

**Clinical Policy: Selexipag (Uptravi)**

Reference Number: CP.PHAR.196

Effective Date: 03.16

Last Review Date: 02.21

Line of Business: Commercial, HIM, Medicaid

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

**Description**

Selexipag (Uptravi<sup>®</sup>) is a prostacyclin receptor agonist.

**FDA Approved Indication(s)**

Uptravi is indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) to delay disease progression and reduce the risk of hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

**Policy/Criteria**

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

It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that Uptravi is **medically necessary** when the following criteria are met:

**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. Request meets one of the following (a or b):
  - a. Tablet: Dose does not exceed 3,200 mcg per day (*if request is for titration, provider must submit a titration plan*).
  - b. Injection: Member is temporarily unable to take oral therapy and does not exceed 3,600 mcg per day (*if request is for titration, provider must submit a titration plan*).

**Approval duration:****Medicaid/HIM – 6 months**

**Commercial – Length of Benefit**

**B. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**II. Continued Therapy**

**A. Pulmonary Arterial Hypertension (must meet all):**

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, or b):
  - a. Tablet: New dose does not exceed 3,200 mcg per day (*if request is for titration, provider must submit a titration plan*).
  - b. Injection: Member is temporarily unable to take oral therapy and new dose does not exceed 3,600 mcg per day (*if request is for titration, provider must submit a titration plan*).

**Approval duration:**

**Medicaid/HIM – 12 months**

**Commercial – Length of Benefit**

**B. Other diagnoses/indications (must meet 1 or 2):**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

**Approval duration: Duration of request or 6 months (whichever is less); or**

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**III. Diagnoses/Indications for which coverage is NOT authorized:**

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

**IV. Appendices/General Information**

*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*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.*

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

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

*Appendix C: Contraindication/Boxed Warnings*

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.	

Treatment Approach*	FC	Status at Rest	Tolerance of Physical Activity (PA)	PA Limitations	Heart Failure
	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  <i>*Member of the prostanoid class of fatty acid derivatives.</i>	Prostacyclin	Epoprostenol	Velettri (IV) Flolan (IV) Flolan generic (IV)	
		Synthetic prostacyclin analog	Treprostinil	Orenitram (oral tablet) Remodulin (IV) Tyvaso (inhalation)	
			Iloprost	Ventavis (inhalation)	
	Endothelin receptor antagonist (ETRA)	Non-prostanoid prostacyclin receptor (IP receptor) agonist	Selexipag	Upravi (oral tablet)	
			Selective receptor antagonist	Ambrisentan	Letairis (oral tablet)
				Nonselective dual action receptor antagonist	Bosentan
	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)	

*Appendix G: General Information*

- Upravi injection is suitable to maintain continuous dosing for short periods of time when oral administration of Upravi is not feasible. Upravi IV is a therapeutic option that will allow patients to avoid short-term treatment interruptions and stay on Upravi therapy, as

uninterrupted treatment is considered key for individuals with PAH. In the pivotal trial, patients treated with stable oral dose were switch to the IV formulation (for total of 3 infusions) and resumed their stable oral dose thereafter throughout the study.

**V. Dosage and Administration**

Indication	Dosing Regimen	Maximum Dose
PAH	200 mcg PO BID, increased at weekly intervals to highest tolerated dose up to 1,600 mcg BID	Tablet: 3,200 mcg/day
	Administer injection BID by IV infusion at a dose that corresponds to the patient’s current dose of Uptravi tablets. Uptravi for injection must be diluted in glass containers only. Withdraw 100 mL of 0.9% Sodium Chloride Injection, USP and transfer into an empty sterile glass container.	Injection: 3,600 mcg/day

**VI. Product Availability**

- Tablets: 200 mcg, 400 mcg, 600 mg, 800 mg, 1,000 mcg, 1,200 mcg, 1,400 mcg, 1,600 mcg
- Injection: 1,800 mcg single dose vial for reconstitution and dilution

**VII. References**

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  10. Yaghi S, Novikov A, Trandafirescu T. Clinical update on pulmonary hypertension. *J Investig Med.* 2020; 0:1-7. doi:10.1136/jim-2020-001291.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Age restriction removed. FC II added to the prostanoid class of PH drugs. Safety criteria were removed unless they 1) represent contraindications or black box warnings not covered by a REMS program, and 2) provide specific lab/imaging parameters that must be met prior to initiation of therapy. An efficacy statement is added to the continuation criteria. Initial and continuation durations increased to 6 and 12 months respectively. Appendices covering PH groups, functional class and therapies reorganized.	02.17	03.17
1Q18 annual review: Policies combined for commercial, HIM and Medicaid; No significant changes from previous corporate approved policy; Medicaid: removed WHO/NYHA classifications from initial criteria since specialist is involved in care; References reviewed and updated.	11.20.17	02.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	11.20.18	02.19
1Q 2020 annual review: no significant changes; added statement that titration plan be submitted; added HIM line of business; references reviewed and updated.	11.26.19	02.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	10.12.20	02.21
RT4: new formulation for injection; references reviewed and updated.	08.19.21	

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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**Note:**

**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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