# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 207947Orig1s000

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**
**Office of Medication Error Prevention and Risk Management**

# RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

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| Date: | September 29, 2015 |
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| Drug Name(s): | Uptravi (selexipag) |
| Therapeutic Class: | Prostacyclin agonist |
| Dosage and Route: | 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg |
| Application Type/Number: | NDA 207947 |
| Applicant: | Actelion Pharmaceuticals, Ltd |
| OSE RCM #: | 2015-288 |

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# 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Uptravi® (selexipag) oral tablets, NDA 207947, received from Actelion Pharmaceuticals, Inc. on December 22, 2014. Actelion did not propose a REMS as part of the submission.

## 1.1 PRODUCT BACKGROUND

Selexipag is a selective prostacyclin $PGI_2$ (IP) receptor agonist with a proposed indication for the treatment of Pulmonary Arterial Hypertension (PAH, WHO Group I) to delay disease progression. Selexipag undergoes enzymatic hydrolysis in the liver to yield its active metabolite, ACT-333679. This metabolite is instrumental to the efficacy of selexipag, as it is present in levels 3 to 4 times higher during steady-state conditions in humans.

Selexipag is administered chronically and the proposed starting dose is 200 mcg twice daily. Selexipag should be titrated weekly by increments of 200 mcg and the maintenance dose is determined by patient tolerability. Selexipag's dosing frequency for those with moderate to severe hepatic impairment is decreased to once daily. If approved, selexipag will be available in 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg and 1600 mcg oral tablets. A new drug application is also under review by the European Medicines Agency for the use of selexipag in PAH therapy.

## 1.2 DISEASE BACKGROUND

PAH is a rare disease affecting fewer than 200,000 people in the U.S.[1] It is marked by an inability of the right ventricle to pump blood through the lungs, due to increased pulmonary arterial pressure and vascular resistance. This resistance is a result of the narrowing and constriction of the pulmonary arteries. The disease is progressive and can ultimately lead to right heart failure and death. The average survival time after diagnoses, with medical care, is four to five years. Causes of PAH may be idiopathic, inherited or associated with connective tissue disease, congenital systemic-to-pulmonary shunts, drugs or toxins, HIV infection or other conditions.[2]

Currently, IP receptor agonists, endothelin receptor antagonists (ERA), Phosphodiesterase-5 inhibitors (PDE-5), and a soluble guanylate cyclase stimulator (SGCS) are all treatments approved for PAH. The other approved IP receptor agonists for PAH are treprostinil, iloprost and epoprostenol. All IP receptor agonists are associated with prostacyclin- associated adverse event (PAAEs), which are generally non-serious, and the development of pulmonary edema (PE) if IP receptor agonist therapy is administered to patients with underlying pulmonary veno-occlusive disease (PVOD). All ERAs and SGCS are associated with a risk of teratogenicity that require

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[1] UPMC. *Pulmonary Arterial Hypertension.* (2015, September 28). Retrieval from http://www.upmc.com/Services/pulmonary-hypertension/conditions/Pages/pulmonary-arterial-hypertension.aspx

[2] Shah, N., Stringham R. *Pulmonary Arterial Hypertension.* Am Fam Physician. 2010 Aug 15;82(4):370-377

mitigation under a REMS with elements to assure safe use (ETASU) to ensure the benefits outweigh this serious risk. In addition to teratogencity, bosentan is associated with hepatotoxicity and its REMS also address this serious risk.

The following table summarizes the approved treatments for PAH and relevant safety concerns:

| DRUG CLASS | NAME | REMS | BOXED WARNING | WARNINGS & PRECAUTIONS |
|---|---|---|---|---|
| ***Selective IP Receptor agonist*** | Uptravi (selexipag) | N | | PAAE, PE |
| ***IP Receptor agonists*** | Remodulin/ Tyvaso (treprostinil) | N | | PAAE, bleeding |
| | Ventavis (iloprost) | N | | PAAE, PE, bronchospasms, insomnia, flu syndrome, palpitations |
| | Flolan (epoprostenol) | N | | PAEE, PE, bleeding, rebound hypertension |
| ***ERA*** | Opsumit (macitentan) | Y | teratogenicity | PE, anemia, nasopharyngitis bronchitis, influenza, urinary tract infection, decreased sperm count |
| | Tracleer (bosentan) | Y | teratogenicity, hepatotoxicity | PE, anemia, respiratory tract infections, decreased sperm count |
| | Letairis (ambrisentan) | Y | teratogenicity | PE, nasal congestion, sinusitis, flushing, decreased sperm count |
| ***PDE-5*** | Revatio (sildenafil) | N | | PE, a/v impairment, epistaxis, H/A, dyspepsia, flushing, insomnia, erythema, dyspnea, rhinitis |
| | Adcirca (tadalafil) | N | | PE, a/v impairment, H/A, priaprism |
| ***SGCS*** | Adempas (riociguat) | Y | teratogenicity | PE, anemia, bleeding, H/A, dyspepsia, dizziness, nausea, diarrhea, vomiting, constipation |

ERA: endothelin receptor antagonists; PDE-5: phosphodiesterase-5 inhibitors; SGCS: soluble guanylate cyclase stimulator; PAAE: prostacyclin-associated adverse event; PE: pulmonary edema; H/A: headache; a/v: adio/visual

### 1.3 REGULATORY HISTORY

The following is a summary of regulatory history relevant for NDA 207947, selexipag:

**April 30, 2010:** Selexipag was granted Orphan Drug Status.

**December 22, 2014:** Applicant submitted NDA 207947 (eCTD Seq No. 0000), selexipag, for PAH indication.

**February 20, 2015:** Proprietary name, Uptravi, granted.

**May 27, 2015:** The Agency requested the following during the Mid-cycle meeting: 1) Provide appropriate dose instruction for patients with moderate to severe hepatic impairment, supported by modeling and simulation report 2) Provide justifications or modified text for proposed labeling of selexipag compared to placebo on 6 minute walking distance (6MWD) and mortality endpoints. Additionally, the Agency communicated to the Applicant that, at this time, the Agency did not believe a REMS was necessary to ensure the benefits outweigh the risks for selexipag.

**July 7, 2015:** Applicant amended the application with the following: 1) Modeling and simulation data to support changes to the USPI to include (b) (4) dosing instructions

for patients with moderate and severe hepatic impairment 2) Modified text to support selexipag compared to placebo on 6MWD and mortality endpoints.

## 2 MATERIALS REVIEWED

The following are materials used to inform our review:

- Actelion Pharmaceuticals LTD. Summary of Clinical efficacy [pulmonary arterial hypertension indication] for Uptravi (selexipag), received December 22, 2014 (eCTD Seq No. 0000)
- Actelion Pharmaceuticals LTD. Summary of Clinical safety [pulmonary arterial hypertension indication] for Uptravi (selexipag), received December 22, 2014 (eCTD Seq No. 0000)
- Actelion Pharmaceuticals LTD. Draft Prescribing Information for Uptravi (selexipag), received December 22, 2014 (eCTD Seq No. 0000)
- Chambers, W. Ophthalmology Consult for selexipag, dated July 27, 2015
- Gordon M, Garnett C. Clinical Review for selexipag, dated September 2, 2015

## 3 CLINICAL DEVELOPMENT PROGRAM

The Applicant conducted 11 Phase 1 studies, two Phase 2 studies and one Phase 3 study for the target indication, PAH. AC-065A302 (GRIPHON) is considered to be the pivotal study. It was a placebo-controlled, event-driven, group-sequential Phase 3 study, which randomized 1156 patients in a 1:1 ratio to selexipag or placebo. The patient population was comprised of those who were PAH medication naïve and those taking ERAs and/or PDE-5i for at least 3 months prior to baseline. The treatment duration was up to 70 weeks and the primary objective was to evaluate if selexipag reduces the risk for morbidity/mortality in patients with PAH. Primary endpoints for determining morbidity/mortality included first events of : death, hospitalization for PAH worsening, PAH worsening resulting in the need for lung transplantation/balloon atrial septostomy, initiation of parental prostanoid therapy, disease progression marked by a decrease $\geq$ 15% in 6MWD or worsening of symptoms/need for additional PAH specific therapy.

### 3.1 OVERVIEW OF EFFICACY

The efficacy of selexipag in the proposed indication is based on data from the GRIPHON Phase 3 clinical trial. In the GRIPHON study, 155 (27.0%) patients in the selexipag group compared to 242 (41.6%) in the placebo group experienced morbidity/mortality events up to the end of treatment plus seven days. In the time-to-event analysis, the hazard ratio for selexipag versus placebo for the occurrence of a morbity/mortality event was 0.60 (99% CI: 0.46, 0.78, 1-sided unstratified log-rank $p < 0.0001$), which was statistically significant.

## 3.2 OVERVIEW OF SAFETY

The Applicant used a pooling strategy to evaluate the safety of selexipag:

Pool 1 is the primary source of safety data and is comprised of data from the GRIPHON study. Pool 1 includes 575 patients treated with selexipag for up to 217 weeks, representing a total exposure of 842 patient-years.

Pool 2 combined safety data from a completed Phase 2 study, as well as, the Phase 3 study and its ongoing open-label extension study. Pool 2 includes 773 patients treated with selexipag for up to 308 weeks, representing 1174 patient-years of exposure.

*Treatment Emergent Adverse Events (TEAEs)*

In Pool 1, the most frequent treatment-emergent adverse events (TEAEs) reported for ≥ 5% of patients (91% selexipag, 62.2% placebo) were PAAEs, which include the following events per the Applicant: headache, flushing, gastro-intestinal symptoms, myalgia and extremity pain. Though frequently occurring, the majority of these AEs were non-serious (91.7% selexipag, 99.5% placebo). Additionally, hypotension was a TEAE that occurred more frequently for selexipag as compared to placebo (5.9% and 3.8% respectively); however, hypotension is an expected event based on the vasodilatory effects of IP receptor agonists.

*Deaths*

When looking at overall survival in the GRIPHON trial, a total of 100 deaths (17.4%) were reported up to study closure for patients who received at least one dose of selexipag, compared to 105 (18.0%) in the placebo group. Of the 100 deaths in the selexipag group, 70% were attributed to PAH worsening. In comparison, 79% of subjects in the placebo group died from PAH complications. Other causes of death included: cardiovascular, thromboembolic, sepsis, respiratory failure, cancer and sudden (not otherwise specified). In the Division of Cardiovascular and Renal Products clinical review, the medical officer stated "Overall, reported fatal outcomes were consistent with underlying condition and there were no unexpected events detected".[3]

*Serious Adverse Events (SAEs)*

The SAEs were predominately related to events associated with the underlying disease and reported less frequently on selexipag (43.7%) than on placebo (47.1%).

Five SAEs were reported more frequently in the selexipag group compared to placebo. These were dyspnea (3.0% selexipag, 2.3% placebo), atrial fibrillation (1.2% selexipag, 0.7% placebo), relapse/progression/worsening of systemic lupus erythematosus (0.7% selexipag, 0.2% placebo), acute pyelonephritis (0.5% selexipag, 0% placebo) and ventricular fibrillation (0.5% selexipag, 0% placebo). All of these AEs are expected in this patient population except acute pyelonephritis, which occurred in three patients and is not a safety concern of interest.

[3] Gordon M, Garnett C. Clinical Review for selexipag, September 2, 2015.

### 3.3 COMPARISON OF SAFETY WITH OTHER APPROVED DRUGS INDICATED FOR PAH

Overall the AE profile of selexipag appears to be consistent with IP receptor agonist therapy. Though selexipag shares many AEs with other IP receptor agonists, it does not carry an increased risk of bleeding with anticoagulant use, as do the others. Additionally, since selexipag is the first oral IP receptor agonist, its AE profile differs from the injectable and inhaled formulations. Selexipag is not associated with injection site reactions, like treprostinil and epoprostenol, which are given intravenously and subcutaneously. Bronchospasm is a safety concern for iloprost, as it is inhaled.

Additionally, due to the different mechanism of action for selexipag as compared with ERAs, PDE-5i's, and a SGCS, the SAEs are different. In particular, selexipag does not have a risk of teratogenicity or hepatotoxicity as is associated with the ERAs or SGCS.

## 4 DISCUSSION

Selexipag is a selective IP receptor agonist with a proposed indication for the treatment of PAH to delay disease progression. It is a new molecular entity that was determined to be efficacious in the pivotal clinical GRIPHON trial by meeting statistical significance in decreasing morbidity and mortality compared to placebo.

Selexipag was well tolerated in the clinical studies. Most of the safety concerns that presented during the clinical trials and occurred more frequently in the selexipag group were expected AEs associated with IP receptor agonist therapy.

The prescribers of selexipag will likely be specialists, specifically cardiologists. Specialists trained to treat PAH have experience with FDA-approved PAH treatment options, including knowledge of common risks and adverse events associated with prostacyclin therapies. Like other IP receptor agonists with the same risks, selexipag does not require a REMS to ensure the benefits outweigh these risks. Notably, they do not have a risk of teratogenicity or hepatotoxicity, unlike the ERAs or SGCS, that do require a REMS.

## 5 CONCLUSION

In conclusion, risk mitigation measures beyond labeling, are not warranted for Uptravi (selexipag). Based on the currently available data, the benefit-risk profile for Uptravi is acceptable for the treatment of PAH and DRISK does not recommend a REMS as necessary to ensure the benefits of Uptravi outweigh the risks at this time.

Should the Division have any concerns or questions, or feel that a REMS may be warranted for this product, please contact DRISK.

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DONELLA A FITZGERALD
09/29/2015

REEMA J MEHTA
09/29/2015
I concur.