CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214275Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	214275
Supporting document/s:	0001
Applicant's letter date:	9/29/2020
CDER stamp date:	9/29/2020
Product:	Selexipag
Indication:	Pulmonary Arterial Hypertension (PAH)
Applicant:	Actelion and Johnson and Johnson
Review Division:	Division of Cardiology and Nephrology
Reviewer:	James M. Willard, Ph.D.
Supervisor/Team Leader:	Jean Q. Wu, M.D., Ph.D.
Division Director:	Norman Stockbridge, M.D., Ph.D.
Project Manager:	Brian Cooney

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 214275 are owned by Actelion and Johnson and Johnson.
Any information or data necessary for approval of NDA 214275 that Actelion and Johnson and Johnson does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 214275.

Table of Contents

1. Executive Summary

1.1 Introduction

Uptravi was approved by the FDA on 12/21/2015 as a twice a day oral dosing for the treatment of pulmonary arterial hypertension. The present NDA is a reformulation of Selexipag for intravenous administration in patients not able to take the oral version. It also provides clinicians with an option of a twice a day infusion versus a continuous infusion required by some of the prostacyclin agonists.

Sponsor utilized the non-clinical data from the previous NDA submission to support the safety overall of Uptravi. The addition of 3 small studies to examine hemolysis risks and local tolerance at the infusion site have been added.

1.2 Brief Discussion of Nonclinical Findings

The 3 studies added to this NDA submission were to examine hemolytic potential of the Uptravi formulation and to examine the effects at the injection site for local tolerance. These studies showed no adverse effects due to the intravenous administration of Uptravi.

The results from all the non-clinical data, including the studies supporting oral use (reviewed in NDA 207947 and associated INDs) and those to support intravenous routes of administration, indicate that Selexipag is a reasonably safe medication for the treatment of Pulmonary Arterial Hypertension.

1.3 Recommendations

1.3.1 Approvability

NDA 214275 is approvable from the non-clinical perspective.

1.3.2 Additional Non-Clinical Recommendations

None.

1.3.3 Labeling

The following updates for nonclinical information in Section 8.1 and Section 13.1 are recommended. Since the exposure multiples are based on the comparison of AUC exposures to the active metabolite in the animals and humans, “the active metabolite” is added in the relevant sentences for clarification.

The result of the Pre- and Post-Natal Development study is added into the label as it was submitted and reviewed in the original NDA 207947 for the oral Selexipag.

Table 1 **Exposure Ratios for Active Metabolite of Selexipag**

Study	Sex	Dose (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µg·hr/mL) after the last dose	Safety margin relative to Human exposure[1]
Carcinogenicity - 26-week Mouse NOAEL	M+F	500 125	66.5 14.95	241 54
Carcinogenicity - 2-year Rat NOAEL	M+F	100 30	126 25.4	458 92
Reproductive Toxicology Embryo-Fetal Development		(Rats) 20 (Rabbits) 30	12.9 13.7	47 50
Rat - Pre- and Post-natal development	F	20	9.6	**35**

1. Human exposure to the active metabolite was determined as AUC0-24hr of 276 ng*hr/mL (2 x AUC 0-12hr of 138 ng*hr/mL) based on the clinical study (Study AC-065A201) following multiple oral doses of 1600 mcg bid.

Proposed revisions in Section 8.1 Pregnancy:

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with UPTRAVI in pregnant women. Animal reproduction studies performed with selexipag showed no clinically relevant effects on embryofetal development and survival. A slight reduction in maternal as well as in fetal body weight was observed when pregnant rats were administered selexipag during organogenesis at a dose producing an exposure to the active metabolite approximately 47 times that in humans at the maximum recommended human dose. No adverse developmental outcomes were observed with oral administration of selexipag to pregnant rabbits during organogenesis at exposures to the active metabolite up to 50 times the human exposure at the maximum recommended human dose.

Data

Animal Data

Pregnant rats were treated with selexipag using oral doses of 2, 6, and 20 mg/kg/day (up to 47 times the exposure to the active metabolite at the maximum recommended human oral dose of 1600 mcg twice daily on an area under the curve [AUC] basis) during the period of organogenesis (gestation days 7 to 17). Selexipag did not cause adverse developmental effects to the fetus in this study. A slight reduction in fetal body weight was observed in parallel with a slight reduction in maternal body weight at the high dose.

Pregnant rabbits were treated with selexipag using oral doses of 3, 10, and 30 mg/kg (up to 50 times the exposure to the active metabolite at the maximum recommended human oral dose of 1600 mcg twice daily on an AUC basis) during the period of organogenesis (gestation days 6 to 18). Selexipag did not cause adverse developmental effects to the fetus in this study.

In a Pre- and Post-Natal Development study, pregnant rats were treated with selexipag from gestation day 7 through lactation day 20 at oral doses of 2, 6, and 20 mg/kg/day (up to 35 times the exposure to the active metabolite at the maximum recommended human dose of 1600 mcg twice daily on an AUC basis). Treatment with selexipag did not cause adverse developmental effects in this study at any dose.

Proposed revisions in Section 13 Nonclinical Toxicology:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In the 2-year carcinogenicity studies, chronic oral administration of selexipag revealed no evidence of carcinogenic potential in rats at 100 mg/kg/day and mice at 500 mg/kg/day which resulted in (b) (4) the exposures to the active metabolite (b) (4) more than 25 (b) (4) times the human exposure at the maximum recommended human oral dose of 1600 mcg twice daily on an AUC basis.

Mutagenesis: Selexipag and the active metabolite are not genotoxic on the basis of the overall evidence of conducted genotoxicity studies.

Fertility: In rats administered with selexipag orally, the no effect dose for effects on fertility was 60 mg/kg/day (b) (4) which resulted in (b) (4) the exposure to the active metabolite (b) (4) approximately 175 times (b) (4) the human (b) (4) exposure at the maximum recommended human oral dose of 1600 mcg twice daily on an AUC basis.

2 Drug Information

2.1 Drug

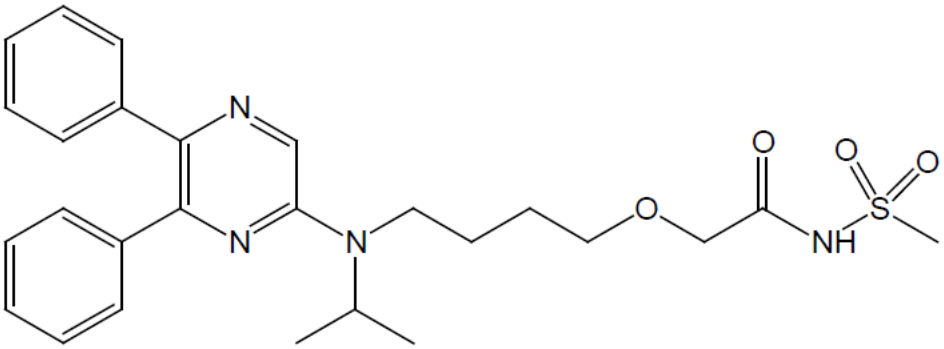
CAS Registry Number (Optional): 475086-01-2

Generic Name - Selexipag

Code Name
Chemical Name 2-{4-(5, 6-diphenylpyrazin-2-yl) (isopropyl) amino butoxy}-N-(methylsulfonyl) acetamide

Molecular Formula/Molecular Weight $C_{26}H_{32}N_4O_4S$ MW 496.62

Structure or Biochemical Description:



Pharmacologic Class: prostacyclin mimetic

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 104504, NDA 207947

2.3 Drug Formulation

Table 1: Composition of the Drug Product

Component	Quality Reference[a]	Function	Quantity per vial (mg)	
			Label Claim	Actual Amount per Vial[b]
JNJ-67896049 (b) (4)	Company specification	Active ingredient	1.80	(b) (4)
Glycine	Ph. Eur./USP	(b) (4)	180.00	
Polysorbate 20	Ph. Eur./NF		10.80	
Phosphoric acid, (b) (4)	Ph. Eur./NF		3.53[d]	
Sodium Hydroxide	Ph. Eur./NF	pH adjusting agent		(b) (4)
(b) (4)	Ph. Eur./USP	(b) (4)	q.s. ad (b) (4)	q.s. ad (b) (4)

[a] Where multiple compendia are listed, the compendium specific to the region of the submission is applied.
[b] An overfill is applied, in order to ensure the withdrawal of the full label dose.
(b) (4)
(b) (4)
(b) (4)

q.s. = Quantum satis
Note: (b) (4)

3. DESCRIPTION OF THE DILUENTS USED FOR RECONSTITUTION

The individual vials of drug product are reconstituted with 8.6 mL of 0.9% (w/v) sodium chloride solution for injection, USP to a nominal concentration of 225 µg/mL of drug substance (hereafter referred to as the reconstituted solution). An aliquot of this reconstituted solution is then further diluted with 0.9% (w/v) sodium chloride solution for injection, USP to the different concentrations depending on the required doses (hereafter referred to as the solution for infusion).

2.4 Comments on Novel Excipients

No novel excipients were used in this formulation.

2.5 Comments on Impurities/Degradants of Concern

No impurities or degradants of concern were seen in this formulation of Selexipag.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population are patients with pulmonary arterial hypertension who are currently treated with oral Uptravi and are temporarily unable to take the Uptravi oral tablets. Patients are anticipated to continue receiving intravenously an equivalent dose of the active metabolite to their previous dose of oral Uptravi. Intravenous dosing will be given B.I.D.

2.7 Regulatory Background

IND 104504 was initially submitted on 9/29/2009, and NDA 207947 was submitted on 12/22/2014, and approved on 12/21/2015.

3 Studies Submitted

3.1 Studies Reviewed

Since the oral Uptravi was approved in 2015, all toxicology data was reviewed with NDA 207947, with the exception of 3 studies submitted with the present IND. These studies, listed below, have all been reviewed in this NDA submission.

In Vitro Hemolytic Compatibility of selexipag and ACT-333679 in Human Peripheral Blood (T-12.667 GLP)

Local Tolerability Study in Rabbits after an IV and PV Injection (T-12.570 GLP)

Local Tolerability Study in Rabbits after IV, PV and IM Injection (T-16.036 GLP)

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

NDA 207947, IND 104504

10 Special Toxicology Studies

The following studies were done to support the submission and the transition to intravenous dosing:

Species/Strain (Sex/No. Per Group)	Route (Vehicle/Formulation)	Concentrations	Noteworthy Findings	Study No./ Location in CTD
Human peripheral blood (3 donors)	In vitro (1% DMSO: 0.9% NaCl)	ACT-293987: 3, 6, 9, 12, 36 and 120 ng/mL ACT-333679: 3, 6, 12, 24, 72 and 240 ng/mL)	No hemolysis. Mean plasma Hb values for ACT-293987 and ACT-333679 were <0.3 g/L (calculated percentage of hemolysis = 0%).	T-12.667 / 4.2.3.6
New Zealand White rabbits (1M+2F/group)	IV, and PV (0.9% NaCl)	8 and 40 µg/mL IV: 10mL/20min PV: 0.5mL/25sec	Well tolerated without any signs of local irritation: no mortality, clinical signs, effect on body weight, microscopic nor macroscopic findings.	T-12.570 / 4.2.3.6
New Zealand White rabbits (2M+2F)	IV, PV, and IM (0.9% NaCl)	36 µg/mL 0.5 mL bolus	Well tolerated without any signs of local irritation: no mortality, clinical signs, effect on body weights, food consumption, microscopic nor macroscopic findings.	T-16.036 / 4.2.3.6

ACT-293987: selexipag; ACT-333679: active metabolite; DMSO: dimethyl sulfoxide; F: female; Hb: plasma hemoglobin; IM: intramuscular; IV: intravenous; M: male, NaCl: sodium chloride; PV: paravenous.

10.1 Study title: The In-vitro Haemolytic Compatibility of ACT-293987 and ACT-333679 in Human Peripheral Blood

Study was done to examine the potential for Selexipag and its active metabolite to cause hemolysis. Selexipag at concentrations of 3, 6, 9, 12, 36, and 120 ng/mL or its active metabolite at concentrations of 3, 6, 9, 12, 24, 72, and 240 ng/mL were mixed with whole blood to determine hemolytic potential, with distilled water used as the positive control. The reason for the study is that the sponsor is developing an

intravenous formulation for use in patients when they are unable to take the oral tablets. The positive control gave appropriate results as expected, showing the validity of the study.

The test results showed that Selexipag (ACT-293987) and the active metabolite (ACT-333679) induced 0% hemolysis in human peripheral blood. The assay used replicates with 4 donor blood samples for Selexipag and 2 donor blood samples for the active metabolite.

Therefore, Selexipag and its active metabolite are not hemolytic and considered safe on a hemolytic basis.

10.2 Study Title: ACT-293987 – Local tolerance in the New-Zealand White Rabbit by the intravenous, paravenous and intramuscular route.

Study was done to examine whether Selexipag in an intravenous, paravenous or intramuscular route caused irritation, necrosis, or other issues when used. The study was done in the New Zealand White Rabbit using a single dose of 36 mcg/mL or vehicle alone (0.9% NaCl). Animals were dosed with a 0.5 mL bolus dose.

Injection sites were examined in the control and treated groups at the different sites. There were some mild erythemas and indurations, however, no more were seen in the Selexipag groups than in the normal saline controls.

Therefore, Selexipag when delivered via intravenous, paravenous or intramuscular routes caused no more irritation than the procedure itself or the vehicle alone. Selexipag is reasonably safe at the delivery site as indicated in this assay.

10.3 Study Title: Local Tolerability Study in Rabbits after an IV and PV injection (T-12.570 GLP)

This study was to examine the irritation potential for Selexipag in intravenous and paravenous modes of delivery. New Zealand White Rabbits were used for the study. Animals were given a single dose with 8 or 40 mcg/mL, with intravenous doses being infused at 0.5 mL/min for 20 min, and paravenous administration being given at 0.5 mL/25 seconds. The vehicle controls were 0.9% NaCl.

Signs of irritation or injury were comparable in the controls and the animals treated with Selexipag. Selexipag appears to be relatively safe for delivery via the intravenous or paravenous routes.

11 Integrated Summary and Safety Evaluation

Selexipag was approved for oral use in NDA 207947 in 2015. Since then the sponsor has developed an intravenous formulation for use in patients when they are unable to take the oral tablets. For this application, no new non-clinical data was submitted, except a hemolysis assay and 2 local tolerance studies to examine possible issues with

the use of an intravenous mode of administration. The studies did not reveal any issues that would affect the delivery of Selexipag in an intravenous route.

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/

JAMES M WILLARD
06/01/2021 01:36:35 PM

JEAN Q WU
06/01/2021 03:24:36 PM