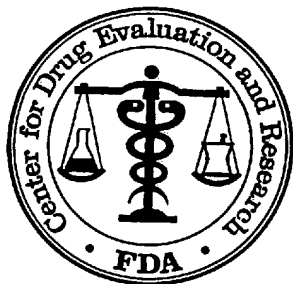


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214275Orig1s000

OTHER REVIEW(S)



DIVISION OF CARDIOLOGY AND NEPHROLOGY

Regulatory Project Manager Review

NDA: 214275
Drug: Upravi (selexipag) injection
Class: Prostacyclin receptor agonist
Applicant: Actelion Pharmaceuticals, Ltd.

Approved Indication: 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.

Received Date: 29 September 2020
Approval date: 29 July 2021
PDUFA date: 29 July 2021

❖ REVIEW TEAM

Office of New Drugs, Office of Cardiology, Hematology, Endocrinology and Nephrology, Division of Cardiology and Nephrology (DCN)

- Norman Stockbridge, MD, PhD – Division Director
- Mary Ross Southworth, PharmD – Deputy Director for Safety
- Michael Monteleone, MS, RAC – Associate Director for Labeling

Office of Pharmaceutical Quality

Office of New Drug Products

- Mohan Sapru, PhD – Application Technical Lead
- Ben Zhang, PhD – Drug Substance Reviewer
- Rao Kambhampati, PhD – Drug Product Reviewer

Office of Pharmaceutical Manufacturing Assessment

- Carl Lee, PhD – Process and Facility Reviewer
- Ash Bekele, PhD – Microbiology Reviewer

Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology

- Jean Wu, MD, PhD – Non-clinical Team Leader
- James Willard, PhD – Non-clinical Reviewer

Office of Clinical Pharmacology, Division of Cardiometabolic & Endocrine Pharmacology

- Doanh Tran, PhD – Cross-Disciplinary Team Leader
- Sudharshan Hariharan, PhD – Clinical Pharmacology Team Leader
- Harisudhan Thanukrishnan, PhD – Clinical Pharmacology Reviewer

Office of Regulatory Operations, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology

- Brian Cooney, MS, PSM – Regulatory Health Project Manager
- Bridget Kane, MS – Sr. Regulatory Health Project Manager

Office of Surveillance and Epidemiology, Division of Medical Error Prevention and Analysis

- Mariette Aidoo, PharmD – Safety Evaluator
- Hina Mehta, PharmD – Secondary Reviewer

Office of Medical Policy

Office of Prescription Drug Promotion

- Carrie Newcomer, PharmD – Regulatory Review Officer

Office of Medical Policy Initiatives, Division of Medical Policy Programs, Patient Labeling Team

- Barbara Fuller, RN, MSN, CWOCN – Team Lead
- Ruth Mayrosh, PharmD – Reviewer

❖ **BACKGROUND**

Upravi (selexipag), a prostacyclin receptor agonist developed by Actelion Pharmaceuticals, was approved in 2015 (NDA 207947) for oral administration (tablet) for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for patients with PAH. In April 2010, selexipag was granted orphan drug designation (#10-3048) for the treatment PAH. PAH is characterized by pulmonary arterial vasoconstriction, vascular remodeling, inflammation, and fibrosis, which eventually may lead to right ventricular failure and death. The efficacy of selexipag for the approved indication was established via the GRIPHON study.

The Applicant has now developed (IND 104504) an intravenous (IV) formulation of selexipag, which is the subject of this new NDA. In July 2016, the Applicant had a Type C meeting (Meeting Minutes dated 16 August 2016) with the Division of Cardiology and Nephrology (DCN) to discuss the development of the IV formulation of selexipag.

On 04 December 2017, the Applicant initiated Study #AC-065A309 titled: “A multicenter, open-label, single-sequence crossover study to assess safety, tolerability, and pharmacokinetics of IV selexipag in subjects with stable PAH switching from an oral stable dose of selexipag”. This study enrolled 20 participants with PAH to demonstrate that the IV formulation of selexipag had similar exposure to the active metabolite (ACT-333679) as that of the approved oral formulation. This study concluded on 29 May 2018. On 19 September 2019, the Applicant requested a Pre-NDA meeting with DCN to obtain agreement with the Division on content and format for an NDA submission (WRO Meeting Minutes dated 15 November 2019).

On 29 September 2020, the Applicant submitted NDA 214275 for Upravi (selexipag) IV injection to treat adult patients with PAH who are currently stable on oral selexipag but are temporarily unable to take tablets orally. To support this NDA, the Applicant submitted data from 2 clinical studies:

- 1) AC-065-110: A single-center, open-label, Phase 1 study consisting of a single-dose pilot phase and a randomized, two-way crossover, single-dose main phase to investigate the absolute bioavailability of a single oral dose of selexipag in healthy male subjects.
- 2) AC-065A309: A multicenter, open-label, single-sequence, cross-over study to assess safety, tolerability, and pharmacokinetics of intravenous selexipag in subjects with stable pulmonary arterial hypertension switching from an oral stable dose of selexipag.

The Applicant also submitted data from in-vitro hemolysis testing and in-vivo local tolerance testing as requested by the Agency (Meeting Minutes dated 16 August 2016) and provided reference to safety and efficacy data generated for NDA 207947, the approved tablet.

The application was filed on 28 November 2020. The Applicant submitted a request for Proprietary Name review on 23 November 2020.

Please see Discipline Review Section for recommendations.

❖ **REGULATORY TIMELINE and APPLICATION DETAILS**

- Pre-NDA Meeting (WRO): 15 November 2019
- NDA Stamp Date: 29 September 2020
- Filing Meeting: 16 November 2020
- Filing Date: 28 November 2020
- 74-day Letter: 07 December 2020
- Mid-cycle Meeting: 25 February 2021
- Labeling Meeting: 30 March 2021
- Team Meeting: 11 May 2021
- Labeling Meeting: 17 June 2021
- PDUFA Date: 29 July 2021

User Fee

There was no user fee associated with this application as selexipag has orphan drug designation for the treatment of PAH.

Facilities

Per the Integrated Quality Assessment (20 June 2021), the Office of Pharmaceutical Manufacturing Assessment has recommended approval for all listed manufacturing facilities for NDA 214275.

Site Inspections

The review team determined clinical site inspections were not needed.

Proprietary Name

DMEPA concluded that the Applicant's proposed Proprietary Name Uptravi was acceptable (Aidoo, 16 February 2021). The Applicant was notified on 17 February 2021.

Pediatric Review Committee (PeRC)

The application was exempt from PREA (21 U.S.C. 355c) because selexipag has orphan drug designation for the treatment of PAH.

Advisory Committee

N/A

Review Status

The Application was designated a Standard Review.

❖ **LABELING REVIEW**

Labeling negotiations began on 31 May 2021 and concluded on July 28, 2021. The attached documents show a summary of changes that were made to the Package Insert (PI) and Patient Package Insert (Patient Information) during the review cycle.

Multiple editorial and formatting changes were made throughout the PI and Patient Information. Language was added throughout the PI and Patient Information to differentiate content pertaining to UPTRAVI tablets only.

The following is a summary of changes made to the PI:

Changes to **HIGHLIGHTS OF PRESCRIBING INFORMATION** and the **FULL PRESCRIBING INFORMATION: CONTENTS** were made to conform with the revisions to the PI.

2 DOSAGE AND ADMINISTRATION

Preparation and dosing instructions pertaining to the injection were added.

In Section **2.6 Dosage Adjustment with Co-administration of Moderate CYP2C8 Inhibitors** the following language was removed.

(b) (4)

(b) (4)

3 DOSAGE FORMS AND STRENGTHS

UPTRAVI for injection and strengths were added.

5 WARNINGS AND PRECAUTIONS

The title of 5.1 was changed to ‘Pulmonary Edema with Pulmonary Veno-Occlusive Disease’.

Reviewer’s Note: Revision made for clarity; content of this subsection is unchanged.

6 ADVERSE REACTIONS

‘UPTRAVI for injection’ and associated infusion site reactions were added to Section **6.1 Clinical Trials Experience**.

8 USE IN SPECIFIC POPULATIONS

In Section **8.1 Pregnancy**, “to the active metabolite” was added for clarification. Language was added to describe results from a pre- and post-natal development study in pregnant rats.

11 DESCRIPTION

A paragraph was added to describe the contents of selexipag injection.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Language was added to describe the pharmacokinetics of IV selexipag in comparison to the oral tablet.

13 NONCLINICAL TOXICOLOGY

Revisions for clarity were made to the Carcinogenesis and Fertility sections.

16 HOW SUPPLIED/STORAGE AND HANDLING

Information describing the carton, container, closure, and storage of selexipag injection was added.

17 PATIENT COUNSELING INFORMATION

‘Patient Package Insert’ was changed to ‘Patient Information’.

The following sentence was removed ‘what to do if they miss a dose’ and was replaced with ‘To take a missed dose as soon as possible, unless the next dose is within the next 6 hours’.

The following changes were made to the PATIENT INFORMATION:

Information about UPTRAVI injection was added. See attached document and Patient Labeling review (13 July 2021) for details.

Carton & Container Labeling

Carton and container labels have been developed for Upravi injection 1800 mcg/vial.

❖ **DISCIPLINE REVIEWS**

Below are the conclusions reached by the primary review team. Please refer to DARRTS for complete reviews.

CDTL Memorandum (20 July 2021 – Tran, Stockbridge)

Recommended Action: Approval

Dr. Tran agreed with the review team’s findings and summarized the basis of approval for Upravi (selexipag) injection, concluding that the IV selexipag dosing regimen was well tolerated in patients with PAH and exhibited similar drug exposure to oral selexipag (NDA 207947). Dr. Stockbridge concurred with Dr. Tran’s summary and conclusions.

Clinical-pharmacology Review (02 July 2021 – Thanukrishnan/Tran)

Recommended Action: Approval

Dr. Thanukrishnan stated that study AC-065A309 “established that a switch from a stable oral dose of selexipag to the intravenous (IV) dose provided comparable exposure to the active metabolite (ACT-333679) and the switching back to the initial oral dose of selexipag was safe and well tolerated across the entire oral dose range, in participants with stable PAH.”

Chemistry, Manufacturing, and Controls (CMC) - Integrated Quality Review (20 June 2021 – Multiple reviewers)

Recommended Action: Approval

Per the CMC review, based on the stability data submitted to date, the expiry dating period for UPTRAVI (selexipag) injection shall be 24 months from the date of manufacture, when stored at 2°C to 8°C (36°F to 46°F) in the commercial packaging, protected from light. See full review located in Panorama for full assessment of each CMC aspect.

Nonclinical Review (01 June 2021 - Willard/Wu)

Recommended Action: Approval

Per the non-clinical review, the 3 studies [non-clinical] added to this NDA submission were to examine hemolytic potential of the Upravi 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 Upravi.

❖ **CONSULT REVIEWS**

The following is a list of consult reviews obtained during this review. Refer to DARRTS for complete reviews.

- OSE/DMEPA (labeling): Aidoo/Mehta – 09 April 2021
- OPDP (labeling): Newcomer – 13 July 2021
- Patient Labeling (labeling): Mayrosh/Newcomer/Fuller/Griffiths – 13 July 2021

❖ **CONCLUSION**

After taking into consideration all primary and consult reviews, the Division issued an approval letter for NDA 214275 on 29 July 2021. The letter was signed by Dr. Norman Stockbridge, Division Director.

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BRIAN T COONEY
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07/29/2021 04:45:37 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: July 13, 2021

To: Brian Cooney, Regulatory Project Manager
Division of Cardiology and Nephrology (DCN)
Office of Drug Evaluation I

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for UPTRAVI® (selexipag) for injection, for intravenous use

NDA: 214275

In response to the Division of Cardiology and Nephrology's (DCN) consult request dated November 20, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for UPTRAVI® (selexipag) for injection, for intravenous use. The purpose of this submission is to seek approval for a new formulation of UPTRAVI (selexipag) for injection, for intravenous use for the treatment of pulmonary arterial hypertension for patients who are currently treated with the tablet formulation but are temporarily unable to take oral therapy.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCN on July 1, 2021 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on July 13, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 25, 2021 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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CARRIE A NEWCOMER
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 12, 2021

To: Brian Cooney, MS, PSM
Regulatory Project Manager
Division of Cardiology and Nephrology (DCN)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Ruth Mayrosh, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): UPTRAVI (selexipag)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: NDA 214275

Applicant: Actelion Pharmaceuticals US, Inc.

1 INTRODUCTION

On September 29, 2020, Actelion Pharmaceuticals US, Inc. submitted for the Agency's review an original New Drug Application (NDA) 214275 for UPTRAVI (selexipag) for injection. The purpose of this submission is to seek approval for a new formulation of UPTRAVI (selexipag) for injection, for intravenous use for the treatment of pulmonary arterial hypertension for patients who are currently treated with the tablet formulation but are temporarily unable to take oral therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on November 20, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for UPTRAVI (selexipag) for injection.

2 MATERIAL REVIEWED

- Draft UPTRAVI (selexipag) for injection PPI received on September 29, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 1, 2021.
- Draft UPTRAVI (selexipag) for injection Prescribing Information (PI) received on September 29, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 1, 2021.
- Approved UPTRAVI (selexipag) tablets labeling dated September 4, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

RUTH I MAYROSH
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CARRIE A NEWCOMER
07/12/2021 02:45:18 PM

BARBARA A FULLER
07/12/2021 07:45:53 PM

LASHAWN M GRIFFITHS
07/13/2021 06:45:26 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 30, 2021
Requesting Office or Division: Division of Cardiology and Nephrology (DCN)
Application Type and Number: NDA 214275
Product Name and Strength: Uptravi (selexipag) for injection, 1800 mcg/vial
Applicant/Sponsor Name: ACTELION PHARMACEUTICALS LTD
OSE RCM #: 2020-2033-1
DMEPA Safety Evaluator: Mariette Aidoo, PharmD, MPH
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on June 25, 2021 for Uptravi (selexipag). We reviewed the revised container label and carton labeling for Uptravi (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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^a Aidoo, M. Label and Labeling Review for Uptravi (NDA 214275). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APRIL 9. RCM No.: 2020-2594.

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/s/

MARIETTE A AIDOO
06/30/2021 02:20:30 PM

HINA S MEHTA
07/01/2021 03:41:54 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 8, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214275
Product Name, Dosage Form, and Strength:	Uptravi (selexipag) for injection, 1,800 mcg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	ACTELION PHARMACEUTICALS LTD (Actelion)
FDA Received Date:	September 29, 2020
OSE RCM #:	2020-2033
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Actelion Pharmaceuticals submitted NDA 214275 for Upravi (selexipag) for injection proposing an intravenous route of administration for patients temporarily unable to take oral therapy with Upravi tablets. We reviewed the submitted container label, carton labeling, patient information sheet and prescribing information for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND INFORMATION

Upravi (selexipag) tablets was approved on December 21, 2015 under NDA 207947 as 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. Upravi tablets are available in 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,000 mcg, 1,200 mcg, 1,400 mcg, and 1,600 mcg.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other – Information Request	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Actelion is proposing a new dosage form (for injection) for Upravi (selexipag) under NDA 214275. The proposed intravenous route of administration is for patients temporarily unable to take oral therapy with Upravi tablets. We note the dose of Upravi for injection is determined by the patient's current dose of Upravi tablets. In Section 2 of the Upravi PI, we note the Applicant places strong emphasis on protecting the vial from light during the preparation and dilution of the product. The vial bears a "protective wrap" around the vial to protect the

contents from light. As such, we sent an Information Request (IR) on March 12, 2021 to Actelion asking them to submit an image depicting the container label portion when it is wrapped around the actual vial and when it is peeled back. On March 18, 2021 Actelion responded stating that the entire vial is (b) (4)

(b) (4) Images of the vial bearing the (b) (4) were provided to illustrate this (see Appendix F).^a We asked the Office of Pharmaceutical Quality (OPQ) if the drug product (powder in the vial), reconstituted solution, or diluted solution can be exposed to light for any amount of time. OPQ stated that if by mistake the drug powder is exposed to ambient light it should be ok for up to 1 hour and if the reconstituted solution or diluted solution is exposed to ambient light they should be ok for up to 2 hours. We note the PI contains instructions to protect the reconstituted solution from light and the infusion should be administered over 80 minutes.

We performed a risk assessment of the proposed Prescribing Information (PI), patient information sheet, carton and container label for Upravi for injection to identify deficiencies that may lead to medication errors or other areas of improvement. Our review of the proposed PI has identified a lack of clarity in the dilution and reconstitution instructions. These factors may confuse the user and inadvertently lead to medication errors. We identified areas of the proposed label and labeling that could be revised to improve clarity and readability of important information. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We find the proposed Upravi patient information sheet is acceptable from a medication error perspective. We have identified areas in the proposed PI, label and labeling for Upravi that may be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Actelion Pharmaceuticals Ltd.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information

1. Dosage and Administration Section

- a. We recommend revising the dosage statement for Upravi for injection to improve readability and add reference statement regarding instructions for preparation and administration.

^a Response to IR: Upravi/NDA 214275-Information Request regarding Label and Labeling Review. Silver Spring (MD): FDA, CDER, OND, DCN (US); 2021 MAR 18. NDA 214275.

- Revise the 5th bullet point to read: UPTRAVI for injection dose is determined by the patient’s current dose of UPTRAVI tablets. Administer UPTRAVI® for injection by intravenous infusion, twice daily. (2.2)
- Add 6th bullet to state: See Full Prescribing Information for instructions on preparation and administration. (2.3).

2. Dosage Forms and Strengths

- a. As currently presented, the product strengths greater than 1000 appear without a comma. We recommend stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands “1000’s” as hundreds “100” or ten-thousands “10000”.

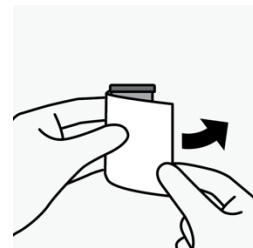
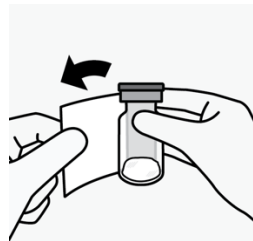
B. Prescribing Information

1. We recommend revising all instances of “(b) (4)” with appropriate terminology. Revise to 0.9% Sodium Chloride Injection, USP.
2. Dosage and Administration Section
 - a. As currently presented, information regarding UPTRAVI Film-coated Tablets and UPTRAVI for Injection are placed in separate sections. We recommend grouping both sub-headings under one section (i.e. Section 2.1 Recommended Dosage).
 - b. Under the Uptravi for Injection sub-heading, revise the first statement to prevent redundancy to state: “UPTRAVI for injection is for patients who are currently treated with UPTRAVI tablets but are temporarily unable to take oral therapy [see *Clinical Studies (14)*].”.
 - c. We recommend adding the infusion time in the recommended dosage section for the intravenous administration. Revise to “Dose of UPTRAVI for injection is determined by the patient’s current dose of UPTRAVI tablets (see Table 1) and should be administered by intravenous infusion over 80 minutes, twice daily.”
 - d. Relocate Table 1 directly beneath the second paragraph of the UPTRAVI for Injection sub-heading and delete the remainder of the section to alleviate redundancy. Please note revision of dose conversion of UPTRAVI for injection as shown below:

TABLE 1: Dosing conversion of UPTRAVI	
Oral tablets twice daily dose (mcg)	Intravenous twice daily dose (mcg)
200	225
400	450
600	675

800	900
1,000	1,125
1,200	1,350
1,400	1,575
1,600	1,800

- e. We recommend placing the preparation instructions before the administration instructions as the product needs to be reconstituted and diluted prior to administration. The heading should be *2.2 Preparation Instructions* and *2.3 Administration Instructions*.
- f. We recommend adding the heading, "Reconstitution" to clearly delineate the reconstitution instructions from the administration instructions.
- g. We recommend adding the heading, "Dilution" to clearly delineate the reconstitution instructions from the administration instructions.
- h. The first statement in Section 2.2 should read "Reconstitute and further dilute UPTRAVI prior to intravenous infusion." (b) (4)
 [Redacted] in the current Section 2.3 and replace with the information below.
- i. We recommend the following in bullet points for ease of readability:
 - Reconstitution:
 - i. Remove the carton of UPTRAVI for injection from the refrigerator and allow to stand for approximately 30 to 60 minutes to reach room temperature (68°F to 77°F [20°C to 25°C]).
 - ii. The vial needs to be protected from light at all times. Ensure the wrap around label is covering the entire vial.
 - iii. Peel back light protective wrap on vial to inspect the contents in the vial. It should appear white to almost white broken cake or powdered material. Close the light protective wrap on the vial.



- iv. Reconstitute UPTRAVI vial using a polypropylene syringe with 8.6 mL of 0.9% Sodium Chloride Injection, USP and slowly inject into the UPTRAVI vial with the stream directed toward the inside wall of the vial to obtain a concentration of 225 mcg/mL of selexipag.
- v. Gently invert the vial until completely dissolved. *Do not shake.*
- vi. Inspect the vial by peeling back the light protective wrap around the label for discoloration (b) (4)
The reconstituted solution should appear clear, colorless and free from foreign material. Do not use if the reconstituted solution is discolored, is cloudy, or contains visible particles. (b) (4)

- Dilution

- i. UPTRAVI must be diluted in glass containers only.
- ii. Withdraw 100 mL of 0.9% Sodium Chloride Injection, USP and transfer into an empty glass container.
- iii. Withdraw the required volume of reconstituted solution from the UPTRAVI vial using a polypropylene syringe and dilute into the glass container containing 100 mL 0.9% Sodium Chloride Injection, USP to (b) (4)
- iv. Mix the diluted solution by gentle inversion of the glass container 5 times. Do not shake.
- v. Protect diluted UPTRAVI from light at all times. Wrap the glass container completely with light protective cover. (b) (4)
- vi. (b) (4)
- vii. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. The diluted infusion solution should be clear and colorless. Discard if particulate matter is observed.

j. For Section 2.3 Administration Instructions (presently depicted as (b) (4)), delete (b) (4) and provide the following in bullet points for ease of readability.

- Administer by intravenous infusion over 80 minutes using an infusion set made of DEHP-free polyvinyl chloride (PVC), natural latex rubber-free microbore tubing.
- Do not use a filter for administration.
- (b) (4)

3. How Supplied/Storage and Handling Section

a. Section 16 How Supplied

- We recommend deleting the following statements:

(b) (4)

4.2 RECOMMENDATIONS FOR ACTELION PHARMACEUTICALS LTD (ACTELION)

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. Consider revising the Active Ingredient statement to read "Each vial contains 1,800 mcg of selexipag."
2. We recommend revising the storage statement to "Store refrigerated at 2°C to 8°C (36°F to 46°F). Store in original carton to protect from light."
We recommend removing the (b) (4) to prevent confusion as the vial size may cause confusion about contents in the vial.

B. Carton Labeling

1. Consider revising the Active Ingredient statement to read "Each vial contains 1,800 mcg of selexipag".
2. We recommend adding the statement "Reconstitute and Dilute prior to (b) (4)." on the principal display panel below the "For Intravenous Infusion Only" to prevent this important information from being overlooked.
3. We recommend revising the storage statement to: "Store refrigerated at 2°C to 8°C (36°F to 46°F). Store in original carton to protect from light."
4. We recommend revising the net quantity from "(b) (4)" to "One Vial".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Uptravi received on September 29, 2020 from ACTELION PHARMACEUTICALS LTD (Actelion), and the listed drug (LD).

Table 2. Relevant Product Information for Uptravi and the Listed Drug		
Product Name	Uptravi (for injection) (NDA 214275)	Uptravi ^b (tablets) (NDA 207947)
Initial Approval Date	NA	12/21/2015
Active Ingredient	selexipag	
Indication	Treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.	
Route of Administration	Intravenous	Oral
Dosage Form	for injection	Tablet
Strength	1,800 mcg/vial	200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg and 1600 mcg
Dose and Frequency	<p>- Uptravi for injection dose is determined by the patient's current dose of UPTRAVI tablets.</p> <p>- UPTRAVI[®] for injection must be administered by intravenous infusion, twice daily.</p>	<p>The recommended starting dose of UPTRAVI is 200 micrograms (mcg) given twice daily, (b) (4)</p> <ul style="list-style-type: none"> To achieve optimal clinical response, the dose is increased in increments of 200 mcg twice daily, usually at weekly intervals, (b) (4) The maximum dose evaluated for efficacy was 1600 mcg twice daily.

^b Uptravi [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2015 DEC 21. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/2015/207947s000lbl.pdf.

		<ul style="list-style-type: none"> • If a patient reaches a dose that cannot be tolerated the dose should be reduced to the previous dose level. • UPTRAVI may be taken with or without food. <p>Tablet should not be split, crushed or chewed.</p>
How Supplied	For Injection: 1,800 mcg of selexipag as a lyophilized powder in a single-dose vial for reconstitution and dilution	Bottle of 60 tablets for 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg and 1600 mcg (all strengths). Bottle of 140 tablets for 200 mcg tablets
Storage	Refrigerate the glass vial package before use from 2°C to 8°C (36°F to 46°F) in the original package in order to protect from light	20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].
Container Closure	10 mL Type I glass vial closed by a stopper and sealed with an aluminum flip-off button.	Bottle

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 17, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, selexipag. Our search identified two previous reviews^{c,d}, and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX F. INFORMATION REQUEST




On March 12, 2021, we sent the following information request to the Applicant:

We refer to your NDA 214275 for UPTRAVI (selexipag) for injection submitted September 29, 2020.

We note the container label contains a portion that is to be used to wrap around the vial. Please submit an image depicting the wrap around the actual vial. In addition, please submit an image depicting the vial when the wrap is peeled back.

Please respond to this request by close of business March 19, 2021

On March 17, 2021, the Applicant responded with images highlighting:

1. Vial is completely covered by the  (b) (4).
2.  (b) (4)
3. Yellow portion allows for visual inspection of the cake and reconstituted solution,  (b) (4)

(b) (4)

^c Aidoo, M. Label and Labeling Review for Uptravi (NDA 207947/S-008). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 25. RCM No.: 2020-1305.

^d Gao, T. Label and Labeling Review for Uptravi (NDA 207947). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAR 13. RCM No.: 2015-257.

^e <\\CDSESUB1\evsprod\nda214275\0012\m1\us\response-12mar2021.pdf>

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Uptravi labels and labeling submitted by ACTELION PHARMACEUTICALS LTD (Actelion).

- Container label received on September 29, 2020
- Carton labeling received on September 29, 2020
- Prescribing Information (Image not shown) received on September 29, 2020, available from <\\CDSESUB1\evsprod\nda214275\0001\m1\us\selexipag-draft-labeling-text-clean.docx>

G.2 Label and Labeling Images

Container (Vial) Label

(b) (4)

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

MARIETTE A AIDOO
04/08/2021 04:26:40 PM

HINA S MEHTA
04/09/2021 01:30:57 PM