CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214275Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	7/19/2021
From	Doanh Tran
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 214275
Applicant	Actelion Pharmaceuticals US, Inc.
Date of Submission	9/29/2020
PDUFA Goal Date	7/29/2021
Proprietary Name	Uptravi for injection
Established or Proper Name	Selexipag
Dosage Form(s)	Lyophilized powder for intravenous injection
Applicant Proposed Indication(s)/Population(s)	For the treatment of Pulmonary Arterial Hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH
Applicant Proposed Dosing Regimen(s)	Uptravi for injection dose is determined by the patient's current dose of Uptravi tablets. Administer Uptravi for injection by intravenous infusion, twice daily.
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	*NA*
Recommended Dosing Regimen(s) (if applicable)	*NA*

Material Reviewed/Consulted	
Integrated Quality Review (6/20/2021)	Ben Zhang, Su Tran, Rao Kambhampati, Carl Lee, Sateesh Sathigari,Ash Bekele, Christine Craig, Mohan Sapru
Pharmacology-Toxicology Review (6/1/2021)	James Willard, Jean Wu
Clinical Pharmacology Review (7/2/2021)	Harisudhan Thanukrishnan, Sudharshan Hariharan, Doanh Tran
Clinical Review	Not applicable.
Division of Medication Error Prevention and Analysis Reviews (2/16/21, 4/9/2021, 7/1/2021)	Mariette Aidoo, Hina Mehta, Chi-Ming Tu
Office of Prescription Drug Promotion Reviews (7/13/2021)	Carrie Newcomer, James Dvorsky
Patient Labeling Team Review (7/13/2021)	Ruth Mayrosh, Carrie Newcomer, Barbara Fuller, LaShawn Griffiths

1. Introduction

On 9/29/2020, Actelion Pharmaceuticals submitted a New Drug Application (NDA) for Uptravi for injection, a sterile lyophylized powder for solution containing 1.8 mg selexipag, for the treatment of PAH (WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

The application primarily relies on the Agency's previous finding of safety and effectiveness for Uptravi oral tablets in NDA 207947. The NDA is supported by a safety and tolerability study with relative bioavailability assessment of intravenous (IV) selexipag in participants with stable PAH switching from an oral stable dose of selexipag (Study AC-065A309), and a two way cross-over study investigating absolute bioavailability of oral tablet versus IV formulation of selexipag in healthy participants (Study AC-065-110).

Overall, the proposed IV selexipag dosing regimen was well tolerated in patients with PAH and exhibited similar drug exposure to oral selexipag. I concur with the review teams and recommend approval of IV selexipag.

2. Background

Selexipag is a prostacyclin receptor agonist. Selexipag is marketed as an oral formulation under the brand name of UPTRAVI®. The applicant has developed an IV formulation of selexipag. The selexipag IV formulation contains the same active pharmaceutical ingredient as oral selexipag and was developed for the treatment of PAH in (b) (4) The target patient population for the IV formulation of selexipag is identical to that for oral selexipag, except that patients are temporarily unable to swallow tablets.

IV selexipag is intended to be administered twice daily at a dose that provides similar exposure to the active metabolite, ACT-333679, to that achieved with corresponding doses of the oral formulation. The active metabolite ACT-333679 has greater selectivity for the prostacyclin receptor and is about 37-times as potent as selexipag in cellular assays.

3. Product Quality

The Integrated Quality Review from the Office of Pharmaceutical Quality recommends approval.

The drug substance reviewer noted that the drug substance selexipag is manufactured by the same process and controls as described in the approved NDA 207947. Acceptance limits of the related substances are as per ICH Q3A qualification limits (NMT 0.15%), except for impurity (b) (4), for which an acceptance limit of NMT (b) (4) is justified based on previously approved levels (NDA 207947).

The proposed drug product is a sterile, white lyophilized powder for intravenous infusion following reconstitution with 8.6 mL of 0.9% sodium chloride solution for injection to a nominal 225 μg/mL concentration. The reconstituted solution is further diluted with 0.9% sodium chloride solution for injection to the different final drug product concentrations per labeling

instructions. The drug product reviewer noted that all the proposed excipients are compendial grade and they are commonly used in the manufacturing of lyophilized drug product powder formulations. The stability data included 24 months of long-term (refrigerated, 2-8°C) and 6 months of accelerated (25°C/65% RH) conditions for three NDA registration batches and three process validation batches. Based on the 24 months long-term and 6 months accelerated stability data, 24 months expiration dating period is granted when the cartons containing drug product vials are stored refrigerated at 2-8°C and protected from light.

Based on facility assessment of the manufacturing risk, in-process controls, and GMP compliance history, all the listed manufacturing and testing facilities have been found to be 'acceptable'.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology review team recommends approval. The applicant relied on the non-clinical data from the previous NDA 207947 submission for Uptravi tablet to support the safety of Uptravi for injection. In addition, there were 3 small studies examining hemolysis risks and local tolerance at the infusion site of the new formulation. The Nonclinical reviewer noted that these studies "showed no adverse effects due to the intravenous administration of Uptravi."

5. Clinical Pharmacology

The Office of Clinical Pharmacology recommends approval of Uptravi for injection for the treatment of patients with WHO Group 1 PAH who cannot swallow Uptravi tablets. The proposed IV selexipag dose is 1.125 times the oral dose. The proposed dosing regimen for IV selexipag is supported by the following:

1. Modelling and simulation of relative bioavailability between oral and IV doses of selexipag based on absolute bioavailability data indicated that an IV dose 1.125 times the corresponding oral dose would result in similar exposure to active metabolite ACT-333679.
2. The results from Study AC-065A309 in patients with PAH supported tolerability, safety, as well as similarity in the PK profile and exposure to the active metabolite when transitioning from the oral dosing of selexipag. The switch from oral to IV selexipag and back to oral was well tolerated with similar tolerability reported for Uptravi tablets and IV selexipag. There was mild infusion site erythema reported in two subjects, but there were no unexpected safety findings observed during the IV treatment period. The relative bioavailability results showed the ratio of geometric means (90% CI) after IV and oral selexipag administration for dose-normalized combined exposure of selexipag plus active metabolite ACT-333679, adjusted for their relative potencies, was 0.82 (0.72, 0.93).
3. Modelling and simulation showed similar exposure between the proposed 80-minute constant infusion rate and the two step 87-minute infusion used in Study AC-065A309.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

As discussed under Clinical Pharmacology, the relative bioavailability assessment provides the bridge to the efficacy findings of the oral Uptravi tablets.

8. Safety

This application primarity relies on the Agency's previous finding of safety for the Uptravi tablets. Safety and tolerability of the IV formulation was also evaluated in 20 patients with PAH in study AC-065A309. The AE profile was consistent with the known safety profile of oral selexipag, with no unexpected safety findings observed during treatment with IV selexipag.

After IV dosing, 7 subjects had at least 1 injection site reaction (pain, erythema, or swelling). Injection site reactions with onset during infusion 2 or 3 were reported for 3 subjects; onset between infusions 1 and 2 were reported for 2 subjects; and onset after infusion 3 were reported for 2 subjects. Clinically significant treatment related infusion site erythema was reported in 2 patients (10%). These were mild intensity infusion site erythema with swelling (1 patient) and mild-to-moderate infusion site erythema (1 patient). During IV infusion period (Period 2), QTcF prolongation to > 450 ms was reported for 3 subjects (16%) and QTcF prolongation to > 480 ms was reported for 4 subjects (20%). Six of these 7 patients reportedly had QTcF prolongation to > 450 ms in Period 1 (prior to the start of IV infusion of selexipag).

9. Advisory Committee Meeting

The application does not raise significant issues regarding the safety or effectiveness of the drug; hence, no Advisory Committee Meeting was held or needed.

10. Pediatrics

The drug product for this indication has orphan drug designation and is exempt from the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) requirements.

11. Other Relevant Regulatory Issues

None.

12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed Uptravi patient information sheet acceptable from a medication error perspective. Recommendations for container label and carton labeling were communicated to the applicant

and the revised label and labeling were acceptable. Recommendations on the prescribing information were included in the label. DMEPA also concluded that the proposed proprietary name, Uptravi, is acceptable. Recommendations by the Office of Prescription Drug Promotions and Patient Labeling Team were considered and incorporated into the prescribing information and patient information, respectively.

13. Postmarketing Recommendations

None.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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