PDL DRUG REVIEW

Proprietary Name: Uptravi®
Common Name: selexipag
PDL Category: Pulmonary Antihypertensives

Comparable Products	Preferred Drug List Status
Orenitram	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Selexipag, the active ingredient of Uptravi®, is a selective non-prostanoid oral prostacyclin receptor (IP receptor) agonist that is structurally distinct from prostacyclin. Selexipag is hydrolyzed to obtain its active metabolite, which is approximately 37-fold as potent as selexipag. Both selexipag and its active metabolite are selective for the IP receptor as compared with other prostanoid receptors.[1] As an agonist of the IP receptor, it results in vasodilation of the pulmonary vascular bed.[2]

Indication: For the treatment of pulmonary arterial hypertension (PAH, 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. Included were patients with idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

There is no pregnancy category listed for this product; however, the risk summary indicates that there are no adequate and well-controlled studies of use in pregnant women. Animal reproduction studies did not show any clinically relevant effects on embryo-fetal development and survival with selexipag use. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Tablets: 200mcg, 400mcg, 600mcg, 800mcg, 1000mcg, 1200mcg, 1400mcg, and 1600mcg; Do not chew split, or crush tablets.

Recommended Dosage: The recommended starting dose is 200mcg BID; if taken with food, tolerability may improve. Increase the dose in increments of 200mcg BID, generally at weekly intervals to the highest tolerated dose up to 1600mcg BID.

Dose adjustments are not required with mild hepatic impairment; however, the recommended starting dose in patients with moderate hepatic impairment is 200mcg QD. Increase in increments of 200mcg QD at weekly intervals as tolerated. The use in patients with severe hepatic impairment should be avoided. Dose adjustments are not needed in patients with renal impairment with estimated glomerular filtration rate of >15ml/min/1.73m^2; however, there is no clinical experience with use in patients undergoing dialysis or in patients with glomerular filtration rates <15ml/min/1.73m^2.

Drug Interactions: The concomitant use of Uptravi® with strong inhibitors of CYP2C8 (e.g. gemfibrozil) should be avoided, as concomitant use may result in a significant increase in exposure to selexipag and its active metabolite.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Uptravi®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence of the active drug was the same as or less than placebo.* The most frequently reported adverse events included headache (33%), diarrhea (24%), jaw pain (20%), nausea (15%), myalgia (10%), vomiting (9%), pain in extremity (9%), flushing (7%), arthralgia (3%), anemia (3%), decreased appetite (3%), and rash (3%). Lab abnormalities included a decrease in hemoglobin concentration to <10g/dl (3.6%).

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Actelion Pharmaceuticals

Analysis: One multicenter, double-blind, placebo-controlled, parallel group, event-driven study (GRIPHON; N=1156) was performed to assess the safety and efficacy of Uptravi® when used for the treatment of patients with symptomatic PAH (WHO Functional Class 1 [0.8%], II [46%], III [53%], and IV [1%]). The primary endpoint was the time to first occurrence up to end-of-treatment of: death; hospitalization for PAH; PAH worsening resulting in need for lung transplantation or balloon atrial septostomy; initiation of parenteral prostanoid therapy or chronic oxygen therapy; or other disease progression based on a 15% decrease from baseline in 6 minute walk distance (6MWD) test plus worsening of Functional Class or need for additional PAH-specific therapy.

Treatment with Uptravi® resulted in a 40% reduction of the occurrence of primary endpoint events as compared to placebo, which was significantly different ($p<0.0001$). The main effect of Uptravi® was mostly attributable to a reduction in hospitalization for PAH and a reduction in other disease progression events. Please refer to the following table for specific results. (**GHS Comment**: The NNT has been calculated for the primary endpoint and added to the table).

Outcomes	Uptravi® (N=574)	placebo (N=582)	Hazard Ratio	P-value	NNT
All primary endpoint events	155 (27%)	242 (41.6%)	0.60	<0.0001	7
As first event:					
Hospitalization for PAH	78 (13.6%)	109 (18.7%)			
Other disease Progression (↓ in 6MWD + worsening functional class or need for other therapy)	38 (6.6%)	100 (17.2%)			
Death	28 (4.9%)	18 (3.1%)			
Parenteral prostanoid or chronic oxygen therapy	10 (1.7%)	13 (2.2%)			
PAH worsening resulting in need for lung transplantation or balloon atrial septostomy	1 (0.2%)	2 (0.3%)			

Note that it is not known if the excess number of deaths in the Uptravi® group is drug-related, and the imbalance was not seen until 18 months into the study. In addition, the treatment effect of Uptravi® on time to the first primary event was consistent regardless of background PAH therapy (i.e. in combination with an ERA, PDE-5 inhibitor, both, or no background therapy).

The 6MWD was a secondary endpoint, to assess exercise capacity. The median absolute change from baseline to week 26 in 6MWD measured at trough was +4m with Uptravi® as compared with -9m with the placebo group. This was a statistically significant difference, with a placebo-corrected median treatment effect of 12m ($p=0.005$).

Place in Therapy: Numerous pharmacologic treatments exist for PAH; however, Uptravi® is the first in its class of FDA approved IP receptor agonists. The 2015 updated European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension includes selexipag.[3] In the guidelines, a Class 1 recommendation is defined as evidence and/or general agreement that a given treatment or

procedure is beneficial, useful, and effective; a Level of Evidence (LOE) A is defined as data derived from multiple randomized clinical trials or meta-analyses whereas LOE B is defined as data derived from a single randomized clinical trial or large non-randomized studies. The guidelines include selexipag and categorize it as a Class 1/LOE 1B for WHO Functional Class (FC) II as well as for WHO FC III. For example, other PAH treatments such as ambrisentan, bosentan, and sildenafil are categorized as Class 1/LOE A for FC II and FC III; macitentan, tadalafil, and riociguat are categorized as Class 1/ LOE B for WHO FC II and III.

There is no evidence at this time to support that Uptravi® is safer or more effective than the currently available, more cost effective medications. It is therefore recommended that Uptravi® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1]Uptravi [package insert]. South San Francisco, CA: Actelion Pharmaceuticals; 2015.
[2] UpToDate desktop reference. Treatment of pulmonary hypertension in adults. Accessed June 2016.
[3]Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Rev EspCardiol*. 2016; 69(2): 177.