RXADVANCE
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Clinical Policy Title:	sildenafil
Policy Number:	RxA.467
Drug(s) Applied:	Revatio®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Sildenafil (Revatio®) is a phosphodiesterase-5 (PDE-5) inhibitor.

Revatio® is indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when Revatio was added to background epoprostenol therapy.

Studies establishing effectiveness were short-term (12 to 16 weeks) and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (25%).

Limitation(s) of use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
sildenafil (Revatio®)	PAH	Tablet and oral suspension: 5 mg or 20 mg PO TID, 4-6 hours apart Injection: 2.5 mg or 10 mg TID as an IV bolus	Tablet/oral suspension: 60 mg/day Injection: 30 mg/day

Dosage Forms

- Tablets: 20 mg
- Oral suspension: 10 mg/mL
- Vial for injection: 10 mg/12.5 mL

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Pulmonary Arterial Hypertension (must meet all):

1. Diagnosis of PAH;
2. Prescribed by or in consultation with a cardiologist or pulmonologist;
3. Failure of a calcium channel blocker (see Appendix B), unless member meets one of the following (a or b):
   a. Inadequate response or contraindication to acute vasodilator testing;
   b. Contraindication or clinically significant adverse effects to calcium channel blockers are experienced;
4. Dose does not exceed 60 mg per day (oral formulations) or 30 mg per day (intravenous formulations) in divided doses.

Approval duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy

A. Pulmonary Arterial Hypertension (must meet all):

1. Member is currently receiving the medication that has been authorized by RxAdvance or the member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 60 mg per day (oral formulations) or 30 mg per day (intravenous formulations) in divided doses.

Approval duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FC: functional class
FDA: Food and Drug Administration
NYHA: New York Heart Association
PH: pulmonary hypertension
WHO: World Health Organization
PAH: pulmonary arterial hypertension
PDE-5: phosphodiesterase-5

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
nifedipine (Adalat CC®, Procardia®, Procardia XL®)	60 mg PO OD; may increase to 120 to 240 mg/day	240 mg/day
diltiazem (Dilt-XR®, Cardizem® CD, Cartia XT®, Tiazac®, Taztia XT®, Cardizem® LA, Matzim® LA)	720 to 960 mg PO OD	960 mg/day
amlodipine (Norvasc®)	20 to 30 mg PO OD	30 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Use with organic nitrates or riociguat
  - History of hypersensitivity reaction to sildenafil or any component of the tablet, injection, or oral suspension

- Boxed warning(s):
  - None

APPENDIX D: Pulmonary Hypertension: WHO Classification

- Group 1: PAH (pulmonary arterial hypertension)
- Group 2: PH due to left heart disease
- Group 3: PH due to lung disease and/or hypoxemia
- Group 4: CTEPH (chronic thromboembolic pulmonary hypertension)
- Group 5: PH due to unclear multifactorial mechanisms

APPENDIX E: Pulmonary Hypertension: WHO/NYHA Functional Classes (FC)

Treatment Approach*	FC	Status at Rest	Tolerance of Physical Activity (PA)	PA Limitations	Heart Failure
Monitoring for progression of PH and treatment of co-existing conditions	I	Comfortable at rest	No limitation	Ordinary PA does not cause undue dyspnea or fatigue, chest pain, or near syncope	
Advanced treatment of PH with PH-targeted therapy: *see Appendix F***	II	Comfortable at rest	Slight limitation	Ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope	
	III	Comfortable at rest	Marked limitation	Less than ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope	
	IV	Dyspnea or fatigue may be present at rest	Inability to carry out any PA without symptoms	Discomfort is increased by any PA	Signs of right heart failure

*PH supportive measures may include diuretics, oxygen therapy, anticoagulation, digoxin, exercise, pneumococcal vaccination. **Advanced treatment options also include calcium channel blockers.

Appendix F: Pulmonary Hypertension: Targeted Therapies

Mechanism of Action	Drug Class	Drug Subclass	Drug	Brand/Generic Formulations
Reduction of pulmonary arterial pressure through vasodilation	Prostacyclin* pathway agonist **Member of the prostanoid class of fatty acid derivatives.*	Prostacyclin	Epoprostenol	Veletri (IV) Flolan (IV) Flolan generic (IV)
		Synthetic prostacyclin analog	Treprostinil	Orenitram (oral tablet) Remodulin (IV) Tyvaso (inhalation)
			Iloprost	Ventavis (inhalation)
		Non-prostanoid prostacyclin receptor (IP receptor) agonist	Selexipag	Uptravi (oral tablet)
	Endothelin receptor antagonist (ETRA)	Selective receptor antagonist	Ambrisentan	Letairis (oral tablet)
		Nonselective dual action receptor antagonist	Bosentan	Tracleer (oral tablet)
			Macitentan	Opsumit (oral tablet)
	Nitric oxide-cyclic guanosine monophosphate enhancer	Phosphodiesterase type 5 (PDE5) inhibitor	Sildenafil	Revatio (IV, oral tablet, oral suspension)
			Tadalafil	Adcirca (oral tablet)
		Guanylate cyclase stimulant (sGC)	Riociguat	Adempas (oral tablet)

References

1. Revatio Prescribing Information. New York, NY: Pfizer Inc.; February 2020. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=645. Accessed September 01, 2020.
2. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association : developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009; 53(17): 1573:1619. Accessed September 01, 2020.
3. Taichman D, Ornelas J, Chung L, et. al. CHEST guideline and expert panel report: Pharmacologic therapy for pulmonary arterial hypertension in adults. Chest. 2014; 146 (2): 449:475. Accessed September 01, 2020.

4. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: Guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015 Nov 24; 132(21): 2037:99. Accessed September 01, 2020.
5. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013; 62(25): Suppl D92:99. Accessed September 01, 2020.
6. Galiè N, Humbert M, Vachiary JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of Pulmonary Hypertension. European Heart Journal. Doi:10.1093/eurheartj/ehv317. Accessed September 01, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Policy title table was updated. 2. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 3. Appendices B and F were updated. 4. References were updated.	09/01/2020	12/07/2020