    - Lynparza will be used as a single agent
- Lynparza will be prescribed as maintenance therapy for one of the following diagnoses:
  - a) Platinum-sensitive, relapsed, epithelial ovarian cancer, fallopian tube or primary peritoneal cancer AND
    - Patient has received 2 or more lines of platinum-based chemotherapy
    - Patient was in objective response (either complete or partial) to most recent treatment regimen
    - Lynparza will not be combined with bevacizumab (Avastin) OR
  - b) Newly diagnosed, advanced, high-grade, epithelial ovarian cancer, fallopian tube or primary peritoneal cancer AND
    - Patient has had a complete or partial response to primary therapy with a platinum-based therapy
    - Lynparza will not be combined with bevacizumab (Avastin)

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, the provider must list the diagnosis.
- Female patients are not pregnant or planning to become pregnant and will take highly effective contraception while taking Lynparza and for 6 months after the last dose.

Other non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**c. rucaparib (Rubraca)**

Manual PA criteria apply to all new users of Rubraca.

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

- Rubraca is prescribed by or in consultation with a hematologist/oncologist
- Patient is 18 years of age or older
- Patient has a deleterious BRCA mutation as detected by an FDA-approved test
- Rubraca will be prescribed for one of the following:
  - a) Treatment of recurrent, high-grade, epithelial ovarian cancer (platinum-sensitive or platinum-resistant), fallopian tube or primary peritoneal cancer AND
    - Patient has received at least 2 prior lines of therapy
    - Rubraca will be used as a single agent
  - b) Maintenance of relapsed platinum-sensitive ovarian cancer, fallopian tube or primary peritoneal cancer AND
    - Patient has received 2 or more lines of platinum-based chemotherapy

- Patient was in objective response (either complete or partial) to most recent treatment regimen
  - Rubraca will not be combined with bevacizumab (Avastin)
- c) Newly diagnosed, advanced, high-grade, ovarian cancer, fallopian tube or primary peritoneal cancer AND
- Patient has had a complete or partial response to primary therapy with a platinum-based therapy
  - Rubraca will not be combined with bevacizumab (Avastin)

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, the provider must list the diagnosis: \_\_\_\_\_.
- Female patients are not pregnant or planning to become pregnant and will take highly effective contraception while taking Rubraca and for 6 months after the last dose.

Other non-FDA-approved uses are not approved.  
Prior authorization does not expire.

## 2. New PA Criteria—PA Implementation

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) new PAs for Ryvent brand and generics, Karbinal ER suspension, Rubraca, Lynparza, and Zejula become effective 90 days after the signing of the minutes. DHA will send letters to beneficiaries affected by the new PA requirements for Ryvent brand and generics and Karbinal ER if applicable, as new and current users will be subject to the PA.

### *Summary of Physician's Perspective:*

- **Carbinoxamine 6 mg tabs (Ryvent) and ER suspension (Karbinal)**

We are seeing more of these products get approved that are only slight variations of older drugs. The PA criteria will apply to the both the 6 mg generic and brand tablets, and the branded suspension. This is very similar to what we saw at the last meeting with another first generation antihistamine syrup (Ryclora).

There are other antihistamines that are available as oral syrups, both as

prescription or OTC products. The Committee could not come up with a clinical reason as to why these two products would be needed instead of the generic 4 mg tablets and immediate release suspension or the other widely available and low cost antihistamine syrups.

- **Insulin Lispro (Humalog) – Brand preferred**

The recommendation here is to prefer the branded Humalog product over the authorized generic. The authorized generic and the branded products all come from the same manufacturer, however the branded product Humalog product is more cost effective than the authorized generics.

If the prescription is written for Humalog, the patient will receive Humalog. The patient will only be subject to the PA if the prescription is written for the authorized generic as “insulin lispro”. Both of these products are charged at the Tier 2 (brand) copay, so there is no need to decrease the Humalog brand to the Tier 1 (generic) copay.

- **Oncology drugs for ovarian cancer (Zejula, Lynparza, and Rubraca)**

The Committee has been reviewing the oncology drugs to determine which ones do not have PAs in place. PAs were recommended for the ovarian cancer drugs, due to safety issues and to ensure that they are used according to the FDA-labeled indication. We will be updating PA requirements for other oncology drugs, so you will see these types of PAs at upcoming meetings.

For all the oncology drugs, the Committee is working with ESI to evaluate PA requests for off-label uses that are included in the NCCN guidelines or for which there is clinical evidence from a published study. This would allow the PAs to be reviewed for the off-label use as part of the initial review, before having the provider file an appeal. We are working with ESI to gradually implement this type of review process as part of the initial PA review.

***Summary of Panel Questions and Comments:***

Dr. Spatz asks for the number of patients impacted by the committee decision for Ryvent and Karinbal ER.

Dr. Khoury replied that he does not have the numbers of patients. What he has is the cost analysis of the comparators that are available. The cost effectiveness of those are about 10 times to 100 times more costly compared to ones that are available.

Dr. Spatz said he doesn't have a problem with that, but are you going to have 500 irate patients or 50,000 irate patients?

Dr. Khoury responded that there is a very small number. In general it's not in the tens

of thousands. It's closer to a few hundred.

Ms. Buchanan interjected that it's 267.

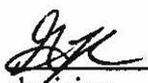
Dr. Khoury asked if that came from the back of the paper. It is 267 and specifically identified as current users in the appendix, and apologizes.

There were no further questions or comments from the Panel. The Chair called for a vote on the New Manual PA Criteria and the PA Implementation Plan for the New Manual PA Criteria.

- **New Manual PA Criteria**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

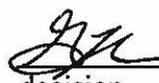
*Director, DHA:*

 These comments were taken under consideration prior to my final decision.

- **New Manual PA Criteria –PA Implementation Plan**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

*Director, DHA:*

 These comments were taken under consideration prior to my final decision.

## V. UTILIZATION MANAGEMENT—UPDATED MANUAL PA CRITERIA

### A. UPDATED PA CRITERIA

#### 1. Updated PA Criteria

Updates to the step therapy and manual PA criteria for several drugs were recommended by the P&T Committee due to a variety of reasons, including expanded FDA indications. The updated manual PAs outlined below will apply to new users.

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) updates to the manual PA criteria for Qsymia, the weight loss agents, Dupixent, Xeljanz/Xeljanz XR, Cimzia, Humira, and Imbruvica. All updated PA criteria apply to new users of these agents.

The updates are as follows:

- **Corticosteroids: Immune Modulators – Atopic Dermatitis Subclass – dupilumab (Dupixent)**—Manual PA criteria were originally recommended for Dupixent for atopic dermatitis during the May 2017 P&T Committee meeting. The Dupixent PA was then updated to reflect the additional FDA-approved indication for asthma in November 2018. In February and May 2019, the FDA lowered the age for both asthma and atopic dermatitis down to 12 years. The P&T Committee updated the PA to reflect the lower age allowance and also lowered the baseline eosinophils requirement from 300 cells/mcL to 150 cells/mcL, as some benefit was seen at the lower range in the clinical trial.
- **Oral Oncologic Agents**—Ibrutinib (Imbruvica) is an oral oncology agent that was designated as UF prior to the Innovator Rule established in August 2015. In May 2018, the P&T Committee recommended PA criteria for both the tablets and capsules. The committee reviewed the NCCN Guidelines and updated the PA to include an allowance for an additional indication that carries a Grade 1, 2A, or 2B recommendation from the NCCN Guidelines.
- **Targeted Immunomodulatory Biologics (TIBs): certolizumab (Cimzia) and adalimumab (Humira)**—Cimzia was granted a new FDA indication in March 2019 for non-radiographic axial spondyloarthritis with objective signs of inflammation (nr-ax SpA). Nr-ax SpA is a subtype of spondyloarthritis, a spectrum of disease that also includes ankylosing spondylitis. Guidelines from the Assessment of SpondyloArthritis international Society (ASAS)/European League Against Rheumatism (EULAR) recommend the TNF inhibitors adalimumab (Humira), certolizumab (Cimzia), etanercept (Enbrel), and golimumab (Simponi) for nr-ax SpA, and state that the price of the TNF inhibitor should influence therapy. The P&T Committee updated the Cimzia PA for this additional indication. Although Humira is not approved for treating nr-ax SpA in the United States, clinical trial data is available and it carries this approval by foreign drug regulatory agencies. Based on the ASAS/EULAR guidelines and clinical trial data, the Humira PA was also updated to allow treatment for nr-ax SpA. Patients with nr-ax SpA will still be required to try Humira prior to Cimzia.
- **Targeted Immunomodulatory Biologics (TIBs): tofacitinib citrate (Xeljanz/Xeljanz XR)**—Xeljanz was originally approved for treating rheumatoid arthritis; the indication was later expanded to include psoriatic arthritis and ulcerative colitis in adults. The committee reviewed the new FDA safety alert for increased risk for pulmonary embolism and death in patients taking a 10 mg twice daily dose for rheumatoid arthritis. This dosage is only approved for patients with ulcerative colitis. The P&T Committee updated the PA to limit the 10 mg twice daily dose for the labeled indication of ulcerative colitis.
- **Weight Loss Agents**—The P&T Committee recommended updates to the manual PA criteria for the branded weight loss agents to provide additional clarity regarding step

therapy. Patients must first try generic phentermine before use of any of the non-phentermine branded drugs for weight loss. All updated PA criteria apply to new users.

- **Weight Loss Agents: topiramate extended-release/phentermine (Qsymia)**—The P&T Committee recommended updates to the manual PA criteria for Qsymia to include safety concerns regarding pregnancy risk and the REMS program.

## 2. Updated PA Criteria—Implementation Plan

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) updates to the current PA criteria for Qsymia, the weight loss agents, Dupixent, Xeljanz/Xeljanz XR, Cimzia, Humira, and Imbruvica in new users become effective 30 days after the signing of the minutes.

### *Summary of Physician's Perspective:*

At every meeting, we present updates to drugs with existing PAs to ensure the latest FDA indications or safety updates are included in our criteria. These updates to the existing PAs will only affect new patients.

For Imbruvica, this is another example of an oncology drug where we would like off-label uses evaluated as part of the initial review, if they meet NCCN guideline recommendations.

For the weight loss drugs, the PA updates were to clarify the recommendation from the November 2017 meeting, and to include a safety alert for one of the drugs (Qsymia).

### *Summary of Panel Questions and Comments:*

There were no questions or comments from the Panel. The Chair called for a vot on the Updated Manual PA Criteria and the PA Implementation Plan for the Updated Manual PA Criteria.

- **Updated Manual PA Criteria**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

*Director, DHA:*

 These comments were taken under consideration prior to my final decision.

- **Updated Manual PA Criteria – PA Implementation Plan**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

*Director, DHA:*

 These comments were taken under consideration prior to my final decision.

**VI. BRAND OVER GENERIC AUTHORIZATION FOR FLUTICASONE/SALMETEROL (ADVAIR DISKUS) (LT COL KHOURY)**

**A. BRAND OVER GENERIC AUTHORIZATION**

Pricing for the branded Advair Diskus product is more cost-effective than the AB-rated generic formulations for fluticasone/salmeterol, which were launched in March 2019. Therefore, the branded Advair Diskus product will continue to be dispensed, and the generic will only be available with prior authorization (i.e., the reverse of the current brand to generic policy). The Tier 1 (generic) copayment will apply to Advair Diskus as outlined in Section IV E on page 17 of the background document. The “brand over generic” requirement for Advair Diskus will be removed administratively when it is no longer cost-effective compared to the AB-rated generics.

**1. Advair Diskus Brand over Generic Requirement and PA Criteria**

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) implementing the requirement to prefer the branded Advair product over generic formulations. Manual PA criteria are required for generic fluticasone/salmeterol in the Retail Network and Mail Order Pharmacy. The prescriber will provide patient-specific justification as to why the branded fluticasone/salmeterol product cannot be used.

**2. Advair Diskus Brand Copayment**

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) that the brand (Tier 2) formulary cost-share for Advair Diskus in the TRICARE Mail Order Pharmacy and the TRICARE Retail Network Pharmacy be lowered to the generic (Tier 1) formulary cost-share.

*Summary of Physician’s Perspective:*

For Advair, we are recommending our usual “brand over generic” preference. This is a little different that the recommendation made above for the authorized generic for the insulin lispro. For Advair, the generic is from a different manufacturer, unlike the

situation with the Humalog authorized generic.

Due to the significant difference in cost in favor of the branded Advair product, this was implemented under administrative authority back on March 6<sup>th</sup>. Patients on the generic inhaler area required to document why they can't use the Advair brand.

Since this is a true generic product, and not an authorized generic, the copay for brand Advair is reduced to the generic copay. The patients on Advair are now benefitting from the Tier 1 (generic) copay.

***Summary of Panel Questions and Comments:***

Dr. Spatz states that he is curious about the discussion with the pulmonologist, when they think someone would be indicated to have the generic over the brand situation.

Dr. Khoury asked if he's asking about the reasoning they would say why?

Dr. Spatz responded the reason why they would have the generic instead of the brand. Dr. Khoury replied that they have not reviewed those comments yet. They are interested in those comments as much as he is.

There were no more questions or comments from the Panel. The Chair called for a vote on the Advair Diskus Brand over Generic Requirement and PA Criteria and the Advair Diskus Brand Copayment.

• **Updated Manual PA Criteria**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

***Director, DHA:***

 These comments were taken under consideration prior to my final decision.

• **Updated Manual PA Criteria – PA Implementation Plan**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

***Director, DHA:***

 These comments were taken under consideration prior to my final decision.

**Brief Listing of Acronyms Used in this Summary**

Abbreviated terms are spelled out in full in this summary; when they are first used, the acronym is listed in parentheses immediately following the term. All of the terms commonly used as acronyms in the Panel discussions are listed below for easy reference. The term “Pan” in this summary refers to the “Uniform Formulary Beneficiary Panel,” the group who’s meeting in the subject of this report.

- 6WMD – 6 Minute Walk Distance
- ACG – American College of Gastroenterology
- ADRs – Association of Adverse Reactions
- AHRQ – Agency for Healthcare Research and Quality
- ANDA - Abbreviated New Drug Application
- ASAS - Assessment of SpondyloArthritis international Society
- BAP – Beneficiary Advisory Panel
- BIA – Budget Impact Analysis
- BRCA – Breast Cancer Gene
- CFR – Code of Federal Regulations
- CIC – Chronic Idiopathic Constipation
- CMA – Cost-minimization analysis
- COPD – Chronic Obstructive Pulmonary Disease
- CTEPH – Chronic Thromboembolic Pulmonary Hypertension
- DHA – Defense Health Agency
- DMT – Disease modifying therapy
- DoD – Department of Defense
- ERAs – Endothelin Receptor Antagonists
- EULAR – European League Against Rheumatism
- FDA – Food & Drug Administration
- GERD – Gastroesophageal Reflux Disease
- GI – Gastrointestinal
- HIV – Human Immunodeficiency Virus
- IOP – Intensive Outpatient Treatment
- LFT – Liver Function Test
- Mg – Milligram
- MHS – Military Health System
- MTF – Military Treatment Facility
- NCCN – National Comprehensive Cancer Network
- NDAA – National Defense Authorization Act
- NF – Non-Formulary
- NSAID – Non-steroidal Anti-Inflammatory Drugs
- ODT – Orally dissolving tablet
- OTC – Over-the-Counter

- P&T – Pharmacy & Therapeutics
- PA – Prior Authorization
- PAH – Pulmonary Arterial Hypertension
- PARP – Poly (adenosine diphosphate [ADP]) Ribose Polymerase
- PDE-5 – Phosphodiesterase Type 5 Inhibitor
- PPI – Proton Pump Inhibitor
- RMS – Rhabdomyosarcoma
- TIBS – Targeted Immunomodulatory



**PHA** Pulmonary Hypertension Association  
Empowered by hope

June 18, 2019

Uniform Formulary Beneficiary Advisory Panel  
c/o Colonel Paul J. Hoerner, USAF  
7700 Arlington Boulevard  
Suite 5101  
Falls Church, VA 22042-5101

Dear Advisory Panel Members:

Thank you for the opportunity to provide input regarding coverage of pulmonary hypertension (PH)-specific therapeutics within the TRICARE Uniform Formulary (UF).

The Pulmonary Hypertension Association (PHA) was the world's first and largest organization dedicated to providing comprehensive PH patient and caregiver support, medical education, research and specialty care services that improve patients' quality of life. PHA's Scientific Leadership Council (SLC) is comprised of leading PH experts in the fields of cardiology, pulmonology and rheumatology and serves as PHA's medical advisory body.

Pulmonary arterial hypertension (PAH) is a rare, progressive lung disease characterized by high blood pressure in the lungs that can lead to right heart failure. PAH is a complex condition that can occur on its own or secondary to another condition, disease or exposure. Average survival from the time of diagnosis has increased from less than three years to more recent estimates of seven to nine years due to the development of multiple FDA-approved targeted therapies. Ultimately, however, PAH remains a fatal, incurable condition.

When treating PAH, there is no one-size-fits-all formula. For physicians, maximizing survival and minimizing high-cost healthcare utilization events for individuals with PAH — such as hospitalization, emergency department visits, and transplantation — requires careful attention to the needs of a specific patient and their response to available therapy options either alone or in combination. Given the limited data owing to the rarity of PAH, variable efficacy among cohorts, lack of comparative effectiveness trials, vastly different drug delivery routes and non-uniform cost-effectiveness studies (utilizing varied methodologies precluding comparisons between studies), caution should be exercised in prioritizing one PAH therapy over another.

Clearly the field has shifted over the last 15 years to individualizing therapy based on comprehensive risk assessment and achieving predictive treatment goals, as explicitly stated in the 6<sup>th</sup> World Symposium on Pulmonary Hypertension.<sup>1</sup> Most importantly, because PAH can progress very rapidly, any delay or disruption in effective therapy, including delays inherent with step therapy, can lead to increased morbidity and mortality.

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With this in mind, we encourage you to consider the following changes when reviewing the recommendations of the Department of Defense Pharmacy and Therapeutics Committee.

#### **IV. PULMONARY ARTERIAL HYPERTENSION (PAH) AGENTS – PROSTACYCLINS, ENDOTHELIN RECEPTOR ANTAGONISTS (ERAS), AND NITRIC OXIDE DRUGS**

##### **“A. PAH Agents – Prostacyclins, ERAs and Nitric Oxide Drugs – Relative Clinical Effectiveness Analysis and Conclusion”**

###### **“Endothelin Receptor Antagonists (ERAS)” – AMBITION Trial**

The AMBITION trial was an event-driven, double-blind study of initial combination therapy of ambrisentan 10mg + tadalafil 40mg, initial monotherapy with ambrisentan 10mg + placebo, or initial monotherapy of tadalafil 40mg + placebo every day in treatment-naïve PAH patients assigned in a 2:1:1 ratio. AMBITION reported that patients receiving ambrisentan + tadalafil had a 50% reduction in the risk of a clinical failure event compared to those receiving either drug in monotherapy + placebo.<sup>i</sup> However, it remains uncertain whether PAH patients uniformly benefit from the combination of any ERA + any PDE5-inhibitor. For example, the COMPASS-2 trial of bosentan 125mg twice daily to PAH patients on stable sildenafil dosing failed to demonstrate a statistically significant effect on the primary efficacy endpoint of time-to-first-morbidity/mortality-event.<sup>ii</sup>

For accuracy, we recommend that the sub-section *Endothelin Receptor Antagonists (ERAs)* be edited to mention by name both therapies included in the AMBITION trial. Specifically, “Data supporting combination therapy with an ERA and a PDE5-inhibitor is available with Letairis® and tadalafil in treatment-naïve patients (AMBITION trial)....”

##### **“C. PAH Agents – Prostacyclins, ERAs, and Nitric Oxide Drugs – UF Recommendations”**

###### **“Nitric Oxide Drugs”**

PHA recommends that tadalafil 20mg (Adcirca®, Alyq™, generics) be classified as “step-preferred” in PAH treatment rather than “non-step-preferred.” Alternatively, because AMBITION did not evaluate the efficacy of sildenafil in combination with ambrisentan, PHA recommends that an exception is made when tadalafil is prescribed in combination with Letairis® (ambrisentan), per the AMBITION protocol. This is in line with expert consensus treatment guidelines in the initial combination therapy recommendation.

As noted above, patients in the AMBITION study randomized to the combination treatment arm of ambrisentan 10mg + tadalafil 40mg demonstrated a 50% risk reduction in the time-to-clinical-failure event compared to patients in either monotherapy arm. This efficacy benefit of an ERA + PDE5-inhibitor has not been uniformly measured in clinical studies with other agents of the same class. This scientific background has led to stronger recommendations of ambrisentan + tadalafil as an initial combination therapy compared to other ERAs + PDE5-inhibitors in expert consensus PAH treatment guidelines. Thus, the barrier of step therapy for tadalafil may delay optimal, guideline-directed initial PAH therapy.

The table and recommendations below represent relevant sections from two expert consensus PAH treatment guideline documents.

**2015 ESC/ERS Guideline for the Diagnosis and Treatment of Pulmonary Hypertension<sup>iii</sup>**

Measure/Treatment	Class-Level			
	WHO-FC II		WHO-FC III	
Ambrisentan + tadalafil	I <sup>1</sup>	B <sup>2</sup>	I <sup>1</sup>	B <sup>2</sup>
Other ERA + PDE5-i	IIa <sup>3</sup>	C <sup>4</sup>	IIa <sup>3</sup> ij	C <sup>4</sup>

**Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report<sup>iv</sup>**

*Every included recommendation in the “Combination Studies of ERAs and Phosphodiesterase Inhibitors” section:*

**“Recommendation #10:** For treatment-naïve PAH patients with WHO FC II and III, we suggest initial combination therapy with ambrisentan and tadalafil to improve 6MWD (weak [conditional] recommendation, moderate quality evidence<sup>5</sup>).”

**“Recommendation #71:** For stable or symptomatic PAH patients on background therapy with ambrisentan, we suggest the addition of tadalafil to improve 6MWD (weak [conditional] recommendation, low quality evidence<sup>6</sup>)”

<sup>1</sup> “Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.”

<sup>2</sup> “Data derived from a single randomized clinical trial or large non-randomized studies.”

<sup>3</sup> “Weight of evidence/opinion is in favour of usefulness/efficacy”

<sup>4</sup> “Consensus of opinion of the experts and/or small studies, retrospective studies, registries.”

<sup>5</sup> “Benefits closely balanced with risks and burden. We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Best action may differ depending on the circumstances or patients’ or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.”

<sup>6</sup> “Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced. Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.”

**“D. PAH Agents – Prostacyclins, ERAs and Nitric Oxide Drugs – Manual PA Criteria”**

**“5. Upravi® and Orenitram ER®” – Step Therapy Requirement**

We find the following step therapy requirement unclear as drafted. We are concerned that this will inappropriately limit access to clinically recommended therapy.

- *Patient meets one of the following criteria*
  - *The patient has tried one oral therapy for PAH from one of the three following different categories (either alone or in combination) each for ≥60 days: one PDE5-inhibitor (tadalafil or sildenafil), one ERA (Letairis, Opsumit, or Tracleer), or Adempas; OR*
  - *The patient has tried one prostacyclin therapy (oral, IV, or nebulized)*

As drafted, coverage for an oral prostacyclin analogue (Orenitram ER®) or selective IP receptor agonist (Upravi®) would not be approved until the PAH patient has been on a therapy acting on the endothelin or nitric oxide pathway for at least sixty (60) days, or unless they have progressed disease/symptomatology that required either an inhaled or parenteral prostacyclin agent.

This coverage recommendation as drafted is counter to expert consensus PAH treatment guidelines and practice patterns in the United States. PAH patients who are considered low- or intermediate-risk are recommended for either initial oral combination therapy or initial oral monotherapy, depending on the patient type.<sup>iii</sup> PAH patients considered high-risk are recommended for initial combination therapy including IV prostacyclin. Following an “inadequate clinical response” to the initial treatment, sequential combination therapy is recommended. PHA notes that these expert consensus guidelines do not define a time period for the “inadequate clinical response,” as this can differ from patient-to-patient. In our experience, “inadequate clinical response,” and the need for modulation of the prostacyclin pathway with an oral agent, can occur before 60 days after the initiation of the first PAH-targeted therapy (ERA and/or PDE5-inhibitor). In addition, in our clinical experience, IV prostacyclin therapy may not be appropriate for all PAH patients, and thus an inappropriate step requirement. This specifically can include patients with connective tissue disease-associated PAH (as these patients can experience great difficulty in mixing their medications), and patients in whom chronic IV access is contraindicated for clinical or social reasons.

We also note the circular logic of allowing previous use an oral prostacyclin therapy as an exception to the step therapy requirement for oral prostacyclin therapy coverage.

For the reasons above, and because a predefined time to demonstrate clinical failure was not defined by the P&T Committee elsewhere in the PAH recommendations, if step therapy is required for PAH patient access to oral Upravi® or Orenitram ER®, we recommend the following edits in order to maximize patient safety, patient outcomes, and clinician judgement:

- *Patient meets one of the following criteria:*
  - *The patient has tried one oral therapy for PAH from one of the three following different categories (either alone or in combination) each for ≥60 days but with an inadequate clinical response after appropriate trial as assessed by the*

*clinician: PDE5-inhibitor (tadalafil or sildenafil), ERA (Letairis, Opsumit, or Tracleer), or Adempas; OR*

- *The patient has tried one prostacyclin therapy (oral, IV, SQ, or nebulized) and is either unable to tolerate therapy due to adverse effects or serious adverse events stemming from the complex delivery system.*

#### **"6. Adempas®" - Step Requirements for WHO Group 1 and 4**

We are very concerned about the recommendation that WHO Group 1 PH (PAH) patients try and fail on both sildenafil and tadalafil before receiving approval for Adempas®. As mentioned previously, PAH is a fatal condition that can progress rapidly, and effective therapy management requires physician judgement to respond to the clinical needs of individual patients. We believe that the time required to complete two step edits before receiving Adempas® may result in irreversible clinical worsening in some patients. Furthermore, the requirement for two step-edits places undue administrative burdens on clinicians and their staffs. Modern PAH clinical trial design includes a blinded period until a patient reaches pre-specified end point(s), followed by an open-label extension where all study patients are on active therapy. Analyses of the open-label extension trials have demonstrated that patients originally randomized to placebo, and thus not on maximal therapy, have worse outcomes than patients originally in the active therapy arm and often fail to "catch up" to the comparator groups who received active treatment during the blinded phase.

We recommend that, if any step therapy is required for Adempas® approval, the requirement be for a trial of a single PDE5-inhibitor, either sildenafil OR tadalafil, **but not both**.

In addition, after careful review of this section, we remain unclear as to the recommendations for patient with Group 4 PH (CTEPH) due to the exact wording and formatting. We believe that the P&T Committee is recommending that a diagnosis of Group 4 PH (CTEPH) exempts the patient from the PDE5-inhibitor step therapy requirements for Adempas® approval. We agree with this recommendation, due to the lack of additional FDA-approved targeted therapy options for this patient population. However, given the formatting of the document, we found the P&T Committee's exact intent difficult to follow.

#### **"7. Adcirca®, Alyq™, and Generics" – Combination Therapy**

As noted above, the AMBITION trial is the only reported clinical trial prospectively researching initial combination therapy in PAH compared to either therapy used as monotherapy. Given the robust evidence from this clinical trial, we believe that physician discretion in utilizing this combination should be preserved, rather than requiring a step failure of a different PDE5-inhibitor that was not included in the clinical trial. We recommend the following edits:

*Manual PA Criteria: Tadalafil 20mg (Adcirca, generics) or Alyq is approved if all criteria are met:*

- *Prescribed by or in consultation with a cardiologist or pulmonologist*
- *Patient has document diagnosis of WHO group 1 PAH*
  - *Patient has had a right heart catheterization (documentation required)*
  - *Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH*

Colonel Paul J. Hoerner, USAF

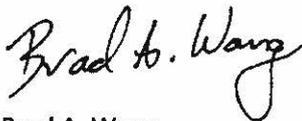
June 18, 2019

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- Patient has had an adequate trial of sildenafil 20mg (Revatio, generics) and failed or did not respond to therapy, *unless prescribed as initial oral combination therapy with ambrisentan per the AMBITION protocol and*
- Patient is not receiving other PDE-5 inhibitors, nitrates, or riociguat (Adempas) concomitantly.

Thank you for your consideration of these recommendations. If you have additional questions or concerns, do not hesitate to contact Brad A. Wong, president and CEO of the Pulmonary Hypertension Association, at 301-565-3004 x741 or [BradW@PHAssociation.org](mailto:BradW@PHAssociation.org).

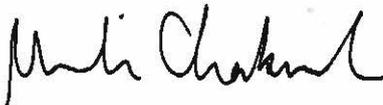
Sincerely,



Brad A. Wong  
President and CEO  
Pulmonary Hypertension Association



Ronald J. Oudiz, MD  
Chair, PHA Scientific Leadership Council  
Professor of Medicine  
Director, Liu Center for Pulmonary Hypertension  
LA Biomedical Research Institute at Harbor – UCLA Medical Center



Murali M. Chakinala, MD, FCCP  
Chair-Elect, PHA Scientific Leadership Council  
Professor of Medicine  
Washington University School of Medicine  
Division of Pulmonary and Critical Care



Erika S. Berman Rosenzweig, MD  
Immediate Past Chair, PHA Scientific Leadership Council  
Professor of Pediatrics (In Medicine)  
Columbia University Medical Center  
New York Presbyterian Hospital

<sup>1</sup> Galiè N, et al. *N Engl J Med*. 2015; 373:834-44

<sup>2</sup> McLaughlin V, et al. *Eur Respir J*. 2015;46(2):405-13

<sup>3</sup> Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119

<sup>4</sup> Klinger, JR, et al. *CHEST*. 2019;155(3): 565-86

## **Uniform Formulary Beneficiary Advisory Panel (BAP)**

Meeting Summary

June 26, 2019

Washington D.C.

### **Present Panel Members**

- Mr. Jon R. Ostrowski, Non-Commissioned Officers Association, Chairperson
- Ms. Theresa Buchanan, National Military Family Association
- Dr. Karen Dager, Health Net Federal Services
- Dr. Jay Peloquin, Express Scripts, Inc.
- Dr. Lindsey Piirainen, USFHP Martin's Point Healthcare

### **New Panel Members**

- Dr. Michael W. Spatz, Humana

### **Absent Panel Members**

- Mr. John R. Du Teil, United States Army Warrant Officers Association
- Dr. Richard Bertin, Commissioned Officer Association (COA) of the United States Public Health Service, Inc.
- Mr. Charles Hostettler, AMSUS
- Ms. Suzanne Walker, Military Officers Association of America

The meeting was held at Naval Heritage Center Theater, 701 Pennsylvania Ave., N.W., Washington D.C., and Col Paul Hoerner called the meeting to order at 9:00 A.M.

### **Agenda**

The Agenda for the meeting of the Panel is as follows:

- Welcome and Opening Remarks
- Public Citizen Comments
- Therapeutic Class Reviews
  1. Drug Class Reviews
    - a) Proton Pump Inhibitors – Capsules and Tablets and Alternative Dosage Form Subclasses
    - b) Pulmonary Arterial Hypertension (PAH) Agents – Prostacyclins, Endothelin Receptor Antagonists (ERAs), and Nitric Oxide Drugs
  2. Newly Approved Drugs per 32 CFR 199.2(g)(5)

- a) benzhydrocodone/acetaminophen (Apadaz) – Narcotic Analgesics and Combinations
- b) cladribine (Mavenclad) – Multiple Sclerosis Agents: Oral Agents
- c) epinephrine injection (Symjepi) – Respiratory Agents Miscellaneous
- d) estradiol 1 mg/progesterone 100 mg capsules (Bijuva) – Gynecological Agents Miscellaneous
- e) levodopa inhalation powder (Inbrija) – Parkinson’s Agents
- f) levothyroxine sodium oral solution (Tirosint-SOL) – Thyroid and Antithyroid Agents
- g) loteprednol etabonate 0.38% ophthalmic gel (Lotemax SM) – Anti-inflammatory Immunomodulatory Ophthalmic Agents: Ophthalmic Anti-inflammatory Agents
- h) meloxicam orally dissolving tablet (Qmiiz ODT) – Pain Agents: NSAID
- i) netarsudil 0.02%/latanoprost 0.005% ophthalmic solution (Rocklatan) – Glaucoma Agents
- j) prucalopride (Motegrity) – Gastrointestinal-2 Agents: Chronic Idiopathic Constipation (CIC) and Constipation-Predominant Irritable Bowel Syndrome (IBS-C)
- k) siponimod (Mayzent) – Multiple Sclerosis Agents: Oral Miscellaneous
- l) stiripentol (Diacomit) – Anticonvulsants-Antimania Agents
- m) tacrolimus oral suspension (Prograf) – Immunosuppressives

### 3. Utilization Management Issues

#### a) Prior Authorization Criteria – New Criteria

- Antihistamine-1: First generation and combinations – Carbinoxamine Maleate 4 mg/5 mL ER oral solution (Karbinal ER) and Carbinoxamine Maleate 6 mg tablets
- Insulins: Rapid Acting Agents: generic insulin lispro (authorized generic for Humalog)
- Oral Oncologic Agents: niraparib (Zejula), olaparib (Lynparza), and rucaparib Rubraca)

#### b) Prior Authorization Criteria – Updated Criteria

- Corticosteroids: Immune Modulators – Atopic Dermatitis Subclass: dupilumab (Dupixent)
- Oral Oncologic Agents: ibrutinib (Imbruvica)
- Targeted Immunomodulatory Biologics (TIBs): tofacitinib citrate (Xeljanz/Xeljanz XR), certolizumab (Cimzia), and adalimumab (Humira)
- Weight Loss Agents: liraglutide 3 mg injection (Saxenda), lorcaserin (Belviq, Belviq XR), naltrexone SR/bupropion SR (Contrave), orlistat (Xenical), and topiramate extended-release/phentermine (Qsymia)

### 4. Brand over Generic Authorization for Fluticasone/Salmeterol (Advair Diskus)

## 5. Panel Discussion

*The Uniform Formulary Beneficiary Advisory Panel will have the opportunity to ask questions to each of the presenters. Upon completion of the presentation and any questions, the Panel will discuss the recommendation and vote to accept or reject the recommendations. The Panel will provide comments on their vote as directed by the Panel Chairman.*

### **Opening Remarks**

Col Paul Hoerner introduced himself as the Designated Federal Officer (DFO) for the Uniform Formulary (UF) Beneficiary Advisory Panel (BAP). The Panel has convened to comment on the recommendations of the DoD Pharmacy and Therapeutics (P&T) Committee meeting, which occurred on May 8-9, 2019.

Col Hoerner indicated Title 10, United States, (U.S.C.) section 1074g, subsection b requires the Secretary of Defense to establish a DoD Uniform Formulary (UF) of the pharmaceutical agent and established the P&T committee to review the formulary on a periodic basis to make additional recommendations regarding the formulary as the committee determines necessary and appropriate.

In addition, 10 U.S.C. Section 1074g, subsection c, also requires the Secretary to establish a UF Beneficiary Advisory Panel (BAP) to review and comment on the development of the Uniform Formulary. The Panel includes members that represent non-governmental organizations and associations that represent the views and interests of a large number of eligible covered beneficiaries. The Panel's comments must be considered by the Director of the Defense Health Agency (DHA) before establishing the UF or implementing changes to the UF.

The Panel's meetings are conducted in accordance of the Federal Advisory Committee Act (FACA).

The duties of the Uniform Formulary Beneficiary Advisory Panel include the following:

- To review and comment on the recommendations of the P&T Committee concerning the establishment of the UF and subsequent recommended changes. Comments to the Director, DHA, regarding recommended formulary status, pre-authorizations, and the effective dates for changing drugs from "formulary" to "non-formulary" status must be reviewed by the Director before making a final decision.
- To hold quarterly meetings in an open forum. The Panel may not hold meetings except at the call of or with the advance approval of the DFO in consultation with the Chairperson of the Panel.
- To prepare minutes of the proceedings and prepare comments for the Secretary or his designee regarding the Uniform Formulary or changes to the Formulary. The minutes will be available on the website and comments will be prepared for the Director, DHA.

The DFO provided guidance regarding this meeting:

- The role of the BAP is to comment on the UF recommendations made by the P&T Committee at their last meeting. While the Department appreciates that the BAP may be interested in the drug classes selected for review, drugs recommended for the basic core formulary (BCF) or specific pricing data, these topics do not fall under the purview of the BAP.
- The P&T Committee met for approximately 16 hours conducting its reviews of the drug class recommendations presented today. Since this meeting is considerably shorter, the Panel will not receive the same extensive information that is presented to the P&T Committee members. However, the BAP will receive an abbreviated version of each presentation and its discussion. The materials provided to the Panel are available on the TRICARE website.
- Detailed minutes of this meeting are being prepared. The BAP minutes, the DoD P&T Committee meeting minutes and the Director's decisions will be available on the TRICARE website in approximately four to six weeks.

The DFO provided a few ground rules for conduct during the meeting:

- The role of the BAP is to comment on the UF recommendations made by the P&T Committee at their last meeting. While the Department appreciates that the BAP may be interested in the drug classes selected for review, drugs recommended for the basic core formulary (BCF) or specific pricing data, these topics do not fall under the purview of the BAP.
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- Detailed minutes of this meeting are being prepared. The BAP minutes, the DoD P&T Committee meeting minutes and the Director's decisions will be available on the TRICARE website in approximately four to six weeks.
- When addressing the Panel or responding to questions, please use the microphone.

Col Hoerner introduced the individual Panel members (see list above) and noted housekeeping considerations.

A written statement from was received from the Pulmonary Hypertension Association. It was forwarded to the Panel for their review and consideration.

**Chairman's Opening Remarks**

Mr. Ostrowski welcomes the Panel and new member Dr. Spatz.

## DRUG CLASS REVIEW PRESENTATION

### (POD Script – LT COL KHOURY)

GOOD MORNING. I am Lieutenant Colonel Ronald Khoury, Chief of the Formulary Management Branch of the DHA Pharmacy Operations Division. Joining me is doctor and retired Army Colonel John Kugler, the Chairman of the Pharmacy and Therapeutics Committee, who will provide the physician perspective and comments on the recommendations made by the P&T Committee. Also joining us today is Dr. Amy Lugo, a clinical pharmacist in the Formulary Management Branch of the DHA Pharmacy Operations Division. I would also like to recognize Mr. Bryan Wheeler, Deputy General Counsel.

The DoD Formulary Management Branch supports the DoD P&T Committee by conducting the relative clinical effectiveness analyses and relative cost-effectiveness analyses of the drugs and drug classes under review and consideration by the DoD P&T Committee for the Uniform Formulary (relative meaning in comparison to the other agents defined in the same class). We are here to present an overview of the analyses presented to the P&T Committee. 32 Code of Federal Regulations (CFR) establishes procedures for inclusion or exclusion of pharmaceutical agents on the Uniform Formulary based upon both relative clinical effectiveness and relative cost-effectiveness.

The goal of this presentation is not to provide you with the same in-depth analyses presented to the DoD P&T Committee but a summary of the processes and analyses presented to the DoD P&T Committee. These include:

- A brief overview of the relative clinical effectiveness analyses considered by the DoD P&T Committee. All reviews include but are not limited to the sources of information listed in 32 CFR 199.21 (e)(1) and (g)(5). All Tier 4/not covered candidates were reviewed in accordance with amended 32 CFR 199.21(e)(3) effective December 11, 2018. Also note that nonformulary medications are generally restricted to the mail order program according to amended section 199.21, revised paragraphs (h)(3)(i) and (ii), effective August 26, 2015.
- A brief general overview of the relative cost-effectiveness analyses. This overview will be general in nature since we are unable to disclose the actual costs used in the economic models. This overview will include the factors used to evaluate the costs of the agents in relation to the safety, effectiveness, and clinical outcomes.
- The DoD P&T Committee's Formulary, Uniform Formulary and Tier 4 recommendations are based upon the Committee's collective professional judgment when considering the analyses from both the relative clinical and relative cost-effectiveness evaluations.

The Committee reviewed the following:

1. The P&T Committee reviewed two Uniform Formulary Drug Classes:
  - a) the Proton Pump Inhibitor (PPI) Agents – Capsules and Tablets subclass and Alternative Dosage Forms subclass and
  - b) the Pulmonary Arterial Hypertension (PAH) Agents – Endothelin Receptor Antagonists, Prostacyclins, and Nitric Oxide Drugs.

A summary table of the UF drug class recommendations and the numbers of affected utilizers is found on pages 36-38 of the background document.

2. The P&T Committee also evaluated 13 newly approved drugs per 32 CFR 199.21(g)(5), which are currently in pending status and available under terms comparable to nonformulary drugs.

and

3. We also discussed prior authorizations (PAs) in the utilization management section for 16 drugs in 6 drug classes.

- a) Antihistamine-1: First generation and combinations
- b) Insulins: Rapid Acting Agents
- c) Oral Oncologic Agents
- d) Corticosteroids: Immune Modulators – Atopic Dermatitis subclass
- e) Targeted Immunomodulatory Biologics (TIBs)
- f) Weight Loss Agents

and

- g) We discussed one product for brand over generic authorization

The DoD P&T Committee will make a recommendation as to the effective date of the agents being changed from the Uniform Formulary tier to the Nonformulary tier or Tier 4/Not Covered. Based on 32 CFR 199.21, such change will not be longer than 180 days from the final decision date but may be less.

## UNIFORM FORMULARY DRUG CLASS REVIEW

### I. UF CLASS REVIEW

#### A. PROTON PUMP INHIBITORS (PPIs) – CAPSULES AND TABLETS AND ALTERNATIVE DOSAGE FORM SUBCLASSES

##### (LT COL KHOURY)

##### 1. PPIs – Capsules and Tablets and Alternative Dosage Form Subclasses

*Background*—The P&T Committee evaluated the relative clinical effectiveness of the Proton Pump Inhibitors (PPIs), including omeprazole (Prilosec), pantoprazole (Protonix), rabeprazole (Aciphex), dexlansoprazole (Dexilant), lansoprazole (Prevacid), omeprazole/sodium bicarbonate (Zegerid), esomeprazole (Nexium), and esomeprazole strontium. Generic formulations of all the products are marketed, except for Dexilant and esomeprazole strontium. Over-the-counter (OTC) formulations of Nexium, Prevacid, Prilosec, and their generics are also available.

The Alternative Dosage Form subclass was also evaluated for UF status and is comprised of 6 products: Prilosec, Protonix, Nexium, and Zegerid packets for oral suspension, Aciphex sprinkle, and Prevacid orally dissolving tablet (ODT). There are no generic PPI alternative dosage forms.

The Committee reviewed new clinical data available since the original class review in May 2007. Nexium was designated NF at the most recent class review in February 2017.

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

- The May 2007 drug class review concluded that PPIs have similar efficacy in treating a wide range of acid-related disorders and are highly therapeutically interchangeable. The P&T Committee did not find new clinical efficacy data that would change the original conclusion.
- The 2013 American College of Gastroenterology (ACG) Gastroesophageal Reflux Disease (GERD) Guidelines also support the May 2007 conclusion in their statement that there are no major differences in efficacy between the different PPIs for symptom relief and healing of erosive esophagitis.
- Several recent meta-analyses and systematic reviews state the PPIs do not have clinically significant differences in efficacy (e.g., 2009 Oregon Health & Science University Drug Effectiveness Review Project; 2018 Utah Medicaid P&T Committee).

- A recent network meta-analysis evaluated the comparative efficacy of PPIs for erosive esophagitis and concluded that at equipotent doses the PPIs do not exhibit superiority of one product over the other (Medicine 2017).
- Head-to-head trials between the PPIs are limited in that comparisons of equipotent doses are not always included.
- Differences in pharmacokinetic properties between the PPIs, such as release mechanism (e.g., delayed release or dual release), salt form (e.g., magnesium strontium or sodium bicarbonate), and chirality (e.g., R- vs. R- and S-enantiomers) have little to no clinical impact.
- With regard to the individual PPIs, the P&T Committee concluded the following:
  - a) Dexlansoprazole (Dexilant) contains the R enantiomer of lansoprazole (Prevacid).
  - b) Although Dexilant provides two releases of medication with peak concentrations at 2 and 5 hours, the link between dual release and therapeutic benefit is not known. Dexilant is only approved for patients 12 years and older and is not manufactured in an alternative dosage form.
  - c) FDA approval for Dexilant was based on two Phase 3 randomized controlled trials showing non-inferiority to Prevacid. Dexilant displayed a higher discontinuation rate due to adverse effects in comparison to Prevacid.
  - d) The 2009 FDA Review noted that although Dexilant was effective for the requested indications, there was no convincing evidence of additional benefit over existing therapies, and the benefit-to-risk profile for Dexilant was unfavorable.
  - e) The 2017 network meta-analysis also found that Dexilant was the PPI with the highest discontinuation rate in comparison to all other products.
  - f) There is no new data to change the May 2009 conclusion that Dexilant does not have a significant clinically meaningful therapeutic advantage in terms of effectiveness, safety, and clinical outcomes compared to other PPI drugs currently included on the UF.
- Esomeprazole strontium contains a different salt formulation from esomeprazole magnesium (Nexium) and is not available in an alternative dosage form.
  - a) FDA approval was based on the data with Nexium, and no clinical trials were conducted with this formulation. Strontium is incorporated into bone and is not recommended for use in children or during pregnancy due to safety.

Esomeprazole strontium is also not recommended in patients with severe renal impairment.

- b) Esomeprazole strontium offers no clinically compelling advantages in comparison to Nexium or the other PPIs.
- Zegerid is only approved for adults. FDA approval was granted based on the original omeprazole studies. Due to the sodium bicarbonate component, it is contraindicated in patients with metabolic alkalosis, hypocalcemia, respiratory alkalosis or those on salt restricted diets (it contains 300 to 400 mg of sodium per tablet). Zegerid offers no compelling clinical advantages over the other PPIs.
  - Prevacid brand and generics have the largest number of FDA-approved indications; however, there is robust evidence for off-label use for all PPIs for all indications. The alternative dosage form of Prevacid ODT contains phenylalanine and should be avoided in patients with phenylketonuria. Prevacid is approved for patients as young as 12.
  - Protonix brand and generics provide an option for flexible mealtime dosing and do not require dosage adjustment for hepatic impairment. Protonix has an alternative dosage form for treating patients down to the age of 5.
  - Aciphex brand and generics also provide an option for those who require flexible mealtime dosing but are not available in a formulation for use in PEG or NG tubes. The Aciphex sprinkle formulation is approved for children down to the age of 12 years.
  - Nexium brand and generics and Prilosec brand and generics have a long history of use, are available OTC, are compatible with NG/PEG tube administration, and the alternative dosage forms carry the youngest FDA-approved age range down to 1 month.
  - The 2013 ACG GERD Guidelines and 2017 American Gastroenterological Association (AGA) Best Practices agree that high-quality evidence recommend 4 weeks to 8 weeks of PPI therapy for GERD. Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce PPI use.
  - Unless otherwise clinically necessary, PPIs should be used for the shortest period possible per label indication. Indications for longer-term PPI use include refractory GERD, erosive esophagitis, Zollinger-Ellison syndrome, NSAID-induced ulcer history, Barret's Esophagus, and chronic anticoagulation after an Upper GI Bleed.
  - With the exception of high discontinuation rates associated with Dexilant, there are no important safety differences in long-term findings between PPI agents, but studies are observational in nature.

- Studies have shown PPIs are not benign and long-term use has been associated with adverse events. FDA safety alerts in 2011, 2012, and 2016 reported that prescription PPIs may cause nutrient malabsorption (vitamin B12, iron, magnesium, calcium) resulting in osteoporosis, hypomagnesemia, vitamin B12 deficiency, and increased infection risk (*Clostridium difficile* infections, salmonella, campylobacter, and pneumonia) and drug-induced cutaneous and systemic lupus erythematosus.
- The updated Beers Criteria published by the American Geriatrics Society in January 2019 reaffirms the 2015 recommendation to avoid prolonged use of PPIs beyond 8 weeks in adults age 65 years or older, unless there is a justified reason to continue use.
- PPI deprescribing campaigns suggest tapering patients, emphasizing therapeutic lifestyle modification, using rescue therapy such as calcium carbonate antacids or histamine blockers (e.g., ranitidine, famotidine), or attempting on-demand or de-escalation of dosing.

## **2. PPIs – Capsules and Tablets and Alternative Dosage Form Subclasses – Relative Cost Effectiveness Analysis and Conclusion**

Cost-minimization analysis (CMA) and budget impact analysis (BIA) were performed to evaluate the PPIs. The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 1 absent) the following:

### Tablets and Capsules Subclass

- CMA results for the Tablets and Capsules subclass showed that esomeprazole strontium, Dexilant, and Zegerid were substantially less cost-effective than the remainder of the class.
- BIA was performed for the Tablets and Capsules subclass to evaluate the potential impact of designating selected agents as formulary, NF, or Tier 4 on the UF. BIA results showed that designating Prilosec brand and generics and Protonix brand and generics as formulary and step-preferred, Nexium brand and generics and Aciphex brand and generics as UF and non-step-preferred, Prevacid brand and generics and Zegerid brand and generics as NF and non-step-preferred, and Dexilant and esomeprazole strontium as Tier 4 demonstrated significant cost avoidance for the Military Health System (MHS).

### Alternative Dosage Form Subclass

- CMA results for the Alternative Dosage Form subclass showed that the 6 PPIs available in these formulations were relatively similar in cost-effectiveness when adjusted for utilization.

- BIA results for the PPI Alternative Dosage Forms showed that designating Nexium packets, Prilosec packets, Protonix packets, and Aciphex sprinkles as UF, and Prevacid ODT and Zegerid packets as NF demonstrated significant cost avoidance for the MHS.

### **3. PPIs – Capsules and Tablets and Alternative Dosage Form Subclasses—UF/Tier 4/Not Covered Recommendation**

The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) the following formulary recommendations for the PPIs as outlined below, based on clinical and cost-effectiveness.

When considering the PPI 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>. The interim rule allows for complete exclusion of drugs from TRICARE pharmacy benefit coverage when certain criteria are met. Tier 4 status will apply to all users of the recommended candidates.

#### **Capsules and Tablets Subclass**

- UF and step-preferred
  - a) omeprazole 20 mg and 40 mg capsules (Prilosec brand and generics)
  - b) pantoprazole tablets (Protonix brand and generics)
- UF and non-step-preferred
  - a) rabeprazole tablets (Aciphex brand and generics)
  - b) esomeprazole capsules (Nexium brand and generics)
- NF and non-step-preferred
  - a) lansoprazole capsules (Prevacid brand and generics)
  - b) omeprazole/sodium bicarbonate capsules (Zegerid brand and generics)
- This recommendation includes step therapy, which requires a trial of Prilosec or Protonix before Nexium and Aciphex and a trial of all the UF step-preferred and non-step preferred products (Prilosec, Protonix, Aciphex, and Nexium) before Prevacid or Zegerid. See the PA section below.

- Tier 4/Not Covered
  - a) dexlansoprazole (Dexilant)—The P&T Committee concluded that Dexilant provides very little to no additional clinical effectiveness relative to the other PPIs; that the risk of use may outweigh any potential benefit including a higher discontinuation rate; and that the FDA reviewer expressed concerns regarding the benefit-to-risk profile. Overall, the P&T Committee found that the needs of TRICARE beneficiaries can be met by the other PPIs.
  - b) esomeprazole strontium—The P&T Committee concluded that esomeprazole strontium has little clinical data to support its use; has very little or no additional clinical effectiveness relative to the other PPIs and that the needs of TRICARE beneficiaries can be met by the other PPIs.

**Alternative Dosage Form Subclass**

- UF
  - a) esomeprazole (Nexium) packet for suspension
  - b) omeprazole (Prilosec) packet for suspension
  - c) pantoprazole (Protonix) packet for suspension
  - d) rabeprazole (Aciphex) Sprinkle
- NF
  - a) lansoprazole ODT (Prevacid ODT)
  - b) omeprazole/sodium bicarbonate (Zegerid) packet for suspension
- Note that step therapy does not apply to the PPI Alternative Dosage Forms.

**4. PPIs – Capsules and Tablets and Alternative Dosage Form Subclasses—Manual Prior Authorization (PA) Criteria**

The PPI class currently has step therapy requirements. The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) updated PA criteria for the PPIs. PA criteria are not required for Prilosec or Protonix. Updated manual and automated step therapy PA criteria were recommended in new users for Aciphex and Nexium, requiring a trial of either of the preferred products (Prilosec or Protonix) first. Additionally, the manual PA criteria for new users of Prevacid and Zegerid

were updated to require a trial of all of the UF products (Prilosec, Protonix, Aciphex, and Nexium) first. Use of the non-preferred PPI is allowed if there is a contraindication, inadequate response, or adverse reaction to the preferred PPI.

The current PA criteria for the Alternative Dosage Forms were also updated. PA criteria are not required for the packets for oral suspension formulations of Prilosec, Nexium, or Protonix, or the Aciphex sprinkles. Manual PA criteria are recommended for Prevacid ODT and Zegerid packets for oral suspension in all new and current users older than age 18. The provider must state why the patient needs an alternative dosage form and why they cannot take all of the formulary alternative dosage forms.

The PA criteria are as follows:

- **Nexium capsules, Aciphex tablets, and generics**

Note that prior authorization is not required for omeprazole capsules or pantoprazole tablets.

Manual and Automated PA criteria apply to all new users of esomeprazole (Nexium brand and generics) and rabeprazole (Aciphex brand and generics).

Automated PA Criteria: The patient has filled an Rx for generic omeprazole OR generic pantoprazole product at any Military Treatment Facility (MTF), retail network pharmacy, or the mail order pharmacy in the previous 365 days.

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

- a) Provider acknowledges that omeprazole and pantoprazole are the DoD's preferred agents
- b) Provider acknowledges that omeprazole and pantoprazole are Uniform Formulary and do not require prior authorization
- c) The patient has a contraindication to omeprazole and pantoprazole  
OR
- d) The patient has had an inadequate response or had an adverse reaction to omeprazole  
OR
- e) The patient has had an inadequate response or had an adverse reaction to pantoprazole

Non-FDA-approved uses are not approved.

PA does not expire.

- **Prevacid capsules and Zegerid capsules**

Manual PA and Automated PA criteria apply to all new users of lansoprazole (Prevacid brand and generics) and omeprazole/sodium bicarbonate (Zegerid brand and generics).

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

- a) Provider acknowledges that omeprazole and pantoprazole are the DoD's preferred agents
- b) Provider acknowledges that omeprazole and pantoprazole are Uniform Formulary and do not require prior authorization
- c) And the patient meets all four of the following criteria:
- d) Has a contraindication, had an inadequate response, or had an adverse reaction to omeprazole

AND

- e) Has a contraindication, had an inadequate response, or had an adverse reaction to pantoprazole

AND

- f) Has a contraindication, had an inadequate response, or had an adverse reaction to esomeprazole

AND

- g) Has a contraindication, had an inadequate response, or had an adverse reaction to rabeprazole

Non-FDA-approved uses are not approved.

PA does not expire.

- **Prevacid ODT and Zegerid packet for suspension**

Age edit applies: Patients 18 years and older will be subject to the PA.

Manual PA criteria apply to all new and current users of Prevacid ODT and Zegerid packet for suspension.

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

- a) Provider acknowledges that omeprazole and pantoprazole tablets and capsules are Uniform Formulary and do not require prior authorization
- b) Provider acknowledges that omeprazole, esomeprazole, and pantoprazole packets for suspension and rabeprazole sprinkles are Uniform Formulary and do not require prior authorization
- c) Provider must document patient-specific clinical rationale of why the patient cannot take ALL alternative PPI agents

Non-FDA-approved uses are not approved.

PA does not expire.

#### **5. PPIs – Capsules and Tablets and Alternative Dosage Form Subclasses—OTC Omeprazole UF Recommendation**

OTC omeprazole and omeprazole magnesium tablets and capsules have been included on the TRICARE Pharmacy benefit since the August 2015 DoD P&T Committee meeting, under provisions of 32 CFR 199.21(h)(5). The P&T Committee reviewed the cost and utilization of the OTC PPIs, including omeprazole, at the three points of service (POS). OTC omeprazole is not cost-effective compared to generic prescription formulations of omeprazole and pantoprazole. Low-cost OTC omeprazole is readily available for purchase at several venues (retail pharmacies, commissary, grocery stores, etc.).

The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 1 absent) removing OTC omeprazole and omeprazole magnesium capsules and tablets from the UF, based on cost-effectiveness.

#### **6. PPIs – Capsules and Tablets and Alternative Dosage Form Subclasses—UF/Tier 4/Not Covered and PA Implementation Plan**

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 2 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 and those affected by the removal of OTC omeprazole and omeprazole magnesium from the UF.

#### **7. Physician’s Perspective**

Currently, we have over 690,000 patients on a PPI; this has decreased from a high of 880,000 patients back in 2015. The decrease is likely due to a combination of factors to include deprescribing efforts and greater awareness of the safety concerns with the class. We currently spend over \$112 million dollars yearly on the PPIs, however, this is likely to decrease due to the reduction in utilization, and also price reductions with the generic PPIs.

With the current recommendations, we are now moving generic Nexium back to formulary status, however it will be non-step-preferred. The approximately 24,000 patients on Nexium will see the reduction in copay.

One other change is that generic Aciphex stays UF, but goes from step-preferred to non-step-preferred. There are currently some supply issues with generic Aciphex. For both Nexium and Aciphex, the new step therapy criteria will only apply to new patients. We will continue to monitor the prices of generic Nexium and Aciphex and consider removing the step therapy requirements once the prices fall closer to that of generic Prilosec and Protonix.

Dexilant has been NF since May 2009, with esomeprazole strontium NF since May 2014. Both drugs have also had the step therapy and PA requirements in place.

For Dexilant, the Tier 4 status was recommended clinically due to lack of a clear clinical benefit relative to other agents, safety issues identified by the FDA, and the high discontinuation rate due to adverse reactions found in the clinical trials. A survey of DOD GI specialists also found that the majority were comfortable with Dexilant being not covered. Safety concerns and lack of data to support a clinical benefit relative to other agents for esomeprazole strontium were the basis for the Tier 4 status recommendation.

The Committee did consider having additional PPI candidates for Tier 4 status, but settled on Dexilant and esomeprazole strontium, due to the aforementioned issues with these two drugs.

The alternate dosage forms all currently have step therapy and PA requirements. The Committee is now recommending removal of PAs for the majority of the alternate dosage forms and only leaving PAs in place for the two drug which are currently NF – Zegerid packets and Prevacid ODT. The Committee did acknowledge that the alternate dosage forms are approved for special populations, such as children or for administration in NG or PEG tubes.

For Prevacid ODT and Zegerid packets, children younger than 18 years will not have to go through the PA. Although all patients older than 18 years will be subject to the new PA criteria for these two drugs, we are removing the current step therapy requirements for all alternate dosage forms, and the provider only has to document why the patient can't take the formulary PPIs.

The PPIs have been on the market for almost 30 years. There are now several safety concerns with the drugs if they are used long-term beyond 8 weeks. The Committee did consider different options to ensure that patients are re-assessed for long-term use. However, from an operations perspective, there is no one method that would work for the entire system. For patients who are subject to the PA, this actually does allow the provider an opportunity to consider whether continued use is necessary.

The Committee also recommended removing OTC omeprazole from the formulary. As a reminder, OTC omeprazole has been available for patients with a prescription for that product specifically. This will affect about 1,000 patients (800 of the patients are at Retail). Inexpensive OTC omeprazole products are widely available – for as low as 24 cents per tablet at Costco. The affected patients would need to get a new prescription for the prescription version of omeprazole, or buy the OTC version on their own.

## 8. Panel Questions and Comments

Mr. Ostrowski asks how many beneficiaries are affected by the Tier 4 decision on Dexilant and esomeprazole strontium

Dr. Khoury replies that Dexilant was reviewed last quarter. Currently there are 18,833 patients using the medication and 22 patients are using esomeprazole.

There were no further questions or comments from the Panel. The Chair called for a vote on the UF/Tier 4/Not Covered, Manual PA Criteria, OTC Omeprazole UF Recommendation and the UF/Tier 4/Not Cover and PA Implementation Plan for the Proton Pump Inhibitors.

- **PPI – UF/Tier 4/Not Covered Recommendation**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

- **PPI – Manual PA Criteria**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

- **PPI – OTC Omeprazole UF Recommendation**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

- **PPI – UF/Tier 4/Not Covered and PA Implementation Plan**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

## II. PULMONARY ARTERIAL HYPERTENSION (PAH) AGENTS – PROSTACYCLINS, ENDOTHELIN RECEPTOR ANTAGONISTS (ERAS), AND NITRIC OXIDE DRUGS

(DR. LUGO)

### A. PAH AGENTS

#### 1. PAH Agents - Prostacyclins, ERAs, and Nitric Oxide Drugs—Relative Clinical Effectiveness Analysis and Conclusion

*Background*—The P&T Committee reviewed the clinical effectiveness of the PAH agents, which are divided into the three subclasses outlined below. The class was last reviewed in February 2015. The intravenous prostacyclins (e.g., Flolan and Remodulin) and PDE-5 inhibitors indicated for erectile dysfunction (e.g., Viagra and Cialis) were not included in the review.

- **Endothelin Receptor Antagonists (ERAs):** bosentan (Tracleer), ambrisentan (Letairis brand and generics), and macitentan (Opsumit);
- **Prostacyclins:** treprostinil nebulized solution (Tyvaso), iloprost nebulized solution (Ventavis), treprostinil extended-release oral tablets (Orenitram ER), and selexipag tablets (Uptravi);
- **Nitric Oxide Drugs:** the soluble guanylate cyclase stimulator, riociguat (Adempas) and the PDE-5 inhibitors sildenafil (Revatio brand and generics) and tadalafil (Adcirca, Alyq, and generics).

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

#### *Guidelines*

- Guidelines from the 6<sup>th</sup> World Symposium on PAH were updated in 2019. Key findings include the following:
  - a) Utilizing risk assessment to determine whether to start initial monotherapy or combination therapy in treatment-naïve patients.
  - b) Initial combination therapy is recommended for most patients with World Health Organization (WHO) Group 1 PAH; however, initial monotherapy may be considered for select patients.
  - c) Clinical trial design in PAH is shifting primary endpoints from a short-term correlate such as six-minute walk distance (6MWD) to long-term clinical efficacy measures such as clinical worsening or clinical failure.

- There are no head-to-head studies between the PAH agents in the individual drug subclasses. Comparative efficacy is limited to indirect comparisons, systematic reviews, and meta-analyses.

#### *Endothelin Receptor Antagonists (ERAs)*

- There is insufficient evidence to suggest one ERA is superior to another in terms of efficacy.
- Letairis and Opsumit have the advantage of once daily dosing, while Tracleer is dosed twice daily.
- Generic formulations of Letairis are available.
- Data supporting combination therapy with an ERA and a PDE-5 inhibitor is available with Letairis in treatment-naïve patients (AMBITION trial) and Opsumit in treatment-experienced patients (SERAPHIN trial). Benefits of combination therapy include an improvement in the composite endpoint of time to clinical failure (AMBITION trial), and reduced morbidity/mortality versus placebo or reduced hospitalization versus background therapy (SERAPHIN trial).
- Letairis may cause peripheral edema, while Tracleer has a higher risk of hepatic impairment and requires liver function test (LFT) monitoring.
- All of the ERAs require a Risk Evaluation and Mitigation Strategies (REMS) program for embryo-fetal toxicity (pregnancy category X rating).

#### *Prostacyclins*

- There is insufficient evidence to suggest one oral prostacyclin is superior to another in terms of efficacy. The oral prostacyclins (Uptravi and Orenitram) have advantages over the inhaled agents (Tyvaso and Ventavis), including ease of administration and less frequent dosing, which has resulted in reduced MHS utilization of the inhaled agents.
- Uptravi in the GRIPHON trial showed a 40% reduction in the occurrence of the primary composite endpoint, which included mortality.
- Results from the FREEDOM-EV study showed that early addition of Orenitram ER in patients receiving one oral background PAH agent significantly delayed disease progression.
- An Agency for Healthcare Research and Quality (AHRQ) systematic review (2013) evaluated the association of adverse reactions (ADRs) with the various PAH drug classes. Inhaled prostacyclins are likely to be associated with ADRs such as headaches,

cough, jaw pain, and flushing. With the exception of cough, similar ADRs are seen with the oral prostacyclins.

### *Nitric Oxide Drugs*

- The PAH nitric oxide agents differ in indication, dosing frequency, and pregnancy risk.
- Adempas is the only soluble guanylate cyclase stimulator, is dosed three times daily, has an additional indication for chronic thromboembolic pulmonary hypertension (CTEPH), and requires a REMS due to a pregnancy category X rating.
- For the PDE-5 inhibitors, sildenafil 20 mg is dosed three times daily and tadalafil is dosed as two 20 mg tablets once daily.
- A Cochrane review (2016) of Adempas showed improved 6MWD; however, the results were not statistically significant. Adempas did reduce pulmonary artery pressures. No significant differences were seen in the endpoints of mortality, change in functional class, or clinical worsening.
- Concomitant use of Adempas and the PDE-5 inhibitors should be avoided due to additive adverse reactions.

### *Overall Conclusion*

- The choice of the PAH drug depends on a variety of factors including FDA-approved indication, labeling, mechanism of action, route of administration, side effect profile, drug interactions, patient preference, and physician experience.

## **2. PAH Agents - Prostacyclins, ERAs, and Nitric Oxide Drugs—Relative Cost-Effectiveness Analysis and Conclusion**

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

- CMA results by formulary subclass showed that Letairis was the most cost-effective ERA followed by Opsumit and Tracleer; Adempas was the least cost-effective nitric oxide drug; Tyvaso was the most cost-effective nebulized prostacyclin, followed by Ventavis; and Orenitram ER was the most cost-effective oral prostacyclin followed by Uptravi.
- BIA was performed to evaluate the potential impact of designating selected agents as formulary or non-formulary on the uniform formulary. BIA results found that designating all the PAH drugs as formulary on the uniform formulary demonstrated cost avoidance for the MHS.

### **3. PAH Agents – Prostacyclins, ERAs, and Nitric Oxide Drugs—UF Recommendation**

#### **Endothelin Receptor Antagonists (ERAs)**

- UF
  - a) bosentan (Tracleer)
  - b) ambrisentan (Letairis brand and generics)
  - c) macitentan (Opsumit)

#### **Prostacyclins**

- UF
  - a) treprostinil nebulized solution (Tyvaso)
  - b) iloprost nebulized solution (Ventavis)
  - c) treprostinil extended-release oral tablets (Orenitram ER)
  - d) selexipag (Uptravi)

#### **Nitric Oxide Drugs**

- UF and step-preferred
  - a) sildenafil 20 mg tablets (Revatio brand and generics)
- UF and non-step-preferred
  - a) tadalafil 20 mg (Adcirca, Alyq, and generics)
  - b) riociguat (Adempas)
- For the nitric oxide drugs, note that this recommendation includes step therapy, which requires a trial of sildenafil 20 mg generic in all new users of Adcirca, Alyq, and tadalafil generics or Adempas.
- Note that sildenafil 10 mg/mL oral suspension is also UF, but not part of the step therapy requirements for the other nitric oxide drugs.
- Note that for all the PAH drugs, no products were recommended for NF status.

#### **4. PAH Agents – Prostacyclins, ERAs, and Nitric Oxide Drugs—Manual PA Criteria**

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) new manual PA criteria in new users for the ERAs (Tracleer, Letairis, and Opsumit) and the prostacyclins (Ventavis, Tyvaso, Orenitram ER, and Uptravi). Updated step therapy and manual PA criteria were recommended in new users for Adempas and Adcirca, Alyq, and tadalafil generics requiring a trial of sildenafil 20 mg.

##### **a. Letairis brand and Opsumit**

Manual PA criteria apply to new users of Letairis or Opsumit.

Manual PA Criteria: Letairis or Opsumit is approved if all criteria are met:

- Prescribed by or in consultation with a cardiologist or a pulmonologist
- Patient has documented diagnosis of WHO group 1 PAH
  - a) Patient has had a right heart catheterization (documentation required)
  - b) Results of the right heart catheterization confirm the diagnosis of World Health Organization (WHO) group 1 PAH
- Patient and provider are enrolled in the Letairis or Opsumit REMS program
- Patient is not pregnant
- Women of childbearing potential must use adequate contraception
- Patient has no history of liver function test (LFT) elevations on previous endothelin receptor antagonist (ERA) therapy accompanied by signs or symptoms of liver toxicity or increases in bilirubin greater than two times the upper limit of normal
- Patient does not have moderate or severe liver impairment (e.g., Child-Pugh Class B or C)

Non-FDA-approved uses are not approved.

Prior authorization does not expire.

##### **b. Generic ambrisentan**

Manual PA criteria apply to new and current users of generic ambrisentan.

Manual PA Criteria: Ambrisentan generics are approved if all criteria are met:

- a) The brand Letairis formulation is the preferred product over generic Letairis (ambrisentan). Although Letairis is a branded product, it will be covered at the generic formulary copayment or cost-share.
- b) The provider must document a patient-specific justification as to why the brand Letairis product cannot be used in this patient.
- c) AND the patient must meet the criteria for Letairis:
- d) Prescribed by or in consultation with a cardiologist or a pulmonologist
- e) Patient has documented diagnosis of WHO group 1 PAH
  - Patient has had a right heart catheterization (documentation required)
  - Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH
- f) Patient and provider are enrolled in the ambrisentan REMS program
- g) Patient is not pregnant
- h) Women of childbearing potential must use adequate contraception
- i) Patient has no history of liver function test (LFT) elevations on previous endothelin receptor antagonist (ERA) therapy accompanied by signs or symptoms of liver toxicity or increases in bilirubin greater than two times the upper limit of normal.
- j) Patient does not have moderate or severe liver impairment (e.g., Child-Pugh Class B or C)

Non-FDA-approved uses are not approved.

Prior authorization does not expire.

**c. Tracleer**

Manual PA criteria apply to new users of Tracleer.

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

- Prescribed by or in consultation with a cardiologist or a pulmonologist
- Patient has diagnosis of WHO group 1 or 4 (see below)

- Patient has documented diagnosis of WHO group 1 PAH
  - a) Patient has had a right heart catheterization (documentation required)
  - b) Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH OR
- Patient has documented diagnosis of Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO group 4) and the patient has tried Adempas or has a contraindication to Adempas
- Patient and provider are enrolled in the Tracleer REMS program
- Patient is not pregnant
- Women of childbearing potential must use adequate contraception
- Patient does not have baseline elevated aminotransferases greater than three times the upper limit of normal due to difficulty in monitoring for hepatotoxicity
- Patient does not have moderate or severe liver impairment (e.g., Child-Pugh Class B or C)

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**d. Ventavis and Tyvaso**

Manual PA criteria apply to new users of Ventavis or Tyvaso.

Manual PA Criteria: Ventavis or Tyvaso is approved if all criteria are met:

- Prescribed by or in consultation with a cardiologist or a pulmonologist
- Patient has documented diagnosis of WHO group 1 PAH
  - a) Patient has had a right heart catheterization (documentation required)
  - b) Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**e. Uptravi and Orenitram ER**

Manual PA criteria apply to new users of Uptravi or Orenitram ER.

Manual PA Criteria: Uptravi or Orenitram ER is approved if all criteria are met:

- Prescribed by or in consultation with a cardiologist or a pulmonologist
- Patient has documented diagnosis of WHO group 1 PAH
  - a) Patient has had a right heart catheterization (documentation required)
  - b) Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH
- Patient meets one of the following criteria
  - a) The patient has tried one oral therapy for PAH from one of the three following different categories (either alone or in combination) each for  $\geq$  60 days: one PDE-5 inhibitor (tadalafil or sildenafil), one ERA (Letairis, Opsumit, or Tracleer), or Adempas; OR
  - b) The patient has tried one prostacyclin therapy (oral, IV, or nebulized)

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**f. Adempas**

Manual PA criteria apply to new users of Adempas.

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

- Prescribed by or in consultation with a cardiologist or a pulmonologist
- Patient has a documented diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) WHO Group 4 PAH

OR

- Patient has documented diagnosis of WHO group 1 PAH
  - a) Patient has had a right heart catheterization (documentation required)
  - b) Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH

- Patient has had an adequate trial of sildenafil 20 mg (Revatio brand or generics) and failed or did not respond to therapy AND
- Patient has had an adequate trial of tadalafil 40 mg (Adcirca brand or generics) and failed or did not respond to therapy AND
- Patient is not receiving PDE-5 inhibitors or nitrates concomitantly

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**g. Adcirca, Alyq, and generics**

Manual PA criteria apply to new users of tadalafil 20 mg (Adcirca brand and generics) and Alyq.

Manual PA Criteria: Tadalafil 20 mg (Adcirca brand and generics) or Alyq is approved if all criteria are met:

- Prescribed by or in consultation with a cardiologist or a pulmonologist
- Patient has documented diagnosis of WHO group 1 PAH
  - a) Patient has had a right heart catheterization (documentation required)
  - b) Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH
- Patient has had an adequate trial of sildenafil 20 mg (Revatio brand and generics) and failed or did not respond to therapy and
- Patient is not receiving other PDE-5 inhibitors, nitrates, or riociguat (Adempas) concomitantly

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**5. PAH Agents – Prostacyclins, ERAs, and Nitric Oxide Drugs—Brand over Generic Requirement for ambrisentan (Letairis) and PA Criteria**

TRICARE Policy requires dispensing of generic products at the Retail Network and Mail Order Pharmacy. However, pricing for the branded Letairis is more cost-effective than the AB-rated generic formulations for ambrisentan, which were launched in March 2019. Therefore, branded Letairis will continue to be dispensed,

and the generic will only be available with prior authorization (i.e., the reverse of the current brand to generic policy).

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) requiring brand Letairis over generic ambrisentan in all new and current users, based on cost-effectiveness. The prescriber will provide patient-specific justification as to why branded Letairis cannot be used. The Tier 1 (generic) copayment will apply to brand Letairis. The “brand over generic” requirement will be removed administratively when it is no longer cost-effective compared to the AB-rated generics.

#### **6. PAH Agents – Prostacyclins, ERAs, and Nitric Oxide Drugs—Brand Letairis Copayment Change**

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) lowering the current cost-share for the endothelin receptor antagonist Letairis to the generic Tier 1 cost-share.

The authority for this recommendation is codified in 32 CFR 199.21(j)(3), which states that "when a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate."

#### **7. PAH Agents – Prostacyclins, ERAs, and Nitric Oxide Drugs—UF and PA Implementation Plan**

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) an effective date of the first Wednesday 90 days after the signing of the minutes in all points of service (POS).

#### **8. Physician’s Perspective**

This is the second time that the PAH drugs have been reviewed. No drugs are currently NF, and no drugs were recommended for NF or Tier 4 status at this review.

There are about 1,000 patients in the MHS with PAH, and yearly expenditures for these drugs (excluding sildenafil and Adcirca) are approximately \$100 million dollars.

The major changes from the previous review are that there are new PA recommendations for the prostacyclins and the ERAs; these drugs don’t currently have PAs in place. The PAs are recommended to ensure that the patient has the diagnosis of PAH, and for safety; for example the ERAs require liver monitoring and are teratogenic.

A review of at least eight other health care plans showed that these drugs all are widely managed with PAs. The PAH clinical specialist we talked to also commented that providers are used to completing PA paperwork, since insurance plans routinely require PAs.

For the prostacyclins and the ERAs, only new users will be affected by the PAs; patients who are currently receiving one of these drugs won't have to go through the PA, so these patients are "grandfathered".

For the nitric oxide drugs Adempas and Adcirca, PA requirements have been in place since the first review in February 2015. One change was requiring that the nitric oxide drugs be prescribed by or in consultation with a pulmonologist or cardiologist. Both sildenafil and tadalafil were recommended to be tried before Adempas, based on the comments from the PAH specialist and cost effectiveness. Adempas has no benefits over the PDE-5 inhibitors, other than for CTEPH patients. Patients with the unique indication of CTEPH do not have to try a PDE-5 inhibitor first.

Adcirca has always had the requirement to try sildenafil first. Even though Adcirca generics have recently entered the market, they are not cost-effective compared to sildenafil. The PAH clinical specialist we spoke with did consider the PDE-5 inhibitors as therapeutically interchangeable for PAH. We will continue to monitor the price of the Adcirca generics, and update PA criteria accordingly.

The Committee did look at the clinical practice guidelines, individual clinical trials, current utilization patterns in DoD, and also consulted with an outside PAH specialist when considering the PA criteria.

## **9. Panel Questions and Comments**

Dr. Peloquin requests clarification on the PA criteria for Uptravi and Orenitram. Does the patient have to try one prostacyclin therapy to meet the criteria? The PA is confusing.

Dr. Lugo responds that is one of the options. If a patient has tried one prostacyclin therapy they do meet the criteria. Basically, the patient has to try one oral therapy for PAH from one of the three categories mentioned in the background information. For example, if the patient has been on a PDE-5 or an ERA they can move to a prostacyclin. If the patient has been on an inhaled prostacyclin, they can move over to an oral prostacyclin.

There were no further questions or comments from the Panel. The Chair called for a vote on the UF Recommendation, Manual PA Criteria, Brand over Generic Requirement for Ambrisentan (Letairis) and PA Criteria, Brand Letairis Copayment change and UF and PA Implementation Plan for the Pulmonary Arterial Hypertension (PAH) Agents.

- **PAH Agents – UF Recommendation**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

- **PAH Agents – Manual PA Criteria**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

- **PAH Agents – Brand over Generic Requirement for ambrisentan (Letairis) and PA Criteria**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

- **PAH Agents – Brand Letairis Copayment Change**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

- **PAH Agents – UF and PA Implementation Plan**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

### **III. NEWLY APPROVED DRUGS PER 32 CFR 199.21(g)(5)**

#### **(DR. LUGO)**

#### **A. Newly Approved Drugs per 32 CFR 199.21(g)(5)**

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

The P&T Committee agreed (17 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).

##### **2. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF Recommendation**

The P&T Committee recommended (group 1: 17 for, 0 opposed, 0 abstained, 1 absent; group 2: 18 for, 0 opposed, 0 abstained, 0 absent; Tirosint-SOL: 10 for, 7 opposed, 1 abstained, 0 absent) the following:

- UF:
  - a) cladribine (Mavenclad) – Multiple Sclerosis Agents: Oral Agents
  - b) epinephrine injection (Symjepi) – Respiratory Agents Miscellaneous\
  - c) levodopa inhalation powder (Inbrija) – Parkinson’s Agents
  - d) levothyroxine sodium oral solution (Tirosint-SOL) – Thyroid and Antithyroid Agents
  - e) loteprednol etabonate 0.38% ophthalmic gel (Lotemax SM) – Anti-inflammatory Immunomodulatory Ophthalmic Agents: Ophthalmic Anti-inflammatory Agents
  - f) netarsudil 0.02%/latanoprost 0.005% ophthalmic solution (Rocklatan) – Glaucoma Agents
  - g) siponimod (Mayzent) – Multiple Sclerosis Agents: Oral Miscellaneous
  - h) stiripentol (Diacomit) – Anticonvulsants-Antimania Agents
  - i) tacrolimus oral suspension (Prograf) – Immunosuppressives
- NF:
  - a) benzhydrocodone/acetaminophen (Apadaz) – Narcotic Analgesics and Combinations
  - b) estradiol 1 mg/progesterone 100 mg capsules (Bijuva) – Gynecological Agents Miscellaneous
  - c) meloxicam ODT (Qmiiz ODT) – Pain Agents: NSAID
  - d) prucalopride (Motegrity) – Gastrointestinal-2 Agents: Chronic Idiopathic Constipation (CIC) and Irritable Bowel Syndrome Constipation-Predominant (IBS-C)

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

The P&T Committee recommended (group 1: 17 for, 0 opposed, 0 abstained, 1 absent; group 2: 18 for, 0 opposed, 0 abstained, 0 absent; Tirosint-SOL: 10 for, 7 opposed, 1 abstained, 0 absent) the following:

- Applying the same manual PA criteria for Rocklatan in new users as is currently in place for Rhopressa.
- Applying manual PA criteria to new and current users of Mavenclad, Mayzent, Motegrity, and Qmiiz ODT.
- Applying manual PA criteria to new users of Inbrija.
- Applying an automated age edit to new and current users of Tirosint-SOL and new users of Prograf solution. Patients younger than 6 years for Tirosint solution and younger than 12 years for Prograf solution will not be subject to the PA.

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

**a. cladribine (Mavenclad)**

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

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

- Prescribed by a neurologist
- Patient has a documented diagnosis of one of the following:
  - a) Relapsing-Remitting Multiple Sclerosis
  - b) Active Secondary Progressive Multiple Sclerosis
- Patient is not currently using a disease-modifying therapy (DMT)
- Patient has failed another DMT
- Mavenclad is not used in patients with:
  - a) Current malignancy
  - b) Pregnant women or breastfeeding
  - c) Men and women of reproductive potential who do not plan to use effective contraception during treatment and 6 months after the last dose
  - d) Active chronic infection (e.g., hepatitis, tuberculosis, or HIV infection)
- Monitoring for hematological and lymphocytic parameters will occur before, during, and after treatment

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**b. levodopa inhalation powder (Inbrija)**

Manual PA criteria apply to all new users.

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

- Age  $\geq$  18 years
- Patient has a diagnosis of Parkinson's disease
- Inbrija is prescribed by or in consultation with a neurologist
- Patient continues to experience wearing off periods, despite optimizing carbidopa/levodopa therapy (e.g., increasing the dose or increasing the frequency of dosing)
- Patient is currently taking and will continue taking carbidopa-levodopa therapy
- Inbrija is not being used concomitantly with, or within 2 weeks of, a non-selective monoamine oxidase (MAO) inhibitor (e.g., phenelzine, tranylcypromine, isocarboxazid, hydracarbazine)
- Patient does not have chronic underlying pulmonary disease (e.g., asthma, COPD)

Non-FDA-approved uses are not approved.  
Prior authorization expires in one year.

Renewal Criteria: PA will be renewed indefinitely if the patient:

- Has had a documented reduction in motor symptoms associated with "off" periods of Parkinson's disease, and
- Is not taking an MAO inhibitor, and does not have a chronic underlying pulmonary disease (e.g., asthma, COPD).

**c. levothyroxine sodium solution (Tirosint-SOL)**

PA does not apply to patients younger than 6 years of age (age edit)

PA criteria apply to all new and current users of Tirosint-SOL 6 years of age and older.

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

- Patient is not able to chew a levothyroxine tablet
- Patient is not able to swallow a capsule or tablet
- Drug is prescribed by or in consultation with an endocrinologist

Non-FDA-approved uses are not approved.

PA expires after 12 months. No renewal allowed; must fill out a new PA.

**d. meloxicam orally disintegrating tablets (ODT) (Qmiiz ODT)**

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

Manual PA Criteria: Coverage for Qmiiz will be approved if:

- Note: Multiple formulary NSAIDs, including meloxicam oral tablets, are available for DoD beneficiaries without a PA.
- The provider must state the clinical rationale of why the patient cannot take any of the formulary NSAIDs.

Non-FDA-approved uses are not approved.

Prior authorization expires in one year.

Renewal criteria – No renewal criteria. PA will be renewed for an additional year if a new PA form is completed.

**e. netarsudil 0.02%/latanoprost 0.005% ophthalmic solution (Rocklatan)**

Manual PA criteria apply to all new users of Rocklatan.

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

- Written by an ophthalmologist or an optometrist
- Patient has had a trial of appropriate duration of 2 different formulary options from different drug classes in combination or separately and has not reached intraocular pressure (IOP) target goals
  - a) Prostaglandin analogs
  - b) Beta-blockers

- c) Alpha 2-adrenergic agonists
- d) Topical carbonic anhydrase inhibitors

Non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**f. prucalopride (Motegrity)**

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

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

- Patient is  $\geq 18$  years of age
- Patient has tried and failed all formulary agents including Amitiza, Linzess, and Trulance
- Patient has documented symptoms for  $\geq 3$  months
- Patient has diagnosis of chronic idiopathic constipation (CIC)
- Patient does not have a GI obstruction
- Patient has no history of suicidal ideation
- Patient has low cardiovascular risk
- Patient has documentation of failure of an increase in dietary fiber/dietary modification
- Patient has tried at least 2 standard laxative classes or has an intolerance or FDA-labeled contraindication to at least 2 standard laxative classes defined as:
  - a) osmotic laxative (e.g., lactulose, sorbitol, magnesium [Mg] citrate, Mg hydroxide, glycerin rectal suppositories)
  - b) bulk forming laxative (e.g., psyllium, oxidized cellulose, calcium polycarbophil) with fluids;
  - c) stool softener (e.g., docusate);
  - d) stimulant laxative (e.g., bisacodyl, sennosides)

- Patient is not taking any of these agents concomitantly (Amitiza, Linzess, Trulance, Symproic, Relistor, Movantik)

Non-FDA-approved uses are not approved.

Initial Expiration date: 1 year; Renewal PA (continuation): 1 year

Renewal PA Criteria: Motegrity will be approved for an additional 12 months if the following are met:

- Patient has had improvement in constipation symptoms
- Patient is not taking any of these agents concomitantly (Amitiza, Linzess, Trulance, Symproic, Relistor, Movantik)
- Patients are monitored for suicidal risk

**g. siponimod (Mayzent)**

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

Manual PA criteria: Coverage will be approved if all criteria are met:

- Prescribed by a neurologist
- A documented diagnosis of one of the following:
  - a) Clinically Isolated Syndrome
  - b) Relapsing-Remitting Multiple Sclerosis
  - c) Active Secondary Progressive Multiple Sclerosis
- Patient is not currently using another disease-modifying therapy (DMT)
- Patient has not failed an adequate course of fingolimod (Gilenya)
- All recommended Mayzent monitoring has been completed, and patient will be monitored throughout treatment as recommended in the label. Monitoring includes complete blood count (CBC), liver function tests (LFT), varicella zoster virus (VZV) antibody serology, genotyping of CYP2C9, electrocardiogram (ECG), and macular edema screening.
- In patients with CYP2C9 \*1/\*3 or \*2/\*3 maintenance dosing will be 1 mg daily
- Mayzent will not be used in patients with a CYP2C9 \*3/\*3 genotype

- Mayzent will not be used in patients with significant cardiac history, including:
  - a) Patients with a recent history (within the past 6 months) of class III/IV heart failure, myocardial infarction, unstable angina, stroke, transient ischemic attack, or decompensated heart failure requiring hospitalization
  - b) Patients with a history or presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless a functioning pacemaker is inserted

Non-FDA-approved uses are not approved.  
 Prior authorization does not expire.

**h. tacrolimus oral suspension (Prograf)**

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

PA criteria apply to all new users of Prograf solution 12 years of age and older.

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

- Prescribed by or in consultation with a transplant specialist AND
- Has severe dysphagia (e.g., severe esophagitis, mucositis) or is completely unable to swallow (e.g., has G-tube) OR
- Patient is < 18 years old and has difficulty swallowing tablets/capsules

Applies to new users (grandfathering allowed).  
 PA does not expire.

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

The P&T Committee recommended (group 1: 17 for, 0 opposed, 0 abstained, 1 absent; group 2: 18 for, 0 opposed, 0 abstained, 0 absent) an effective date upon the first Wednesday two weeks after the signing of the minutes in all points of service.

**5. Physician’s Perspective**

There were a total of 13 new drugs reviewed. The decrease from the usual number of 30 drugs was likely due to the Federal government shutdown last Fall, which resulted in a lower number of year end approvals than we normally see.

For the 13 new drugs, 9 were recommended for UF status, with 4 recommended for NF status. No drugs were selected for Tier 4 status.

A total of 8 drugs were recommended for PAs. Of these 8 drugs, four were recommended to have “no grandfathering”, in that both new and current users will be affected by the PA. “No grandfathering” was recommended for the 2 MS drugs (Mavenclad and Mayzent) due to safety concerns. For Motegrity, the PA is very similar to the other chronic idiopathic constipation drugs that were reviewed in November 2018 that also affected new and current users. The NSAID Qmiiz is just an orally dissolving formulation of meloxicam, which has been available as a generic for several years.

Two of the drugs that are marketed in oral solutions both the thyroid drug Tirosint and the anti-rejection drug Prograf, have age edits in the PA criteria so that children won't be affected by the PA.

## **6. Panel Questions and Comments**

Dr. Peloquin notices there was a 10-7 vote on the Tirosint and asks if more can be shared regarding the vote.

Dr. Lugo responds that it was a split vote because the committee could not decide if it should be Formulary, Non-formulary or Tier 4.

Dr. Lugo states that the committee did vote to move the Tirosint to Uniform Formulary. There was a lot of discussion on whether to add a PA, not add PA, or move Levothyroxine to Tier 4 because it has been around for a really long time. There were also questions/concerns about age criteria for the PA. The pediatric endocrinologist stated that 3-year olds can chew and swallow the tablet. Due to the concerns voiced by the committee, the age criteria was increased to 6 years old. The pediatric endocrinologist said that a 4 years old patients can chew the tablet. The PA expires annually to re-evaluate whether or not the patient can chew the tablets.

Dr. Dager has questions about the PA process for current users. Do they come off the medication or is it renewed?

Dr. Khoury responds, as of June 17, Qmiiz, Mayzent, and Mavenclad have no current users in our system. The manual PA criteria for these three drugs impacts new and current users. The manual PA criteria also impacts new and current users for Motegrity and Tirosint. Motegrity having new and current users be impacted is a result of it being part of a class with similar recommendations. When we reviewed the class, the PA was a requirement for all new and current users. The committee followed the same approach for this decision. There were safety and clinical efficacy concerns. For instance, the patients did not maintain the drug over time. There were a lot of reasons we wanted to make sure new and current users were reassessed. Currently, 43 patients are impacted by the committee decision for the Tirosint solution. The majority are not in the 0-4 year old age group but are patients over 18

years old. We want ensure and validate that those patients need the drug.

Dr. Dager asks for clarification about the process to implement the PA operationally when patients are already on the drug.

Dr. Khoury replies that when the claim comes through they'll be faced with the prior authorization.

Ms. Buchanan asks why they are looking at UF and PA Implementation plan effective upon the first Wednesday 2 weeks after the signing.

Lugo responded that she misspoke. It's not 90 days; it 2 weeks after the signing of the minutes.

Ms. Buchanan asks if that's enough time.

Dr. Lugo answered that it is given our number of utilizers on these agents.

Dr. Khoury states it is our intent to move new drugs as appropriate off of non-formulary status as quickly as possible. Otherwise, the patient would be forced to pay the \$53 co-pay at mail for a 90-day supply or a \$54 co-pay at retail for 30-day supply. The 2-week implementation period benefits the patient because they avoid paying the higher co-pay.

Dr. Spatz brings it back to initial question regarding the vote for Tirosint. What is driving this discussion? Is it an issue with the age criteria for the PA or is it about the cost of the solution as compared to the tablets

Dr. Khoury responded that it was a very lengthy discussion and multiple providers had differences of opinion on both. Whether it should be formulary and available to patients. Whether it was needed. Dr. Lugo mentioned that the committee members were supportive of moving it to Tier 4 because they saw no clinical need for the medication. According to the endocrinologist, there were other options available to the patients. The committee also expressed concerns about who really needs the medication and methods to ensure those patients receive it. Others supported a formulary status over non-formulary to ensure patients were aware of the cost perspective from the system side. Also, the committee wanted to ensure, via the PA process, that the medication was needed. As you saw with the vote, there was no unanimity among the committee members. There were opinions on both sides.

Dr. Spatz responds, there was never a question of clinical efficacy for the drug, it was just about the cost differential between the generic and the levothyroxine which has been around since whenever as compared to this agent.

Dr. Khoury responds yes, it is the new formulation, specifically.

Dr. Piirainen looked at the PAs. It states that Non-FDA or usage not approved. Do you require prescribers to put in a diagnosis code or something to show what they will use it for?

Dr. Khoury replied that depends on the PA. It is not a requirement as a standard.

Dr. Piirainen responds it is just a statement for them to be aware but not required.

Dr. Khoury answered if there is an alternate diagnosis the patient is trying to use the drug for, the language is there for them to abide by that.

There were no further questions or comments from the Panel. The Chair called for a vote on the UF Recommendation, PA Criteria, and UF and PA Implementation plan for the Newly Approved Drugs per 32 CFR 199.21(g)(5).

- **Newly Approved Drugs per 32 CFR 199.21(g)(5) – UF Recommendation**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

- **Newly Approved Drugs per 32 CFR 199.21(g)(5) –PA Criteria**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

- **Newly Approved Drugs per 32 CFR 199.21(g)(5) – UF and PA Implementation**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

#### **IV. UTILIZATION MANAGEMENT—NEW MANUAL PA CRITERIA**

**(LT COL KHOURY)**

**New PA Criteria:** New manual PA criteria were recommended for the following drugs, which will be discussed below.

##### **A. NEWLY APPROVED DRUGS NOT SUBJECT TO 32 CFR 199.21(g)(5)**

- 1. NEWLY APPROVED DRUGS NOT SUBJECT TO 32 CFR 199.21(g)(5):  
Antihistamine-1: First generation and combinations – Carbinoxamine maleate 6 mg tablets (Ryvent brand and generics) and Carbinoxamine maleate 4 mg/5 mL ER oral suspension (Karbinal ER)**

Ryvent brand and generics and Karbinal ER are new drugs 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 or new drug

reviews. These ANDA-approved products contain ingredients that are currently available in generic products or were included in formulations previously removed from the market.

Carbinoxamine maleate is a first-generation antihistamine and is available in 4 mg and 6 mg generic tablets, 6 mg brand tablets (Ryvent), 4 mg/5 mL immediate release oral solution, and a 4 mg/5 mL ER suspension (Karbinal ER). Ryvent brand and generics and Karbinal ER are not cost-effective relative to the generic 4 mg tablets and 4 mg/5 mL IR oral solution. Cost-effective generic formulations of carbinoxamine 4 mg oral tablets and IR solution are available on the UF without a PA required. Low-cost OTC tablet formulations for diphenhydramine, fexofenadine, or dimenhydrinate tablets and low-cost OTC liquid formulations for diphenhydramine, fexofenadine, or loratadine are widely available.

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) manual PA criteria for Ryvent brand and generics and Karbinal ER in new and current users, due to the significant cost differences and lack of clinically compelling benefits over generic alternatives.

The manual PA criteria are as follows:

Manual PA criteria apply to all new and current users of carbinoxamine 6 mg tablets (Ryvent brand and generics) and 4 mg/5 mL ER oral suspension (Karbinal ER).

**Note:** Carbinoxamine generic IR liquid and 4 mg tablets are available without a PA; providers are encouraged to consider changing the prescription to generic IR liquid or 1 or 2 of the 4 mg tablets.

Coverage for carbinoxamine 6 mg tablets (Ryvent brand and generics) or Karbinal ER suspension will be approved if:

- This agent has been identified as having cost-effective alternatives. The provider must describe why this drug is required as opposed to available alternatives.

Non-FDA-approved uses are not approved.

Prior authorization does not expire.

- **Insulins: Rapid Acting Agents: generic insulin lispro (authorized generic for Humalog)**

An authorized generic for Humalog entered the market in April 2019. An “authorized generic” is the brand company's own product repackaged and marketed as a generic drug. An authorized generic is considered therapeutically equivalent to the name brand drug because it is the same drug. The FDA does not consider authorized generics as AB-rated generic formulations.

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) manual PA criteria for the authorized generic insulin lispro in new and current

users, requiring a trial of branded Humalog, due to cost-effectiveness. The PA requirement will be removed when it is no longer cost advantageous. The manual PA criteria are as follows:

Manual PA criteria apply to all new and current users of insulin lispro (authorized generic for Humalog). Coverage is approved if all criteria are met:

- a) Note: Brand Humalog is the preferred insulin lispro product in the DoD. If the prescription is for Humalog, prior authorization is not required.
- b) The provider must provide a patient-specific justification as to why the brand Humalog product cannot be used.

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

- **Oral Oncologic Agents: niraparib (Zejula), olaparib (Lynparza), and rucaparib (Rubraca)**

PA criteria have not previously been required for the ovarian cancer drugs (PARP inhibitors). The P&T Committee reviewed three oral oncologic agents, Zejula, Lynparza, and Rubraca. PA criteria were recommended for these three products in new users, in order to assure prescribing in accordance with FDA-approved indications or a National Comprehensive Cancer Network (NCCN) Guideline-endorsed indication.

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) manual PA criteria for new users.

- a. niraparib (Zejula)**

Manual PA criteria apply to all new users of Zejula.

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

- Zejula is prescribed by or in consultation with a hematologist/oncologist
- Patient is 18 years of age or older
- Patient has a deleterious or suspected deleterious BRCA mutation as detected by an FDA-approved test
- Zejula will be prescribed as a maintenance therapy for one of the following diagnoses:

a) Recurrent epithelial ovarian cancer, fallopian tube or primary peritoneal cancer

AND

b) Patient has received 2 or more lines of platinum-based chemotherapy

AND

c) Patient was in objective response (either complete or partial) to most recent treatment regimen AND

d) Zejula will not be combined with bevacizumab (Avastin)

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, the provider must list the diagnosis.
- Female patients are not pregnant or planning to become pregnant and will take highly effective contraception while taking Zejula and for 6 months after the last dose.

Other non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**b. olaparib (Lynparza)**

Manual PA criteria apply to all new users of Lynparza.

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

- Lynparza is prescribed by or in consultation with a hematologist/oncologist
- Patient is 18 years of age or older
- Patient has a deleterious or suspected deleterious BRCA mutation as detected by an FDA-approved test
- Patient will use Lynparza as either treatment or maintenance therapy for one or more of the following diagnoses:
  - a) Recurrent or Stage IV Triple negative breast cancer OR

- b) Recurrent or Stage IV hormone receptor (+) (ER, PR, or both) HER2 (-) breast cancer AND the patient was either:
    - Previously treated with prior endocrine therapy OR
    - The patient was not an appropriate candidate for endocrine therapy OR
  - c) Recurrent advanced ovarian cancers (either platinum-sensitive or platinum-resistant), fallopian tube or primary peritoneal cancers AND
    - Patient has received at least 3 prior lines of therapy
    - Lynparza will be used as a single agent
  - Lynparza will be prescribed as maintenance therapy for one of the following diagnoses:
    - a) Platinum-sensitive, relapsed, epithelial ovarian cancer, fallopian tube or primary peritoneal cancer AND
      - Patient has received 2 or more lines of platinum-based chemotherapy
      - Patient was in objective response (either complete or partial) to most recent treatment regimen
      - Lynparza will not be combined with bevacizumab (Avastin) OR
    - b) Newly diagnosed, advanced, high-grade, epithelial ovarian cancer, fallopian tube or primary peritoneal cancer AND
      - Patient has had a complete or partial response to primary therapy with a platinum-based therapy
      - Lynparza will not be combined with bevacizumab (Avastin)
- 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, the provider must list the diagnosis.

- Female patients are not pregnant or planning to become pregnant and will take highly effective contraception while taking Lynparza and for 6 months after the last dose.

Other non-FDA-approved uses are not approved.  
Prior authorization does not expire.

**c. rucaparib (Rubraca)**

Manual PA criteria apply to all new users of Rubraca.

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

- Rubraca is prescribed by or in consultation with a hematologist/oncologist
- Patient is 18 years of age or older
- Patient has a deleterious BRCA mutation as detected by an FDA-approved test
- Rubraca will be prescribed for one of the following:
  - a) Treatment of recurrent, high-grade, epithelial ovarian cancer (platinum-sensitive or platinum-resistant), fallopian tube or primary peritoneal cancer AND
    - Patient has received at least 2 prior lines of therapy
    - Rubraca will be used as a single agent
  - b) Maintenance of relapsed platinum-sensitive ovarian cancer, fallopian tube or primary peritoneal cancer AND
    - Patient has received 2 or more lines of platinum-based chemotherapy
    - Patient was in objective response (either complete or partial) to most recent treatment regimen
    - Rubraca will not be combined with bevacizumab (Avastin)
  - c) Newly diagnosed, advanced, high-grade, ovarian cancer, fallopian tube or primary peritoneal cancer AND

- Patient has had a complete or partial response to primary therapy with a platinum-based therapy
- Rubraca will not be combined with bevacizumab (Avastin)

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, the provider must list the diagnosis: \_\_\_\_\_.
- Female patients are not pregnant or planning to become pregnant and will take highly effective contraception while taking Rubraca and for 6 months after the last dose.

Other non-FDA-approved uses are not approved.  
Prior authorization does not expire.

## 2. New PA Criteria—PA Implementation

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) new PAs for Ryvent brand and generics, Karbinal ER suspension, Rubraca, Lynparza, and Zejula become effective 90 days after the signing of the minutes. DHA will send letters to beneficiaries affected by the new PA requirements for Ryvent brand and generics and Karbinal ER if applicable, as new and current users will be subject to the PA.

## 3. Physician’s Perspective

- **Carbinoxamine 6 mg tabs (Ryvent) and ER suspension (Karbinal)**

We are seeing more of these products get approved that are only slight variations of older drugs. The PA criteria will apply to the both the 6 mg generic and brand tablets, and the branded suspension. This is very similar to what we saw at the last meeting with another first generation antihistamine syrup (Ryclora).

There are other antihistamines that are available as oral syrups, both as prescription or OTC products. The Committee could not come up with a clinical reason as to why these two products would be needed instead of the generic 4 mg tablets and immediate release suspension or the other widely available and low cost antihistamine syrups.

- **Insulin Lispro (Humalog) – Brand preferred**

The recommendation here is to prefer the branded Humalog product over the

authorized generic. The authorized generic and the branded products all come from the same manufacturer, however the branded product Humalog product is more cost effective than the authorized generics.

If the prescription is written for Humalog, the patient will receive Humalog. The patient will only be subject to the PA if the prescription is written for the authorized generic as “insulin lispro”. Both of these products are charged at the Tier 2 (brand) copay, so there is no need to decrease the Humalog brand to the Tier 1 (generic) copay.

- **Oncology drugs for ovarian cancer (Zejula, Lynparza, and Rubraca)**

The Committee has been reviewing the oncology drugs to determine which ones do not have PAs in place. PAs were recommended for the ovarian cancer drugs, due to safety issues and to ensure that they are used according to the FDA-labeled indication. We will be updating PA requirements for other oncology drugs, so you will see these types of PAs at upcoming meetings.

For all the oncology drugs, the Committee is working with ESI to evaluate PA requests for off-label uses that are included in the NCCN guidelines or for which there is clinical evidence from a published study. This would allow the PAs to be reviewed for the off-label use as part of the initial review, before having the provider file an appeal. We are working with ESI to gradually implement this type of review process as part of the initial PA review.

#### **4. Panel Questions and Comments**

Dr. Spatz asks for the number of patients impacted by the committee decision for Ryvent and Karinbal ER.

Dr. Khoury replied that he does not have the numbers of patients. What he has is the cost analysis of the comparators that are available. The cost effectiveness of those are about 10 times to 100 times more costly compared to ones that are available.

Dr. Spatz said he doesn't have a problem with that, but are you going to have 500 irate patients or 50,000 irate patients?

Dr. Khoury responded that there is a very small number. In general it's not in the tens of thousands. It's closer to a few hundred.

Ms. Buchanan interjected that it's 267.

Dr. Khoury asked if that came from the back of the paper. It is 267 and specifically identified as current users in the appendix, and apologizes.

There were no further questions or comments from the Panel. The Chair called for a

vote on the New Manual PA Criteria and the PA Implementation Plan for the New Manual PA Criteria.

- **New Manual PA Criteria**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

- **New Manual PA Criteria –PA Implementation Plan**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

## V. UTILIZATION MANAGEMENT—UPDATED MANUAL PA CRITERIA

(LT COL KHOURY)

### A. UPDATED PA CRITERIA

#### 1. Updated PA Criteria

Updates to the step therapy and manual PA criteria for several drugs were recommended by the P&T Committee due to a variety of reasons, including expanded FDA indications. The updated manual PAs outlined below will apply to new users.

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) updates to the manual PA criteria for Qsymia, the weight loss agents, Dupixent, Xeljanz/Xeljanz XR, Cimzia, Humira, and Imbruvica. All updated PA criteria apply to new users of these agents.

The updates are as follows:

- **Corticosteroids: Immune Modulators – Atopic Dermatitis Subclass – dupilumab (Dupixent)**—Manual PA criteria were originally recommended for Dupixent for atopic dermatitis during the May 2017 P&T Committee meeting. The Dupixent PA was then updated to reflect the additional FDA-approved indication for asthma in November 2018. In February and May 2019, the FDA lowered the age for both asthma and atopic dermatitis down to 12 years. The P&T Committee updated the PA to reflect the lower age allowance and also lowered the baseline eosinophils requirement from 300 cells/mcL to 150 cells/mcL, as some benefit was seen at the lower range in the clinical trial.
- **Oral Oncologic Agents**—Ibrutinib (Imbruvica) is an oral oncology agent that was designated as UF prior to the Innovator Rule established in August 2015. In May 2018, the P&T Committee recommended PA criteria for both the tablets and capsules. The committee reviewed the NCCN Guidelines and updated the PA to include an allowance

for an additional indication that carries a Grade 1, 2A, or 2B recommendation from the NCCN Guidelines.

- **Targeted Immunomodulatory Biologics (TIBs): certolizumab (Cimzia) and adalimumab (Humira)**—Cimzia was granted a new FDA indication in March 2019 for non-radiographic axial spondyloarthritis with objective signs of inflammation (nr-ax SpA). Nr-ax SpA is a subtype of spondyloarthritis, a spectrum of disease that also includes ankylosing spondylitis. Guidelines from the Assessment of SpondyloArthritis international Society (ASAS)/European League Against Rheumatism (EULAR) recommend the TNF inhibitors adalimumab (Humira), certolizumab (Cimzia), etanercept (Enbrel), and golimumab (Simponi) for nr-ax SpA, and state that the price of the TNF inhibitor should influence therapy. The P&T Committee updated the Cimzia PA for this additional indication. Although Humira is not approved for treating nr-ax SpA in the United States, clinical trial data is available and it carries this approval by foreign drug regulatory agencies. Based on the ASAS/EULAR guidelines and clinical trial data, the Humira PA was also updated to allow treatment for nr-ax SpA. Patients with nr-ax SpA will still be required to try Humira prior to Cimzia.
- **Targeted Immunomodulatory Biologics (TIBs): tofacitinib citrate (Xeljanz/Xeljanz XR)**—Xeljanz was originally approved for treating rheumatoid arthritis; the indication was later expanded to include psoriatic arthritis and ulcerative colitis in adults. The committee reviewed the new FDA safety alert for increased risk for pulmonary embolism and death in patients taking a 10 mg twice daily dose for rheumatoid arthritis. This dosage is only approved for patients with ulcerative colitis. The P&T Committee updated the PA to limit the 10 mg twice daily dose for the labeled indication of ulcerative colitis.
- **Weight Loss Agents**—The P&T Committee recommended updates to the manual PA criteria for the branded weight loss agents to provide additional clarity regarding step therapy. Patients must first try generic phentermine before use of any of the non-phentermine branded drugs for weight loss. All updated PA criteria apply to new users.
- **Weight Loss Agents: topiramate extended-release/phentermine (Qsymia)**—The P&T Committee recommended updates to the manual PA criteria for Qsymia to include safety concerns regarding pregnancy risk and the REMS program.

## 2. Updated PA Criteria—Implementation Plan

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) updates to the current PA criteria for Qsymia, the weight loss agents, Dupixent, Xeljanz/Xeljanz XR, Cimzia, Humira, and Imbruvica in new users become effective 30 days after the signing of the minutes.

## 3. Physician’s Perspective

At every meeting, we present updates to drugs with existing PAs to ensure the latest

FDA indications or safety updates are included in our criteria. These updates to the existing PAs will only affect new patients.

For Imbruvica, this is another example of an oncology drug where we would like off-label uses evaluated as part of the initial review, if they meet NCCN guideline recommendations.

For the weight loss drugs, the PA updates were to clarify the recommendation from the November 2017 meeting, and to include a safety alert for one of the drugs (Qsymia).

#### **4. Panel Questions and Comments**

There were no questions or comments from the Panel. The Chair called for a vot on the Updated Manual PA Criteria and the PA Implementation Plan for the Updated Manual PA Criteria.

- **Updated Manual PA Criteria**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

- **Updated Manual PA Criteria – PA Implementation Plan**

Concur: 6                      Non-Concur: 0                      Abstain: 0                      Absent: 4

## **VI. BRAND OVER GENERIC AUTHORIZATION FOR FLUTICASONE/SALMETEROL (ADVAIR DISKUS) (LT COL KHOURY)**

### **A. BRAND OVER GENERIC AUTHORIZATION**

Pricing for the branded Advair Diskus product is more cost-effective than the AB-rated generic formulations for fluticasone/salmeterol, which were launched in March 2019. Therefore, the branded Advair Diskus product will continue to be dispensed, and the generic will only be available with prior authorization (i.e., the reverse of the current brand to generic policy). The Tier 1 (generic) copayment will apply to Advair Diskus as outlined in Section IV E on page 17 of the background document. The “brand over generic” requirement for Advair Diskus will be removed administratively when it is no longer cost-effective compared to the AB-rated generics.

#### **1. Advair Diskus Brand over Generic Requirement and PA Criteria**

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) implementing the requirement to prefer the branded Advair product over generic formulations. Manual PA criteria are required for generic fluticasone/salmeterol in the Retail Network and Mail Order Pharmacy. The prescriber will provide patient-

specific justification as to why the branded fluticasone/salmeterol product cannot be used.

## **2. Advair Diskus Brand Copayment**

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) that the brand (Tier 2) formulary cost-share for Advair Diskus in the TRICARE Mail Order Pharmacy and the TRICARE Retail Network Pharmacy be lowered to the generic (Tier 1) formulary cost-share.

## **3. Physician's Perspective**

For Advair, we are recommending our usual “brand over generic” preference. This is a little different that the recommendation made above for the authorized generic for the insulin lispro. For Advair, the generic is from a different manufacturer, unlike the situation with the Humalog authorized generic.

Due to the significant difference in cost in favor of the branded Advair product, this was implemented under administrative authority back on March 6<sup>th</sup>. Patients on the generic inhaler area required to document why they can't use the Advair brand.

Since this is a true generic product, and not an authorized generic, the copay for brand Advair is reduced to the generic copay. The patients on Advair are now benefitting from the Tier 1 (generic) copay.

## **4. Panel's Questions and Comments**

Dr. Spatz states that he is curious about the discussion with the pulmonologist, when they think someone would be indicated to have the generic over the brand situation.

Dr. Khoury asked if he's asking about the reasoning they would say why?

Dr. Spatz responded the reason why they would have the generic instead of the brand. Dr. Khoury replied that they have not reviewed those comments yet. They are interested in those comments as much as he is.

There were no more questions or comments from the Panel. The Chair called for a vote on the Advair Diskus Brand over Generic Requirement and PA Criteria and the Advair Diskus Brand Copayment.

### **• Updated Manual PA Criteria**

Concur: 6

Non-Concur: 0

Abstain: 0

Absent: 4

- **Updated Manual PA Criteria – PA Implementation Plan**

Concur: 6

Non-Concur: 0

Abstain: 0

Absent: 4

Ostrowski ends the meeting and thanks everyone for attending He thanks Col Hoerner and the Staff for their preparation, and thanks the Panel for their time.

*Meeting Adjourned*



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Mr. Jon Ostrowski  
UF BAP Chairperson

**Brief Listing of Acronyms Used in this Summary**

Abbreviated terms are spelled out in full in this summary; when they are first used, the acronym is listed in parentheses immediately following the term. All of the terms commonly used as acronyms in the Panel discussions are listed below for easy reference. The term “Pan” in this summary refers to the “Uniform Formulary Beneficiary Panel,” the group who’s meeting in the subject of this report.

- 6WMD – 6 Minute Walk Distance
- ACG – American College of Gastroenterology
- ADRs – Association of Adverse Reactions
- AHRQ – Agency for Healthcare Research and Quality
- ANDA - Abbreviated New Drug Application
- ASAS - Assessment of SpondyloArthritis international Society
- BAP – Beneficiary Advisory Panel
- BIA – Budget Impact Analysis
- BRCA – Breast Cancer Gene
- CFR – Code of Federal Regulations
- CIC – Chronic Idiopathic Constipation
- CMA – Cost-minimization analysis
- COPD – Chronic Obstructive Pulmonary Disease
- CTEPH – Chronic Thromboembolic Pulmonary Hypertension
- DHA – Defense Health Agency
- DMT – Disease modifying therapy
- DoD – Department of Defense
- ERAs – Endothelin Receptor Antagonists
- EULAR – European League Against Rheumatism
- FDA – Food & Drug Administration
- GERD – Gastroesophageal Reflux Disease
- GI – Gastrointestinal
- HIV – Human Immunodeficiency Virus
- IOP – Intensive Outpatient Treatment
- LFT – Liver Function Test
- Mg – Milligram
- MHS – Military Health System
- MTF – Military Treatment Facility
- NCCN – National Comprehensive Cancer Network
- NDAA – National Defense Authorization Act
- NF – Non-Formulary
- NSAID – Non-steroidal Anti-Inflammatory Drugs
- ODT – Orally dissolving tablet
- OTC – Over-the-Counter

- P&T – Pharmacy & Therapeutics
- PA – Prior Authorization
- PAH – Pulmonary Arterial Hypertension
- PARP – Poly (adenosine diphosphate [ADP]) Ribose Polymerase
- PDE-5 – Phosphodiesterase Type 5 Inhibitor
- PPI – Proton Pump Inhibitor
- RMS – Rhabdomyosarcoma
- TIBS – Targeted Immunomodulatory



**PHA** Pulmonary Hypertension Association  
Empowered by hope

June 18, 2019

Uniform Formulary Beneficiary Advisory Panel  
c/o Colonel Paul J. Hoerner, USAF  
7700 Arlington Boulevard  
Suite 5101  
Falls Church, VA 22042-5101

Dear Advisory Panel Members:

Thank you for the opportunity to provide input regarding coverage of pulmonary hypertension (PH)-specific therapeutics within the TRICARE Uniform Formulary (UF).

The Pulmonary Hypertension Association (PHA) was the world's first and largest organization dedicated to providing comprehensive PH patient and caregiver support, medical education, research and specialty care services that improve patients' quality of life. PHA's Scientific Leadership Council (SLC) is comprised of leading PH experts in the fields of cardiology, pulmonology and rheumatology and serves as PHA's medical advisory body.

Pulmonary arterial hypertension (PAH) is a rare, progressive lung disease characterized by high blood pressure in the lungs that can lead to right heart failure. PAH is a complex condition that can occur on its own or secondary to another condition, disease or exposure. Average survival from the time of diagnosis has increased from less than three years to more recent estimates of seven to nine years due to the development of multiple FDA-approved targeted therapies. Ultimately, however, PAH remains a fatal, incurable condition.

When treating PAH, there is no one-size-fits-all formula. For physicians, maximizing survival and minimizing high-cost healthcare utilization events for individuals with PAH — such as hospitalization, emergency department visits, and transplantation — requires careful attention to the needs of a specific patient and their response to available therapy options either alone or in combination. Given the limited data owing to the rarity of PAH, variable efficacy among cohorts, lack of comparative effectiveness trials, vastly different drug delivery routes and non-uniform cost-effectiveness studies (utilizing varied methodologies precluding comparisons between studies), caution should be exercised in prioritizing one PAH therapy over another.

Clearly the field has shifted over the last 15 years to individualizing therapy based on comprehensive risk assessment and achieving predictive treatment goals, as explicitly stated in the 6<sup>th</sup> World Symposium on Pulmonary Hypertension.<sup>1</sup> Most importantly, because PAH can progress very rapidly, any delay or disruption in effective therapy, including delays inherent with step therapy, can lead to increased morbidity and mortality.

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Brad A. Wong

With this in mind, we encourage you to consider the following changes when reviewing the recommendations of the Department of Defense Pharmacy and Therapeutics Committee.

#### **IV. PULMONARY ARTERIAL HYPERTENSION (PAH) AGENTS – PROSTACYCLINS, ENDOTHELIN RECEPTOR ANTAGONISTS (ERAS), AND NITRIC OXIDE DRUGS**

##### **“A. PAH Agents – Prostacyclins, ERAs and Nitric Oxide Drugs – Relative Clinical Effectiveness Analysis and Conclusion”**

###### **“Endothelin Receptor Antagonists (ERAs)” – AMBITION Trial**

The AMBITION trial was an event-driven, double-blind study of initial combination therapy of ambrisentan 10mg + tadalafil 40mg, initial monotherapy with ambrisentan 10mg + placebo, or initial monotherapy of tadalafil 40mg + placebo every day in treatment-naïve PAH patients assigned in a 2:1:1 ratio. AMBITION reported that patients receiving ambrisentan + tadalafil had a 50% reduction in the risk of a clinical failure event compared to those receiving either drug in monotherapy + placebo.<sup>i</sup> However, it remains uncertain whether PAH patients uniformly benefit from the combination of any ERA + any PDE5-inhibitor. For example, the COMPASS-2 trial of bosentan 125mg twice daily to PAH patients on stable sildenafil dosing failed to demonstrate a statistically significant effect on the primary efficacy endpoint of time-to-first-morbidity/mortality-event.<sup>ii</sup>

For accuracy, we recommend that the sub-section *Endothelin Receptor Antagonists (ERAs)* be edited to mention by name both therapies included in the AMBITION trial. Specifically, “Data supporting combination therapy with an ERA and a PDE5-inhibitor is available with Letairis® and tadalafil in treatment-naïve patients (AMBITION trial)...”

##### **“C. PAH Agents – Prostacyclins, ERAs, and Nitric Oxide Drugs – UF Recommendations”**

###### **“Nitric Oxide Drugs”**

PHA recommends that tadalafil 20mg (Adcirca®, Alyq™, generics) be classified as “step-preferred” in PAH treatment rather than “non-step-preferred.” Alternatively, because AMBITION did not evaluate the efficacy of sildenafil in combination with ambrisentan, PHA recommends that an exception is made when tadalafil is prescribed in combination with Letairis® (ambrisentan), per the AMBITION protocol. This is in line with expert consensus treatment guidelines in the initial combination therapy recommendation.

As noted above, patients in the AMBITION study randomized to the combination treatment arm of ambrisentan 10mg + tadalafil 40mg demonstrated a 50% risk reduction in the time-to-clinical-failure event compared to patients in either monotherapy arm. This efficacy benefit of an ERA + PDE5-inhibitor has not been uniformly measured in clinical studies with other agents of the same class. This scientific background has led to stronger recommendations of ambrisentan + tadalafil as an initial combination therapy compared to other ERAs + PDE5-inhibitors in expert consensus PAH treatment guidelines. Thus, the barrier of step therapy for tadalafil may delay optimal, guideline-directed initial PAH therapy.

The table and recommendations below represent relevant sections from two expert consensus PAH treatment guideline documents.

**2015 ESC/ERS Guideline for the Diagnosis and Treatment of Pulmonary Hypertension<sup>iii</sup>**

Measure/Treatment	Class Level			
	WHO-FC II		WHO-FC III	
Ambrisentan + tadalafil	I <sup>1</sup>	B <sup>2</sup>	I <sup>1</sup>	B <sup>2</sup>
Other ERA + PDE5-i	IIa <sup>3</sup>	C <sup>4</sup>	IIa <sup>3ii</sup>	C <sup>4</sup>

**Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report<sup>iv</sup>**

*Every included recommendation in the “Combination Studies of ERAs and Phosphodiesterase Inhibitors” section:*

“Recommendation #10: For treatment-naïve PAH patients with WHO FC II and III, we suggest initial combination therapy with ambrisentan and tadalafil to improve 6MWD (weak [conditional] recommendation, moderate quality evidence<sup>5</sup>).”

“Recommendation #71: For stable or symptomatic PAH patients on background therapy with ambrisentan, we suggest the addition of tadalafil to improve 6MWD (weak [conditional] recommendation, low quality evidence<sup>6</sup>)”

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<sup>1</sup> “Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.”

<sup>2</sup> “Data derived from a single randomized clinical trial or large non-randomized studies.”

<sup>3</sup> “Weight of evidence/opinion is in favour of usefulness/efficacy”

<sup>4</sup> “Consensus of opinion of the experts and/or small studies, retrospective studies, registries.”

<sup>5</sup> “Benefits closely balanced with risks and burden. We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Best action may differ depending on the circumstances or patients’ or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.”

<sup>6</sup> “Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced. Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.”

**“D. PAH Agents – Prostacyclins, ERAs and Nitric Oxide Drugs – Manual PA Criteria”**

**“5. Uptravi® and Orenitram ER®” – Step Therapy Requirement**

We find the following step therapy requirement unclear as drafted. We are concerned that this will inappropriately limit access to clinically recommended therapy.

- *Patient meets one of the following criteria*
  - *The patient has tried one oral therapy for PAH from one of the three following different categories (either alone or in combination) each for ≥60 days: one PDE5-inhibitor (tadalafil or sildenafil), one ERA (Letairis, Opsumit, or Tracleer), or Adempas; OR*
  - *The patient has tried one prostacyclin therapy (oral, IV, or nebulized)*

As drafted, coverage for an oral prostacyclin analogue (Orenitram ER®) or selective IP receptor agonist (Uptravi®) would not be approved until the PAH patient has been on a therapy acting on the endothelin or nitric oxide pathway for at least sixty (60) days, or unless they have progressed disease/symptomatology that required either an inhaled or parenteral prostacyclin agent.

This coverage recommendation as drafted is counter to expert consensus PAH treatment guidelines and practice patterns in the United States. PAH patients who are considered low- or intermediate-risk are recommended for either initial oral combination therapy or initial oral monotherapy, depending on the patient type.<sup>iii</sup> PAH patients considered high-risk are recommended for initial combination therapy including IV prostacyclin. Following an “inadequate clinical response” to the initial treatment, sequential combination therapy is recommended. PHA notes that these expert consensus guidelines do not define a time period for the “inadequate clinical response,” as this can differ from patient-to-patient. In our experience, “inadequate clinical response,” and the need for modulation of the prostacyclin pathway with an oral agent, can occur before 60 days after the initiation of the first PAH-targeted therapy (ERA and/or PDE5-inhibitor). In addition, in our clinical experience, IV prostacyclin therapy may not be appropriate for all PAH patients, and thus an inappropriate step requirement. This specifically can include patients with connective tissue disease-associated PAH (as these patients can experience great difficulty in mixing their medications), and patients in whom chronic IV access is contraindicated for clinical or social reasons.

We also note the circular logic of allowing previous use an oral prostacyclin therapy as an exception to the step therapy requirement for oral prostacyclin therapy coverage.

For the reasons above, and because a predefined time to demonstrate clinical failure was not defined by the P&T Committee elsewhere in the PAH recommendations, if step therapy is required for PAH patient access to oral Uptravi® or Orenitram ER®, we recommend the following edits in order to maximize patient safety, patient outcomes, and clinician judgement:

- *Patient meets one of the following criteria:*
  - *The patient has tried one oral therapy for PAH from one of the three following different categories (either alone or in combination) each for ≥60 days but with an inadequate clinical response after appropriate trial as assessed by the*

*clinician: PDE5-inhibitor (tadalafil or sildenafil), ERA (Letairis, Opsumit, or Tracleer), or Adempas; OR*

- *The patient has tried one prostacyclin therapy (~~oral~~, IV, SQ, or nebulized) and is either unable to tolerate therapy due to adverse effects or serious adverse events stemming from the complex delivery system.*

#### **“6. Adempas®” - Step Requirements for WHO Group 1 and 4**

We are very concerned about the recommendation that WHO Group 1 PH (PAH) patients try and fail on both sildenafil and tadalafil before receiving approval for Adempas®. As mentioned previously, PAH is a fatal condition that can progress rapidly, and effective therapy management requires physician judgement to respond to the clinical needs of individual patients. We believe that the time required to complete two step edits before receiving Adempas® may result in irreversible clinical worsening in some patients. Furthermore, the requirement for two step-edits places undue administrative burdens on clinicians and their staffs. Modern PAH clinical trial design includes a blinded period until a patient reaches pre-specified end point(s), followed by an open-label extension where all study patients are on active therapy. Analyses of the open-label extension trials have demonstrated that patients originally randomized to placebo, and thus not on maximal therapy, have worse outcomes than patients originally in the active therapy arm and often fail to “catch up” to the comparator groups who received active treatment during the blinded phase.

We recommend that, if any step therapy is required for Adempas® approval, the requirement be for a trial of a single PDE5-inhibitor, either sildenafil OR tadalafil, **but not both**.

In addition, after careful review of this section, we remain unclear as to the recommendations for patient with Group 4 PH (CTEPH) due to the exact wording and formatting. We believe that the P&T Committee is recommending that a diagnosis of Group 4 PH (CTEPH) exempts the patient from the PDE5-inhibitor step therapy requirements for Adempas® approval. We agree with this recommendation, due to the lack of additional FDA-approved targeted therapy options for this patient population. However, given the formatting of the document, we found the P&T Committee’s exact intent difficult to follow.

#### **“7. Adcirca®, Alyq™, and Generics” – Combination Therapy**

As noted above, the AMBITION trial is the only reported clinical trial prospectively researching initial combination therapy in PAH compared to either therapy used as monotherapy. Given the robust evidence from this clinical trial, we believe that physician discretion in utilizing this combination should be preserved, rather than requiring a step failure of a different PDE5-inhibitor that was not included in the clinical trial. We recommend the following edits:

*Manual PA Criteria: Tadalafil 20mg (Adcirca, generics) or Alyq is approved if all criteria are met:*

- *Prescribed by or in consultation with a cardiologist or pulmonologist*
- *Patient has document diagnosis of WHO group 1 PAH*
  - *Patient has had a right heart catheterization (documentation required)*
  - *Results of the right heart catheterization confirm the diagnosis of WHO group 1 PAH*

Colonel Paul J. Hoerner, USAF

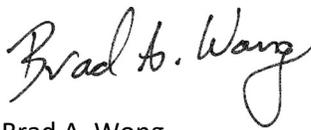
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- Patient has had an adequate trial of sildenafil 20mg (Revatio, generics) and failed or did not respond to therapy, *unless prescribed as initial oral combination therapy with ambrisentan per the AMBITION protocol* and
- Patient is not receiving other PDE-5 inhibitors, nitrates, or riociguat (Adempas) concomitantly.

Thank you for your consideration of these recommendations. If you have additional questions or concerns, do not hesitate to contact Brad A. Wong, president and CEO of the Pulmonary Hypertension Association, at 301-565-3004 x741 or [BradW@PHAssociation.org](mailto:BradW@PHAssociation.org).

Sincerely,



Brad A. Wong  
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<sup>i</sup> Galiè N, et al. *N Engl J Med*. 2015; 373:834-44

<sup>ii</sup> McLaughlin V, et al. *Eur Respir J*. 2015;46(2):405-13

<sup>iii</sup> Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119

<sup>iv</sup> Klinger, JR, et al. *CHEST*. 2019;155(3): 565-86