MEDICATION COVERAGE POLICY

PHARMACY AND THERAPEUTICS ADVISORY COMMITTEE

Health Plan of San Joaquin

POLICY:	Pulmonary Hypertension	**P&T DATE:**	12/22/2021
CLASS:	Respiratory Disorders	**REVIEW HISTORY:** (*month/year*)	9/20, 5/19, 5/18, 12/16, 11/15, 5/13
LOB:	MCL		

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the HPSJ Pharmacy and Therapeutic Advisory Committee.

OVERVIEW

Table 1: Formulary Pulmonary Hypertension Agents *(Current as of 10/2021)*

Therapeutic Class	Drug	Available Strengths	Formulary Limits	Avg Cost/Rx	Notes/Restriction Language
Calcium Channel Blockers (CCB)	**Dihydropyridine:**				
	Amlodipine (Norvasc) Dose range for PAH: 20 - 30 mg qd	**Tablets:**			
		2.5 mg	**QL**	$0.44	Restricted to 1 tablet per day. Submit PA for larger quantities For PAH Group I patients, PA is required to dose at 20 to 30 mg per day.
		5 mg		$0.37	
		10 mg		$0.51	
	Nifedipine (Adalat CC, Afeditab CR, Nifediac CC, Nifedical XL, Procardia XL) Dose range for PAH: 180 – 240 mg qd	**IR Capsules:**			
		10 mg	--	$27.34	--
		20 mg	--	$63.11	--
		24 Hour ER Tablets:			
		30 mg	--	$7.27	--
		60 mg	--	$8.11	--
		90 mg	--	$15.43	--
		XL Tablets:			
		30 mg	--	$8.38	--
		60 mg	--	$9.12	--
		90 mg	--	$13.17	--
	Non-Dihydropyridine:				
	Diltiazem (Cardizem, Cardizem CD, Cardizem LA, Cartia XT, Dilacor XR, Dilt-XR, Martizem LA, Tiazac XC) Dose range for PAH: 720 – 960 mg qd	**CD Capsules:**			
		120 mg	**--**	$6.76	--
		180 mg	**--**	$10.00	--
		240 mg	**--**	$10.81	--
		300mg	**--**	$14.35	--
		360 mg	**NF**	--	--
		XR capsules:			
		120 mg	**--**	$14.41	--

		180 mg	**--**	$20.19	--
		240 mg	**--**	$17.41	--
		12 Hour ER Capsules:			
		60 mg	**NF**	$97.59	--
		90 mg	**NF**	$158.78	--
		120 mg	**NF**	$105.88	--
		24 Hour ER Capsules:			
		120 mg	--	$8.50	--
		180 mg	--	$13.47	--
		240 mg	--	$16.23	--
		300 mg	--	$19.89	--
		360 mg	NF	--	--
		420 mg	--	--	--
		IR Tablets:			
		30mg	--	$7.40	--
		60 mg	--	$11.55	--
		90 mg	--	$18.28	--
		120 mg	--	$12.23	--
		ER Tablets:			
		180 mg	--	$67.13	--
		240 mg	--	$74.82	--
		300 mg	--	$146.89	
		360 mg	--	$105.14	--
		Cardizem LA Tablets			
		120 mg	--	$116.85	--
		Cartia XT Capsules:			
		120 mg	**NF**	--	--
		180 mg	**NF**	--	--
		240 mg	**NF**	--	--
		300 mg	**NF**	--	--
		Taztia XT Capsules:			
		120 mg	**NF**	--	--
		180 mg	**NF**	--	--
		240 mg	**NF**	--	--
		360 mg	**NF**	--	--
		Matzim LA Tablets:			
		180 mg	**NF**	--	--
		240 mg	**NF**	--	--

Phosphodiesterase-5 Inhibitors (PDE-5i)	**Sildenafil (Revatio)** Dose range for PAH: 20 mg every 8 hours, up to 80 mg every 8 hours	20 mg	**PA**	$21.19	WHO FC II-IV with: (-) vasoreactivity test **OR** (+) vasoreactivity test and dose optimized CCB for 3 months
		5 MG	**NF**	--	--
	Tadalafil (Adcirca)	20 MG	**PA**	$48.47	WHO FC II-IV with: (-) vasoreactivity test dose optimized CCB for 3 months who have tried and failed, or intolerant to, dose optimized therapy with Sildenafil for 3 months. **OR** (+) vasoreactivity test and dose optimized CCB for 3 months who have tried and failed, or intolerant to, dose optimized therapy with Sildenafil for 3 months.
Endothelin Receptor Antagonists (ERA)	**Bosentan (Tracleer)**	62.5 mg	**PA**	--	WHO FC II-IV with: Inadequate response or contraindication to either Ambrisentan or Macitentan
		125 mg		$4,405.34	
	Ambrisentan (Letairis)	5 mg		$1,899.53	WHO FC II-IV with: [1] Inadequate response to dose optimized PDE-5i for 3 months for (-) vasoreactive patients OR [2] Inadequate response to dose optimized combination therapy of CCB and PDE5i for 3 months for (+) vasoreactive patients OR [3] Contraindications to PDE5i
		10 mg		$2,621.06	
	Macitentan (Opsumit)	10 mg		$10,300.94	
Prostanoids	**Epoprostenol (Flolan, Veletri)**	**VELETRI IV Solution:**			
		0.5mg	**PA**	--	[1] WHO FC IV **OR** [2] Inadequate response to dose optimized PDE-5i and ERA for 3 months for (-) vasoreactive patients **OR** [3] Inadequate response to dose optimized CCB plus PDE-5i AND ERA for 3 months for (+) vasoreactivity test **OR** [4] Patients with clinical evidence of Right Ventricle (RV) failure or moderate to rapid rate of progression of symptoms/disease
		1.5mg		--	
	Iloprost Tromethamine (Ventavis)	**Ventavis Inhalation Solution:**			
		10 mcg/mL	**PA**	--	
		20 mcg/mL		--	

	Treprostinil	**Remodulin (IV or SQ):**			
		1 mg/mL	**PA**	--	
		2.5 mg/mL		$6,231.31	
		5 mg/mL		$14,481.12	
		10 mg/mL		$30,559.68	
		Orenitram ER tablets:			
		0.125mg	**NF**	$248.17	--
		0.25 mg		$1,745.87	
		1 mg		$5,714.44	
		2.5mg		$10,115.48	
		5 mg		$43,838.51	
		Tyvaso Inhalation:			
		Starter Kit (includes nebulizer).	**PA**	$20,365.71	[1] WHO FC III **AND one of the following:** [2] Inadequate response to dose optimized PDE-5i and ERA for 3 months for (-) vasoreactive patients **OR** [3] Inadequate response to dose optimized CCB plus PDE-5i AND ERA for 3 months for (+) vasoreactive patients **OR** [4] Contraindication to PDE-5i, Riociguat and ERA
		Refill Kit		$18,359.06	
Soluble Guanyl Cyclase (sGC) Stimulants	**Riociguat (Adempas)**	0.5 mg	**PA**	$11,045.73	[1] WHO Group IV (Chronic Thromboembolic Pulmonary Hypertension- CTPH): after surgical treatment or inoperable or recurrent disease **OR** [2] WHO Group I PAH FC II to III: as a sequential add on to Bosentan*** with treatment failure to Sildenafil or contraindication to Sildenafil
		1 mg		$11,211.38	
		1.5 mg		$11.708.32	
		2 mg		$11.310.77	
		2.5 mg		$10,642.27	
IP Receptor Agonists	**Selexipag Oral Tablets (Uptravi)**	200 mcg	**PA**	$13,647.41	[1] WHO FC III to IV **AND one of the following:** [2] Inadequate response to dose optimized PDE-5i and ERA for 3 months for (-) vasoreactive patients **OR** [3] Inadequate response to dose optimized CCB plus PDE-5i AND ERA for 3 months for (+) vasoreactivity test **OR** [4] Contraindication to PDE-5i, Riociguat and ERA
		400 mcg		$14,132.71	
		600 mcg		$18,502.66	
		800 mcg		$18,313.53	
		1,000 mcg		--	
		1,200 mcg		--	
		1,400 mcg		$19,094.75	
		1,600 mcg		$13,718.49	
		200 mcg-800mcg Therapy Pack		$28,698.82	

PA = Prior Authorization, QL = Quantity Limit, NF = Non-formulary

EVALUATION CRITERIA FOR APPROVAL/EXCEPTION CONSIDERATION

Below are the coverage criteria and required information for each agent. These coverage criteria have been reviewed approved by the HPSJ Pharmacy & Therapeutics (P&T) Advisory Committee. For conditions not covered under this Coverage Policy, HPSJ will make the determination based on Medical Necessity as described in HPSJ Medical Review Guidelines (UM06).

Basic Criteria: [1] Prescribed by a Cardiologist, Pulmonologist, or Critical care
[2] Diagnosis of Pulmonary Arterial Hypertension, WHO GROUP I
[3] WHO Functional Class (WHO FC) II-IV
[4] Right Heart Catheterization with Vasoreactivity test

Phosphodiesterase-5 Inhibitors (PDE-5i): Sildenafil, Tadalafil

Sildenafil (Revatio)

- ❒ **Coverage Criteria:** Reserved for patients with IPAH WHO FC II-IV with: (-) vasoreactivity test **OR** (+) vasoreactivity test and dose optimized CCB for 3 months.
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** Basic criteria as listed above plus all of the following: clinical documentation of inadequate response to dose optimized CCB for 3 months evidenced by worsening of symptoms (i.e. decline in 6MWD) and pharmacy fill history.

Tadalafil (Adcirca)

- ❒ **Coverage Criteria:** Reserved for patients with IPAH WHO FC II-IV with: (-) vasoreactivity test **OR** (+) vasoreactivity test and dose optimized CCB for 3 months who have tried and failed, or intolerant to, dose optimized therapy with Sildenafil for 3 months.
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** Basic criteria as listed above plus all of the following: clinical documentation of inadequate response to dose optimized CCB and Sildenafil for 3 months evidenced by worsening of symptoms (i.e. decline in 6MWD) and pharmacy fill history for (+) vasoreactive patients OR for (-) vasoreactive patients, clinical documentation of inadequate response to dose optimized Sildenafil for 3 months evidenced by worsening of symptoms (i.e. decline in 6MWD) and pharmacy fill history

Endothelin Receptor Antagonists (ERAs): Bosentan, Ambrisentan, Macitentan

Macitentan (Opsumit), Ambrisentan (Letairis)

- ❒ **Coverage Criteria:** Adequate trial of dose optimized PDE-5i for 3 months for [-]vasoreactive patients **OR** adequate trial of dose optimized CCB and PDE-5i for 3 months for [+]vasoreactive patients **OR** contraindication to PDE-5i.
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** Basic criteria as listed above plus all of the following: clinical documentation of inadequate response to dose optimized PDE-5i for 3 months for [-]vasoreactive patients or inadequate response to dose optimized PDE-5i and CCB for 3 months for [+]vasoreactive patients evidenced by worsening of symptoms (i.e. decline in 6MWD) and pharmacy fill history, or the nature of the contraindication to PDE-5i.

Bosentan (Tracleer)

- ❒ **Coverage Criteria:** Inadequate response or contraindication to either Ambrisentan or Macitentan
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** Basic criteria as listed above and clinical documentation of inadequate response or contraindication to either Ambrisentan or Macitentan evidenced by pharmacy fill history +/- documentation of the nature of contraindication.

Prostanoids: Epoprostenol, Iloprost, Tresprostinil

Epoprostenol (Flolan, Veletri), Iloprost (Ventavis), Treprostinil (Orenitram ,Remodulin)

- ❒ **Coverage Criteria:** [1] WHO FC IV **OR** [2] Inadequate response to dose optimized PDE-5i and ERA for 3 months for (-) vasoreactive patients **OR** [3] Inadequate response to dose optimized CCB plus

PDE-5i AND ERA for 3 months for (+) vasoreactivity test **OR** [4] Patients with clinical evidence of Right Ventricle (RV) failure or moderate to rapid rate of progression of symptoms/disease

- ❒ **Limits:** None
- ❒ **Required Information for Approval:** Basic criteria as listed above, clinical documentation of inadequate response evidenced by worsening of symptoms (i.e. decline in 6MWD), and pharmacy fill history or clinical evidence of Right Ventricle (RV) failure or moderate to rapid rate of progression of symptoms/disease
- ❒ **Non-Formulary: Orenitram ER tablets**

Treprostinil Inhalation (Tyvaso)

- ❒ **Coverage Criteria:** WHO FC III **AND one of the following:** [1] Inadequate response to dose optimized PDE-5i and ERA for 3 months for (-) vasoreactive patients **OR** [2] Inadequate response to dose optimized CCB plus PDE-5i AND ERA for 3 months for (+) vasoreactive patients **OR** [3] Contraindication to PDE-5i, Riociguat and ERA
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** Basic criteria as listed above, clinical documentation of inadequate response evidenced by worsening of symptoms (i.e. decline in 6MWD), and pharmacy fill history +/- documentation of the nature of contraindication

Soluble Guanylate Cyclase Stimulants: Riociguat

Riociguat (Adempas)

- ❒ **Coverage Criteria:** [1] WHO Group IV (Chronic Thromboembolic Pulmonary Hypertension- CTPH): after surgical treatment or inoperable or recurrent disease **OR** [2] WHO Group I PAH FC II to III: as a sequential add on to Bosentan with treatment failure to Sildenafil or contraindication to Sildenafil.
- ❒ **Limits:** None
  Required Information for Approval: Basic criteria plus specific coverage criteria as listed above, clinical documentation of inadequate response evidenced by worsening of symptoms (i.e. decline in 6MWD), and pharmacy fill history +/- documentation of the nature of contraindication.

Prostacyclin IP Receptor Agonist: Selexipag (Uptravi)

Selexipag (Uptravi)

- ❒ **Coverage Criteria:** WHO FC III to IV **AND one of the following:** [1] Inadequate response to dose optimized PDE-5i and ERA for 3 months for (-) vasoreactive patients **OR** [2] Inadequate response to dose optimized CCB plus PDE-5i AND ERA for 3 months for (+) vasoreactivity test **OR** [3] Contraindication to PDE-5i, Riociguat and ERA.
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** Basic criteria plus specific coverage criteria clinical documentation of inadequate response evidenced by worsening of symptoms (i.e. decline in 6MWD), and pharmacy fill history +/- documentation of the nature of contraindication.

Clinical Justification:

Diagnosis of Pulmonary Hypertension requires Right Heart Catheterization (RHC)[5]. Following the current Pulmonary Arteriole Hypertension recommendation, HPSJ formulary has set RHC and vasoreactivity test as a part of the requirements and restricts medications based on clinical evidence. Calcium channel blockers are the preferred agent in patients who can tolerate them, and who have shown good response during right heart catheterization, unless contraindicated. Drugs are restricted based on WHO Functional Class and patient's prior use of PAH medications. ERAs are not benign drugs. They are teratogenic, can potentially cause LFT elevations in patients who take them chronically, and can cause fluid retention. Sildenafil is widely available and relatively benign, thus carries few restrictions, while intravenous prostanoids carry significant risk, and should not be used unless all other therapeutic agents have been exhausted. Although 2019 Chest Guideline suggests Ambrisentan and Tadalafil as an initial therapy for WHO FC II and II, weak recommendation resulting from borderline clinically significant improvement in 6MWD, no change in WHO FC, variabilities of end points in clinical trial and studies, and the fact that the guideline does not prefer one regimen over the other in this treatment group, HPSJ has decided not to modify current PAH coverage criteria.

REFERENCES

1. HPSJ Formulary Criteria
2. Sitbon O., Channick R., Chin KM, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med* 2015; 373:2522-33
3. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2016; 37(1):67-119.
4. Whelton PK, Carey RM, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, Journal of the American College of Cardiology (2017), doi: 10.1016/j.jacc.2017.11.006
5. Hoeper MM et al. Definitions and diagnosis PH. JACC 2013; 62:D42-50.
6. Burger C, Pulmonary Hypertension Guidelines 5th World Symposium. *Am Coll Cardiol* 2009; 53:1573-1619.
7. Galiè N et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2009; 30:2493-537.
8. Gaile N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. J AM Coll Cardiol 2013;62:D60-72
9. McLaughlin V, Badesch D, Barst R, 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. Circulation. 2009;119:2250 –2294.
10. Galie N, Barbera J, Frost A, et al. Initial use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. August 27, 2015 *N Engl J Med* 2015; 373:834-844 DOI: 10.1056/NEJMoa1413687
11. Taichman D., Ornelas J., Chung L., et al. Pharmacologic Therapy for Pulmonary Arterail Hypertension in Adults CHEST Guideline and Expert Panel Report. CHEST 2014; 146 (2): 449 – 475
12. Falk J., Phillip K., and Schwarz R., The emergence of oral tadalafil as a once-daily treatment for pulmonary arterial hypertension. Vasc Health Risk Manag. 2010; 6: 273–280.
13. Lajoie AC, Lauzière G, Lega J., et. al., Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis. Lancet Respir Med. 2016 Apr;4(4):291-305. doi: 10.1016/S2213-2600(16)00027-8. Epub 2016 Feb 27.
14. Galiè N, Brundage BH, Ghofrani HA., et. al., Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Possible blunting effect of Bosentan on Tadalafil due to Drug drug interactions -- Tadalafil therapy for pulmonary arterial hypertension. Circulation. 2009 Jun 9; 119(22):2894-903.
15. J Klinger, C Elliot, D Levine et al., Therapy for Pulmonary Arterial Hypertension in Adults Update of the CHEST Guideline and Expert Panel Report. CHEST 2019; 155(3):565-586.
16. Galiè N, McLaughlin VV, Rubin LJ, *et al*. An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respi J* 2019; 53: 1802148 [https://doi.org/10.1183/13993003.02148-2018].
17. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019;53:1801913.
18. Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. Eur Respir J 2019; 53: 1801904 [https://doi.org/10.1183/13993003.01904-2018].
19. Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J 2019; 53 1801889 [https://doi.org/10.1183/13993003.01889- 2018].

REVIEW & EDIT HISTORY

Document Changes	Reference	Date	P&T Chairman
Creation of Policy	PAH Class Review 5-21-2013.docx	5/2013	Jonathan Szkotak, PharmD BCACP
Update Policy	Drug Class Review – Respiratory disorders – Pulmonary Hypertension 2015-11.docx	11/2015	Johnathan Yeh, PharmD
Update Policy	HPSJ Coverage Policy – Respiratory disorders – Pulmonary Hypertension 2016-12.docx	12/2016	Johnathan Yeh, PharmD
Update Policy	HPSJ Coverage Policy – Respiratory disorders – Pulmonary Hypertension 2018-05.docx	5/2018	Johnathan Yeh, PharmD

Update Policy	HPSJ Coverage Policy – Respiratory disorders – Pulmonary Hypertension 2019-05.docx	5/2019	Matthew Garrett, PharmD
Review of Policy	Pulmonary Hypertension	9/2020	Matthew Garrett, PharmD
Review of Policy	Pulmonary Hypertension	12/2021	Matthew Garrett, PharmD

Note: All changes are approved by the HPSJ P&T Committee before incorporation into the utilization policy