

Selexipag (UPTRAVI)**Criteria for Use****December 2017**

VHA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph for selexipag at www.pbm.va.gov or <https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx/> for further information.

EXCLUSION CRITERIA (If the answer to ANY item below is met, then the patient should NOT receive selexipag)

- Concomitant use with strong CYP2C8 inhibitors (e.g., gemfibrozil)
- Concomitant use with other prostacyclins such as epoprostenol, treprostinil, and iloprost (has not been studied)

INCLUSION CRITERIA

All of the following must be selected for patient to be eligible:

- Definitive diagnosis of PAH confirmed by right-heart catheterization including hemodynamic diagnosis: mean pulmonary artery pressure [mPAP] >25 mmHg, pulmonary artery wedge pressure [PAWP] or left ventricular end diastolic pressure [LVEDP] ≤15 mm Hg¹, and pulmonary vascular resistance (PVR) >3 Wood units
- World Health Organization (WHO) Group 1 PAH^{2,4}
- Under the care of a VA authorized, experienced provider in the management of PAH
- Patient is treated with or has been assessed for adjunct therapies such as oxygen, diuretics, digoxin and oral anticoagulant
- If acute vasoreactivity test positive, calcium channel antagonist therapy has been tried unless right heart failure is present⁵
- Patient has had an inadequate response (e.g., progression, deterioration) or a documented contraindication or inability to tolerate a (phosphodiesterase type 5) PDE-5 inhibitor **AND** an endothelin receptor antagonist (ERA) prior to consideration of selexipag (See Issues for Consideration)

DOSAGE AND ADMINISTRATION (Refer to prescribing information for further details)

- **Initial dose:** The starting dose for selexipag is 200 mcg orally twice daily.
- **Titration:** Increase selexipag dose by 200 mcg twice daily at weekly intervals to the highest tolerated dose, up to a maximum of 1600 mcg twice daily.
- **Interruptions and discontinuations:** If medication is missed for 3 days or longer, restart selexipag at a reduced dose and re-titrate.

ISSUES FOR CONSIDERATION

- **Consideration of PDE-5 inhibitor and ERA prior to selexipag:** The efficacy of selexipag was established in the GRIPHON study in patients with WHO Group 1 PAH and functional class II or III symptoms. Most patients (80%) were already receiving PAH therapy with a PDE-5 inhibitor and/or ERA at baseline. Selexipag was found to reduce morbidity (e.g., disease progression and hospitalization), though there was no mortality benefit.
- **Patients with functional class IV symptoms:** The efficacy of selexipag was established in the GRIPHON study in patients with WHO Group 1 PAH and functional class II or III symptoms. Only 1% of patients included in GRIPHON were classified as having class IV symptoms at baseline. While there are meaningful advantages in administration, ease of use, etc. of an orally administered prostacyclin agonist such as selexipag over other prostacyclin therapies that require either continuous infusions or inhalation, the efficacy of selexipag has not been established in patients with the most severe class IV symptoms. European guidelines from 2015 continue to provide a strong recommendation for the use of intravenous epoprostenol in patients with functional class IV symptoms, with alternative therapies including other prostacyclins and selexipag given weaker recommendations.
- **Mortality:** There was an excess of all-cause deaths reported in the selexipag group vs. placebo when outcomes were examined until the end of the treatment period in the GRIPHON study. No evidence of a specific toxicity was identified per the FDA review, and the FDA concluded that the increase in events was likely due to chance. A post-approval safety review conducted by the EMA prompted by 5 deaths reported in France found no suggestion of increased mortality with selexipag beyond what is observed with other PAH medications.
- **Tolerability:** Overall, the safety profile for selexipag is consistent with what is expected and observed with other systemic vasodilators and primarily affects the tolerability of the drug (e.g., headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing, arthralgia, rash. Selexipag is initiated at a low starting dose and titrated slowly as tolerated. If there is an interruption of treatment for 3 days or longer, restart selexipag at a lower dose and re-titrate.
- **Combination therapy:** More evidence is becoming available on the use of combination therapy in PAH (using agents from different drug classes together), though results have been inconsistent. Most of the patients in the GRIPHON study were on combination PAH therapy with a PDE-5 inhibitor and/or ERA at baseline. Per subgroup analysis, efficacy appeared to be consistent in patients on combination therapy and monotherapy. Combination therapy with prostacyclins and selexipag was not allowed in GRIPHON and has not been studied. Other studies using different PAH therapy combinations have shown inconsistent results. The appropriateness of combination PAH

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therapy should be assessed by a provider who specializes in PAH and in consideration of potential drug interactions, potentially additive adverse effects, and current evidence.

CONSIDERATIONS FOR RENEWAL

- In those patients who are severely ill, continuous infusion of a prostacyclin (e.g., intravenous epoprostenol) remains the preferred therapy.
- Routine evaluation of patients by the PAH provider to assess both effectiveness and tolerability of selexipag therapy is mandatory; those patients with a poor response should be considered for continuous infusion of prostacyclin.
- Provider needs to give criteria (e.g., NYHA functional class assessment, etc.) and a timepoint (e.g., 1 month, 3 months, 6 months, or other as appropriate) for evaluation and continuation of treatment with selexipag prior to beginning therapy.

1. PAWP/LVEDP ≤ 15 mmHg is a measure traditionally used and guideline-recommended in the hemodynamic diagnosis of PAH to aid in ruling out pulmonary hypertension due to left-heart disease, where PAH-specific therapies (including ERAs) have not been shown to benefit and may result in harm. REVEAL U.S. registry data suggests that PAH may exist in patients with PAWP 16-18 mmHg. Survival in patients with PAH and a PAWP 16-18 mmHg at diagnosis did not significantly differ from those with PAWP ≤ 15 mm Hg. Decisions to use PAH-specific therapy including ERAs in patients with a PAWP 16-18 mmHg at diagnosis should be made by PAH specialists and in the context of the individual patient.

2. The WHO classification of pulmonary hypertension divides the disease into 5 groups (Simonneau et al. J Am Coll Cardiol. 2013;62:D34-41.):

Group	Classification
1	Pulmonary arterial hypertension (PAH): including idiopathic (IPAH), heritable, BMPR2, ALK-1, ENG, SMAD9, CAV1, KCNK3, unknown, drug and toxin induced, pulmonary veno-occlusive disease, persistent pulmonary hypertension of the newborn, and associated with: connective tissue disease, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis
2	Pulmonary hypertension due to left heart disease
3	Pulmonary hypertension due to lung diseases and/or hypoxia
4	Chronic thrombotic pulmonary hypertension
5	Pulmonary hypertension with unclear multifactorial mechanisms

3. WHO Functional Classes for PH (Rubin. Chest. 2004;126:7S-10S):

I	No limitation in physical activity; ordinary physical activity does not cause dyspnea or fatigue
II	Slight limitations in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest
III	Marked limitation of physical activity; less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest
IV	Unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest; discomfort increased by any physical activity

4. Treatment of non-WHO Group 1 pulmonary hypertension is aimed at the underlying disease. Current evidence does not support the use of selexipag in non-WHO Group 1 PAH. If therapy is considered in this setting, enrollment into a clinical trial is strongly encouraged. Outside of a clinical trial setting, treatment should be considered on a case-by-case basis.

5. Positive acute vasodilator response defined as a fall in mPAP of ≥ 10 mm Hg to ≤ 40 mm Hg with an increase or no change in cardiac output. A small percentage of patients (6.8%) have been shown to have a long term response to calcium-channel antagonists as predicted by acute vasodilator testing (Sitbon et al. Circulation. 2005;111:3105-11).

Prepared by Lisa Longo, Pharm.D., BCPS, VA Pharmacy Benefits Management Services