CLINICAL UPDATE

Brand Name	Uptravi®
Generic Name	selexipag
Drug Manufacturer	Actelion Pharmaceuticals US, Inc.

Clinical Update

TYPE OF CLINICAL UPDATE

New Dosage Form

FDA APPROVAL DATE

July 29, 2021

LAUNCH DATE

August 16, 2021

REVIEW DESIGNATION

Standard; Orphan

TYPE OF REVIEW

Type 3 - New Dosage Form; New Drug Application (NDA): 214275

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Uptravi® is a prostacyclin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

MECHANISMS OF ACTION

Selexipag is a prostacyclin receptor (IP receptor) agonist that is structurally distinct from prostacyclin. Selexipag is hydrolyzed by carboxylesterase 1 to yield its active metabolite, which is approximately 37-fold as potent as selexipag. Selexipag and the active metabolite are selective for the IP receptor versus other prostanoid receptors (EP1-4, DP, FP, and TP).

DOSAGE FORM(S) AND STRENGTH(S)

- Tablets: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg.
- For Injection: 1800 mcg of selexipag as a lyophilized powder in a singledose vial for reconstitution and dilution.

DOSE & ADMINISTRATION

- Uptravi® tablets starting dose: 200 mcg twice daily.
- Increase the dose by 200 mcg twice daily at weekly intervals to the highest tolerated dose up to 1600 mcg twice daily.
- Maintenance dose is determined by tolerability.

- Moderate hepatic impairment: Starting dose 200 mcg once daily, increase the dose by 200 mcg once daily at weekly intervals to the highest tolerated dose up to 1600 mcg.
- Uptravi® for injection dose is determined by the patient's current dose of Uptravi® tablets. Administer Uptravi® for injection by intravenous infusion, twice daily.

EFFICACY

The effect of Uptravi® tablets on progression of PAH was demonstrated in a multi-center, double-blind, placebo-controlled, parallel group, event-driven study (GRIPHON) in 1,156 patients (mean age was 48 years), with symptomatic (WHO Functional Class I [0.8%], II [46%], III [53%], and IV [1%]) PAH. Patients were randomized to either placebo (N=582), or Uptravi® tablets (N=574). The dose was increased in weekly intervals by increments of 200 mcg twice a day to the highest tolerated dose up to 1600 mcg twice a day.

Idiopathic or heritable PAH was the most common etiology in the study population (58%) followed by PAH associated with connective tissue disease (29%), PAH associated with congenital heart disease with repaired shunts (10%), drugs and toxins (2%), and HIV (1%). At baseline, the majority of enrolled patients (80%) were being treated with a stable dose of an endothelin receptor antagonist (15%), a PDE-5 inhibitor (32%), or both (33%).

Patients on Uptravi® tablets achieved doses within the following groups: 200-400 mcg (23%), 600-1000 mcg (31%) and 1200-1600 mcg (43%).

Treatment with Uptravi® tablets resulted in a 40% reduction (99% CI: 22 to 54%; two-sided log-rank p-value<0.00001) of the occurrence of primary end point events compared to placebo. The beneficial effect of Uptravi® was primarily attributable to a reduction in hospitalization for PAH and a reduction in other disease progression events. The observed benefit of Uptravi® was similar regardless of the dose achieved when patients were titrated to their highest tolerated dose.

Table: Primary Endpoints and Related Components in GRIPHON

	UPTRAVI N=574		Placebo N=582		Hazard Ratio (99% CI)	p-value
	n	%	n	%		
Primary endpoint events up to the end of treatment						
All primary endpoint events	155	27.0	242	41.6	0.60 [0.46, 0.78]	<0.0001
As first event:						
• Hospitalization for PAH	78	13.6	109	18.7		
• Other disease Progression (Decrease in 6MWD plus 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		

6-Minute Walk Distance (6MWD):

Exercise capacity was evaluated as a secondary endpoint. Median absolute change from baseline to week 26 in 6MWD measured at trough (i.e., at approximately 12 hours post-dose) was +4 meters with Uptravi® and -9 meters in the placebo group. This resulted in a placebo-corrected median treatment effect of 12 meters (99% CI: 1, 24 meters; two-sided p = 0.005).

Long-Term Treatment of PAH:

In long-term follow-up of patients who were treated with Uptravi® in the pivotal study and the open-label extension (N=574), Kaplan-Meier estimates of survival of these patients across the GRIPHON study and the long-term extension study at 1, 2, 5 and 7 years were 92%, 85%, 71%, and 63%, respectively. The median exposure to Uptravi® was 3 years. These uncontrolled observations do not allow comparison with a control group not given Uptravi® and cannot be used to determine the long-term effect of Uptravi® on mortality.