RXADVANCE
2 Park Central Drive
Southborough, MA 01772

Clinical Policy Title:	bosentan
Policy Number:	RxA.521
Drug(s) Applied:	Tracleer®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Bosentan (Tracleer®) is an endothelin receptor antagonist. It is indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1):

- In adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with New York Heart Association (NYHA) Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%).
- In pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
bosentan (Tracleer®)	PAH	• Patients >12 years of age and >40 kg, Initial (4 weeks): 62.5 mg PO BID Maintenance (after 4 weeks): 125 mg PO BID	250 mg/day
		• Patients >12 years of age and <40 kg, Initial (4 weeks): 62.5 mg PO BID Maintenance (after 4 weeks): 62.5 mg PO BID	125 mg/day
		• Patients ≤ 12 years of age and ○ ≥4-8 kg: initial and maintenance dose 16 mg PO BID; ○ >8-16 kg: initial and maintenance dose 32 mg PO BID; ○ >16-24 kg: initial and maintenance dose 48 mg PO BID; ○ >24-40 kg: initial and	≥4-8 kg: 32 mg/day >8-16 kg: 64 mg/day >16-24 kg: 96 mg/day >24-40 kg: 128 mg/day

		maintenance dose 64 mg PO BID.	

Dosage Forms

- Tablets: 62.5 mg, 125 mg
- Dispersible Tablet for oral suspension: 32 mg

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. Member must be enrolled in the Bosenten REMS program;
4. 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;
5. Dose does not exceed 250 mg (4 tablets) per day.

Approval duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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 the 250mg (4 tablets) per day.

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
PAH: pulmonary arterial hypertension
PH: pulmonary hypertension
WHO: World Health Organization

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):
  - Pregnancy
  - Use with cyclosporine A
  - Use with glyburide
  - Hypersensitivity

- Boxed Warning(s):
  - Risk of hepatotoxicity
  - Embryo-fetal toxicity

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.	

Treatment Approach*	FC	Status at Rest	Tolerance of Physical Activity (PA)	PA Limitations	Heart Failure
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

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	Selective receptor antagonist	ambrisentan	Letairis® (oral tablet)

Mechanism of Action	Drug Class	Drug Subclass	Drug	Brand/Generic Formulations
	antagonist (ETRA)	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®s (oral tablet)
		Guanylate cyclase stimulant (sGC)	riociguat	Adempas® (oral tablet)

References

1. Tracleer® Prescribing Information. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; May 2019. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/TRACLEER-pi.pdf . Accessed September 9, 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 9, 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 9, 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.
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 9, 2020.
6. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Kardiol Pol. 2015;73(12):1127-206. doi: 10.5603/KP.2015.0242. Accessed September 9, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Clinical policy title was updated 2. Lines of business policy applies to was updated to all lines of business.	09/09/2020	12/07/2020

3. Dosing regimen was updated: included the age and weight based dosing criteria as mentioned in the PI. 4. Initial criteria updated to include: Member must be enrolled in the Bosenten REMS program; 5. Initial and Continued approval duration criteria for Commercial was updated from "Length of benefit" to 6 months and 12 months respectively. 6. Continued therapy approval criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance…". 7. Updated Appendix B: removed brand Dilacor® XR & Afeditab® CR as they both were discontinued. 8. References were reviewed and updated.		