

MTF Formulary Management for the Nitric Oxide Agents Used in the Treatment of Pulmonary Arterial Hypertension (PAH)

Defense Health Agency Pharmacy Operations Division

Bottom Line:

- Nitric oxide agents include the Phosphodiesterase-5 (PDE-5) inhibitors and the soluble guanylate cyclase stimulator riociguat (Adempas).
- Sildenafil 20mg tabs and brand Revatio are now Extended Core Formulary (ECF) & step-preferred.
- Step therapy (Prior Authorization) requires a trial of sildenafil 20 mg tabs or brand Revatio (the step-preferred drugs), before using other drugs.
- Tadalafil (Adcirca) is now Uniform Formulary but not step-preferred (behind the step).
- Riociguat is Uniform Formulary but not step-preferred (behind the step).

Uniform Formulary Decision: The Director, DHA approved the recommendations from the February 2015 DoD P&T Committee meeting on 5 May 2015, with an implementation date of 19 August 2015.

Uniform Formulary (UF) Agents		Non-Formulary Agents
PDE-5s on ECF MTFs <u>must</u> have on formulary	PDE5-s on UF MTFs <u>may</u> have on formulary	PDE-5s MTFs <u>must not</u> have on formulary
<i>Step-preferred</i> • Sildenafil 20mg tabs • Sildenafil (Revatio)	<i>Non step-preferred</i> • Riociguat (Adempas) • Tadalafil (Adcirca)	None
Step Therapy applies to new users of Nitric Oxide agents used in the treatment of PAH; grandfathering applies for existing users. See below for detailed criteria.		

Clinical Summary

- There are no head to head comparisons among the different nitric oxide drugs, therefore no evidence-based first line treatment can be proposed.
- In one systematic review all the nitric oxide drugs increased the six-minute walk distance (6MWD) when compared to placebo. Comparisons between agents, however, are inconclusive (Strength of Evidence [SOE] = Moderate).
- PDE-5 monotherapy resulted in lower hospitalization rates compared to combination therapy (SOE = Moderate). PDE-5 inhibitors when used in combination with other agents for PAH do not result in significant improvements in hospitalization rates or 6MWD; there was no mortality benefit observed compared to monotherapy.
- For the PDE-5 inhibitors, there was no new data to change the conclusion from the previous Uniform Formulary review (November 2009).
 - Sildenafil and tadalafil show similar improvements in 6-minute walking distance (6MWD), based on indirect comparisons of clinical trial results.
 - The product labeling for the two drugs is similar with regard to contraindications, precautions, and warnings.
 - Tadalafil (Adcirca) is dosed once daily, which is more convenient compared to the three-times daily dosing required with sildenafil (Revatio).
- Riociguat significantly improved exercise capacity and secondary efficacy end points in patients with PAH compared to placebo. Patients on 2.5 mg of riociguat experienced an increase of approximately 30 meters in 6MWD, while placebo-treated patients had a decrease of approximately 6 meters. Patients with more severe disease (World Health Organization functional class III or IV) had a greater benefit than those in functional class I or II.
- Mortality benefits have not been proven with riociguat. Riociguat has an additional indication for chronic thromboembolic pulmonary hypertension (CTEPH).

Safety

- The most commonly assessed and reported adverse drug events (ADEs) for PDE-5 inhibitors included: headaches, peripheral edema, and flushing.
- Riociguat has a pregnancy category X rating.
- Choice of the drug depends on a variety of factors including indication, patient preference, and physician experience.

Step Therapy Prior Authorization (PA) Criteria:

- Automated PA criteria
 - The patient has filled a prescription for sildenafil 20mg generic or sildenafil brand (Revatio) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or Mail Order) during the previous 180 days.
 - Claims are stopped for Adempas and Adcirca in new patients (i.e., patient has not received a Rx for Adempas or Adcirca in the last 180 days).
 - Applies to new users of Adempas or Adcirca (i.e. current users are grandfathered).
 - New User: A patient who has been prescribed a non-preferred agent but has not tried the preferred agent
- Manual PA: A trial of sildenafil or Revatio is not required if the following are met:
 - Riociguat (Adempas)
 - Patient has CTEPH
 - Patient has tried a PDE-5 inhibitor and failed or did not respond to therapy
 - Patient has had an adverse drug reaction with a PDE-5 inhibitor
 - Tadalafil (Adcirca)
 - Patient has tried sildenafil or Revatio and failed or did not respond to therapy

References

- DoD P&T Committee minutes: <http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee/Meeting-Minutes>
- Current/future drug classes under review by the DoD P&T Committee: <http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee>
- TRICARE Formulary Search Tool: <http://www.express-scripts.com/tricareformulary>
- Prior Authorization/Medical Necessity forms: See Formulary Search Tool above.
- Point of contact for additional information: usarmy.jbsa.medcom-ameddcs.list.pecuf2@mail.mil
- AHRQ 2013; CER #117 & CHEST 2014;145(5):1055–1063.
- Ghofrani, HA, et al. Riociguat for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med* 2013;369:330-40.

Price Comparison at MTF	
Drug	MTF Cost/Month (Feb 2015)
Extended Core Formulary	
Revatio	\$ Most Cost-Effective
Sildenafil 20mg tabs	\$ Most Cost-Effective
Uniform Formulary	
Tadalafil (Adcirca)	\$\$ Cost-Effective
Riociguat (Adempas)	\$\$\$ Less Cost-Effective
Non-Formulary	
None	
Legend: \$ = "Most Cost-Effective" Represents Rx's with the <u>lowest cost</u> and best clinical efficacy \$\$ = "Less Cost-Effective" Represents <u>higher cost</u> Rx's similar clinical efficacy \$\$\$ = "Less Cost-Effective" Represents <u>next higher cost</u> Rx's with similar clinical efficacy \$\$\$\$ = "Least Cost-Effective" Represents Rx's with the <u>highest cost</u> with similar clinical efficacy	