CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214275Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 214275
UPTRAVI® (selexipag) for injection

Integrated Quality Review

Recommendation: Approval

Drug Name	UPTRAVI® (selexipag) for injection
Dosage Form; Type of Product	Injectable
Indication	Indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH
Strength	1800 mcg/vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Actelion Pharmaceuticals, Ltd
Submissions (s) Reviewed	NDA 214275, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ben Zhang	OPQ/ONDP/DNDAPI/NDB3
Drug Product	Rao Kambhampati	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Carl Lee	OPQ/OPMA/DPMAIV/PMB12
Microbiology	Ash Bekele	OPQ/OPMA/DMAI/MAB3
Application Technical Lead	Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5

RBPM: Grafton Adams (OPQ/OPRO/DRBPMI/RBPMB2)

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 214275 is recommended for approval. Based on the stability data submitted to date, the expiry dating period for UPTRAVI® (selexipag) for 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.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Quality Assessment Summary

I. Background: The Applicant, Actelion Pharmaceuticals, Ltd., has sought U.S. marketing approval for NDA 214275 in accordance with Section 505(b)(1) of the FD&C Act. The proposed product, a low dose injectable product of selexipag, has been developed to provide a selexipag treatment option for patients with PAH, who are temporarily unable to take the oral selexipag formulation. Selexipag is currently marketed as an oral formulation under the brand name of UPTRAVI®, and this application is submitted for an intravenous formulation of the same active pharmaceutical ingredient. The biopharmaceutic properties of selexipag and its active metabolite have previously been described in support of the oral selexipag formulation UPTRAVI®, which is approved for chronic treatment of patients with pulmonary arterial hypertension (PAH). The overall safety evaluation of the proposed intravenous formulation of selexipag is based on data from a Phase 3 clinical study and a Phase 1 clinical pharmacology study.

2. Drug Substance (Selexipag): The drug substance selexipag is manufactured by the same process and controls as described in the approved NDA 207947. Hence, the drug substance information is referenced to the approved information in NDA 207947 (also filed by Actelion Pharmaceuticals US, Inc., for Uptravi®, immediate release film-coated tablets). The proposed release specification for the drug substance, involving testing of critical quality attributes (CQAs), is adequate. 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).

3. Drug Product

3.1. Product Design, Release Specification and Packaging: 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 is a low dose injectable product of selexipag. (b) (4)

(b) (4), (b) (4) The proposed container closure system (glass vial, rubber stopper, and flip-off seal) is adequate for the intended use. The vials are also secondary packaged in cartons, (b) (4). The composition of the proposed commercial formulation remains unchanged from the Phase 3 formulation, with a slight increase of the fill weight so that reconstituted solution can be drawn precisely with commercially available syringes. None of the excipients used in the formulation is classifiable as novel excipient or of human or animal origin. The analytical methods have been validated and batch analysis data are adequate. The proposed product release specification, which includes testing the critical quality attributes, is adequate to assure product quality.

3.2. Manufacturing: The manufacturing process involves (b) (4) (b) (4) (b) (4) Based on the control strategy, including in-process controls, the manufacturing process is adequately controlled.

3.3. Microbiological Aspects: Microbiological controls for the manufacturing process, including (b) (4) are adequate. Type II DMF (b) (4) and Type III DMF (b) (4) referenced for the (b) (4), and (b) (4), (b) (4), respectively, have been previously reviewed and found adequate. The provided information and data concerning (b) (4) and process validation are adequate. Sterility and bacterial endotoxins are tested at release and on stability in accordance with USP <71> and USP <85>, respectively. The product specification meets regulatory expectations for a sterile drug product.

3.4. Expiration Date & Storage Conditions: Based on the 24-month long-term and 6-month accelerated stability data, 24 months expiration dating period is granted when the product is stored refrigerated at 2-8°C; protected from light.

III. Assessment of Manufacturing Facilities

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'.

IV. Environmental Exclusion

The Applicant's claimed categorical exclusion from the environmental assessment requirements per 21 CFR Part 25.31(b) is acceptable.

V. Life Cycle Knowledge Information

Final Risk Assessment

NDA 214275: UPTRAVI® (selexipag) for injection

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	**H (High)**	(b) (4)	Acceptable	
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	**M (Moderate)**		Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels may need to be evaluated based on the proposed maximum daily dose
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)		Acceptable	
Uniformity of Dose - Fill/ Deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	**L (Low)**		Acceptable	

From Initial Risk Identification	Review Assessment

QUALITY ASSESSMENT

Attribute/ CQA	Factors Affecting CQA	Initial Risk Ranking	Risk Mitigation or Aggravation	Final Risk Evaluation	Comments
Product Degradation Impurities	Formulation Product stability Process parameters Scale/equipment/ site	L (Low)	(b) (4)	Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	M (Moderate)		Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)		Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 214275 is recommended for approval. Based on the stability data submitted to date, the expiry dating period for UPTRAVI® (selexipag) for 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.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Division of Cardiology and Nephrology
ONDP/DNDPIII/NDPB5

Mohan K. Sapru -S

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LABELING REVIEW
NDA 214275

Note: The prescribing information document contains information for the approved Uptravi® (selexipag) tablets and the proposed Uptravi® (selexipag) for injection but in this labeling review assessment of the proposed selexipag for injection only was included.

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling	N/A	

requirement may be applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Inadequate	Quantities of all inactive ingredients should be included.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Inadequate	Sterility statement should be included.
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): Not applicable

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Inadequate	Since the drug product is provided as a lyophilized solid in a vial, "(b) (4) " should be deleted from the following statement: (b) (4): Each (b) (4) vial contains 1800 mcg of selexipag (b) (4).
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Inadequate	Amounts of inactive ingredients should be included.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: A*dequate after the deficiencies listed in the "Items for additional assessment" are addressed satisfactorily.*

Overall Assessment and Recommendation: *Adequate after the following changes are made to the current versions of the PI and container and carton labels:*

ITEMS FOR ADDITIONAL ASSESSMENT:

1) **Include sterility statement and, amounts of inactive ingredients in the Prescribing Information (11. Description Section) document and on the vial label and carton label.**

2) **Since the drug product is provided as a lyophilized solid in a vial, '** (b) (4) **" should be removed from the vial label and carton label.**

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Primary Labeling Assessor Name and Date: Rao V. Kambhampati, Ph.D. 5-14-2021

Rao Kambhampati

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Mohan Sapru

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	The drug product is indicated for the treatment of Pulmonary Arterial Hypertension (PAH).
NDA Number	214275
Assessment Cycle Number	1
Drug Product Name/ Strength	Selexipag (UPTRAVI®) for injection, 1800 µg/vial
Route of Administration	Intravenous
Applicant Name	Actelion Pharmaceuticals US Inc.
Therapeutic Classification/ OND Division	Division of Cardiovascular & Renal Drug Products
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: Recommended for Approval

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq 0001 (1)	09/29/2020
Seq 0009 (9), IR response-Microbiology	02/17/2021
Seq 0013 (13), IR response-Microbiology	03/30/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The current NDA provides an IV formulation of Selexipag (UPTRAVI®) for injection (a.k.a. IV selexipag), 1.8 mg/vial. The drug product, presented as eight different strengths (200 to 1600 µg selexipag/tablet), has been approved as an oral formulation under the brand name of UPTRAVI®.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): None.

Supporting Documents:

Type II DMF [redacted] is referenced for the [redacted] regarding the [redacted] The most recent sterility assurance review of the DMF [redacted] ([redacted]) was deemed adequate, dated 3/31/2020.

Type III DMF [redacted] is referenced for the [redacted], [redacted] validation of the [redacted] bag. The most recent requalification data in the DMF [redacted] were found adequate ([redacted].docx on 25 June 2019; [redacted].docx on 01 July 2019; [redacted].docx on 03 March 2021).

S DRUG SUBSTANCE

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