Clinical Policy Title:	sildenafil
Policy Number:	RxA.467
Drug(s) Applied:	Revatio®
Original Policy Date:	03/06/2020
Last Review Date:	07/18/2022
Line of Business Policy Applies to:	All lines of business

Background

Sildenafil (Revatio®) is a phosphodiesterase-5 (PDE-5) inhibitor. It 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®)	Pulmonary arterial hypertension	Tablet and oral suspension: 5 mg or 20 mg Orally three times a day, 4-6 hours apart Injection: 2.5 mg or 10 mg three times a day as an Intravenous 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. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Pulmonary Arterial Hypertension (must meet all):

1. Diagnosis of pulmonary arterial hypertension;
2. Prescribed by or in consultation with a cardiologist or a 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 medication that has been authorized by RxAdvance or the member has 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®)	**For Adalat® CC**: Initial, 30 mg orally once daily, maintenance, 30 to 60 mg once daily **For Procardia XL®:** Initial, 30 or 60 mg orally once daily	**For Adalat® CC**: 90 mg/day **For Procardia XL®:** 120 mg/day

diltiazem (Dilt-XR®, Cardizem® CD, Cartia XT®, Tiazac®, Taztia XT®, Cardizem® LA, Matzim® LA)	**For Tiazac®, Taztia XT®:** 120 to 240 mg once daily **For Dilt-XR®, Cardizem® CD, Cartia XT®, Cardizem® LA, Matzim® LA:** 180 to 240 mg once daily	**For Tiazac®, Taztia XT®:** 540 mg /day **For Dilt-XR®, Cardizem® CD, Cartia XT®, Cardizem® LA, Matzim® LA:** 480 mg once daily
amlodipine (Norvasc®)	**Adult starting dose**: 5 mg once daily **Pediatric starting dose**: 2.5 mg to 5 mg once daily	Adult: 10 mg/day Pediatric starting dose: 5 mg/day

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

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

* Contraindications listed reflect direct statements made in the manufacturer's package insert; for additional uses, warnings, and precautions, please refer to clinical guidelines.

- Boxed warning(s):
  - None reported.

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 by6 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)
			Bosentan	Tracleer® (oral tablet)

		Nonselective dual action receptor antagonist	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

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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.	09/01/2020	12/07/2020

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.		
Policy was reviewed: 1. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 2. Continued Therapy Criteria II.A.1 was rephrased to “Member is currently receiving medication that has been authorized by RxAdvance…”. 3. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 4. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 5. References were reviewed and updated.	08/28/2021	12/7/2021
Policy was reviewed: 1. Continued Therapy Approval Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 2. Appendix B, Dosing Regimen, nifedipine (Adalat® CC, Procardia, Procardia XL®): Updated dosing information from “60 mg orally once daily; may increase to 120 to 240 mg/day” to “For Adalat® CC: Initial, 30 mg orally once daily, maintenance, 30 to 60 mg once daily For Procardia XL®: Initial, 30 or 60 mg orally once daily” for indication PAH. 3. Appendix B, Maximum Dose, nifedipine (Adalat® CC, Procardia, Procardia XL®): Updated maximum dose information from	04/01/2022	07/18/2022

240 mg/day to For Adalat® CC: 90 mg/day For Procardia XL®: 120 mg/day. 4. Appendix B, Dosing Regimen, diltiazem (Dilt-XR®, Cardizem® CD, Cartia XT®, Tiazac®, Taztia XT®, Cardizem® LA, Matzim® LA): Updated dosing information from 720 to 960 mg orally once daily to For Tiazac®, Taztia XT®: 120 to 240 mg once daily, For Dilt-XR®, Cardizem® CD, Cartia XT®, Cardizem® LA, Matzim® LA: 180 to 240 mg once daily for indication PAH. 5. Appendix B, Maximum Dose, diltiazem (Dilt-XR®, Cardizem® CD, Cartia XT®, Tiazac®, Taztia XT®, Cardizem® LA, Matzim® LA): Updated maximum dose information from 960 mg/day to For Tiazac®, Taztia XT®: 540 mg /day, For Dilt-XR®, Cardizem® CD, Cartia XT®, Cardizem® LA, Matzim® LA: 480 mg once daily for indication PAH. 6. Appendix B, Dosing Regimen, amlodipine (Norvasc®): Updated dosing information from Initial: 2.5 mg orally once daily; increase cautiously and progressively up to the maximum tolerated dose to Adult starting dose: 5 mg once daily, Pediatric starting dose: 2.5 mg to 5 mg once daily for indication PAH. 7. Appendix B, Maximum Dose, amlodipine (Norvasc®): Updated maximum dose information from 20 mg/day to Adult: 10 mg/day, Pediatric starting dose: 5 mg/day for indication PAH. 8. Disclaimer about contraindications "Contraindications listed reflect statements made in the manufacturer's package insert..." was added to Appendix C. 9. References were reviewed and updated.		