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®) 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® 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® CC, Afeditab® CR, Procardia®, Procardia XL®)	60 mg PO QD; may increase to 120 to 240 mg/day	240 mg/day
diltiazem (Dilacor XR®, Dilt-XR®, Cardizem® CD, Cartia XT®, Tiazac®, Taztia XT®, Cardizem® LA, Matzim® LA)	720 to 960 mg PO QD	960 mg/day
amlodipine (Norvasc®)	20 to 30 mg PO QD	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: 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 **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)

Appendix G: General Information

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

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>PAH</td><td>200 mcg PO BID, increased at weekly intervals to highest tolerated dose up to 1,600 mcg BID

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.

<table>
<tr><th>Uptravi tablet dose (mcg) for BID dosing</th><th>Corresponding Uptravi IV dose (mcg) for BID dosing</th><th>Reconstituted transfer volume (mL) for dilution</th></tr>
<tr><td>200</td><td>225</td><td>1</td></tr>
<tr><td>400</td><td>450</td><td>2</td></tr>
<tr><td>600</td><td>675</td><td>3</td></tr>
<tr><td>800</td><td>900</td><td>4</td></tr>
<tr><td>1000</td><td>1125</td><td>5</td></tr>
<tr><td>1200</td><td>1350</td><td>6</td></tr>
<tr><td>1400</td><td>1575</td><td>7</td></tr>
<tr><td>1,600</td><td>1,800</td><td>8</td></tr>
</table>
</td><td>Tablet: 3,200 mcg/day

Injection: 3,600 mcg/day</td></tr>
</table>

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

1. Uptravi Prescribing Information. South San Francisco, CA: Actelion Pharmaceuticals US, Inc.; July 2021. Available at: https://www.uptravi.com. Accessed August 19, 2021.
2. ClinicalTrials.gov. Safety Study of the Switch From Oral Selexipag to Intravenous Selexipag in Subjects With Stable Pulmonary Arterial Hypertension. Available at: https://clinicaltrials.gov/ct2/show/NCT03187678. Accessed August 19, 2021.
3. 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.
4. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults: update of the CHEST guideline and expert panel report. *CHEST*. 2019;155(3):565-586.
5. 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.
6. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol.* 2013; 62(25): Suppl D92-99.
7. 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.
8. Simmonneau G, Montani D, Celermajer D, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019; 53:1801913.
9. Sitbon O, Humber M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation*. 2005;111(23);3105;11.
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.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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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.