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 6th World Symposium on Pulmonary Hypertension.[1] 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.

801 Roeder Road, Suite 1000 | Silver Spring, MD 20910
TEL: 301–565–3004 | FAX: 301–565–3994
www.PHAssociation.org | pha@PHAssociation.org
Support Line: 800-748-7274

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.[i] 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.[ii]

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[iii]

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

Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report[iv]

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[5])."

"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[6])"

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[1] "Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective."

[2] "Data derived from a single randomized clinical trial or large non-randomized studies."

[3] "Weight of evidence/opinion is in favour of usefulness/efficacy"

[4] "Consensus of opinion of the experts and/or small studies, retrospective studies, registries."

[5] "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."

[6] "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.[iii] 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*

- *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.

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

[i] Galiè N, et al. *N Engl J Med*. 2015; 373:834-44
[ii] McLaughlin V, et al. *Eur Respir J*. 2015;46(2):405-13
[iii] Galiè N, et. al. *Eur Heart J*. 2016;37(1):67-119
[iv] Klinger, JR, et al. *CHEST*. 2019;155(3): 565-86