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APPLICATION NUMBER:

217686Orig1s000

PRODUCT QUALITY REVIEW(S)

Title:	New Drug Application (NDA) Integrated Quality Assessment Template
Document ID:	OPQ-ALL-TEM-0004
Effective Date:	04 Nov 2022 Revision: 08
Total Pages:	8

Template Revision: 03

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 217686
Assessment # 1

Drug Product Name	Aprocitentan tablet
Dosage Form	Tablet
Strength	12.5 mg (b) (4)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Idorsia Pharmaceuticals Ltd
US agent, if applicable	Idorsia Clinical Development US Inc., Cherry Hill, New Jersey
Proposed Indication(s) including Intended Patient Population	Treatment of hypertension in patients who are not adequately controlled on other drugs
Duration of Treatment	N/A
Maximum Daily Dose	(b) (4) mg once daily
Alternative Methods of Administration	None

Submission(s) Assessed (eCTD Sequence)	Document Date	Discipline(s) Affected
0001	12/19/2022	Quality (Original NDA Submission)
0010	03/10/2023	Quality
0011	03/24/2023	Quality
0013	04/18/2023	Quality
0014	04/20/2023	Quality
0015	04/26/2023	Quality
0018	05/12/2023	Quality
0020	05/16/2023	Quality
0022	05/26/2023	Quality
0027	06/28/2023	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Ben Zhang	Zhengfu Wang
Drug Product	Ali Mohamadi	Akm Khairuzzaman
Manufacturing	Liya Tang	Feiyan Jin
Biopharmaceutics	Rebecca Moody	Haritha Mandula
Environmental	Ali Mohamadi	Akm Khairuzzaman
Regulatory Business Process Manager	Grafton Adams	
Application Technical Lead	Akm Khairuzzaman	

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Adequate	07/12/2023	All DMFs is acceptable per the drug product reviewer to support this NDA. Required information are provided in the NDA and were found to be adequate by the reviewer
	III			Adequate		
	III			Adequate		
	III			Adequate		
	III			Adequate		

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

LOA provided to reference the NDA-204410 for OPSUMIT® (macitentan), approved on 18 October 2013 for the treatment of pulmonary arterial hypertension.

Document	Application Number	Description
End of Phase 2 Meeting Minutes Reference ID: 4164217	IND 122772	Meeting minutes dated 10/06/2017
Pre-NDA Meeting Minutes Reference ID: 4949804	IND 122772	Meeting minutes dated 03/09/2022

2. CONSULTS None

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

From the chemistry, manufacturing, and controls (CMC)/quality perspective, this NDA for Aprocitentan Tablet, 12.5 mg, (b) (4) is **recommended for approval**. Product shelf-life of 24 months is approved when the drug product is stored at 20 °C to 25 °C (68 °F to 77 °F) in the proposed commercial container closure system. Excursions are permitted from 15 °C to 30 °C (59 °F to 86 °F).

II. SUMMARY OF QUALITY ASSESSMENTS

Aprocitentan is a small synthetic new molecular entity indicated for the treatment of hypertension. The applicant, Idorsia Pharmaceuticals Ltd has sought U.S. marketing approval for Aprocitentan Tablet, 12.5 mg, (b) (4) in accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. The proposed drug product is an oral immediate release tablet, formulated with commonly used pharmaceutical grade excipients. Based on adequate characterization of the physicochemical characteristics of the drug substance, thorough understanding of the selected excipients and their interaction with the drug substance and drug product design, manufacturing process control along with data from multiple batches, and stability studies; the applicant has adequately defined the quality target product profile (QTPP), critical quality attributes (CQAs), and the required manufacturing process control for commercial manufacturing of the proposed new drug product, Aprocitentan Tablet, 12.5 mg (b) (4). All listed manufacturing facilities are currently GMP compliant to manufacture this product commercially. Therefore, from overall quality perspective, the proposed control strategies are adequate to ensure consistent product quality regarding the identity, strength, purity, potency, and stability.

A. Quality Assessment Overview

Drug Substance: Adequate

Aprocitentan is a small synthetic new molecular entity which has been adequately characterized. The molecule has no chirality and no counterion. The (b) (4) is adequately controlled by acceptable manufacturing process. The designated regulatory starting materials and their specification is found to be adequate by the reviewer. All identified impurities are adequately controlled in the drug substance. The risk for (b) (4) impurities in the drug substance is also found to be very minimal. During the review, the reviewer identified that polymorphism and particle sizes of the drug substance are the most critical quality attributes because the drug substance has low solubility and high permeability across the pH range of the gastrointestinal tract (pH 1.2–6.8) in aqueous buffer systems. The reviewer concludes that an acceptable regulatory specification is in place for these critical attributes along

with other quality attributes that can ensure consistent quality of the drug substance for every batch prior to its use for the manufacture of the drug product, commercially. The stability data support a (b) (4)-month re-test period under long-term storage conditions (b) (4) The drug substance is adequately packed in (b) (4) .

Drug Product: Adequate

Aprocitentan Tablet, 12.5 mg (b) (4) is an immediate release film coated tablet dosage form which is formulated with the following commonly used excipients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, (b) (4) yellow, and (b) (4). All excipients are USP-NF compendial including the components of film coating materials (i.e., (b) (4) yellow, and (b) (4)) and are controlled as per their monographs. The quantitative amount of all these excipients used in the formulation composition do not exceed the reported IIG limit in the FDA's database. The drug product is supplied in the HDPE bottle and blister. The drug product reviewer concludes that an acceptable regulatory specification for routine quality control is in place which includes the following tests for the identified critical quality attributes (CQAs): appearance, identification, impurity, assay, dissolution, (b) (4), uniformity of dosage forms, and microbial limits. The drug product reviewer in consultation with the non-clinical reviewer concludes that the degradation impurity (i.e., (b) (4)) is qualified at NMT (b) (4) %. During the review, (b) (4) This has been resolved by requesting additional analytical data from the Applicant, which demonstrates that the risk is very low. All the analytical methods have been adequately validated. Critical analytical methods were also verified by the FDA's Office of Testing and Research (OTR) and are found to be adequate. Finally, the drug product reviewer accepted the proposed shelf life of 24 months when the drug product is stored at 20 °C to 25 °C (68 °F to 77 °F) in the proposed commercial container closure system. Excursions are permitted from 15 °C to 30 °C (59 °F to 86 °F).

Labeling: Adequate

Minor editorial changes are made in the package insert under CMC section. Overall, the reviewer made an acceptable recommendation for the labeling including container closures.

Manufacturing: Adequate

(b) (4) The manufacturing process reviewer concludes that the

manufacturing process is adequately controlled by appropriate control strategy, including in-process controls.

Biopharmaceutics: Adequate

The biopharmaceutics reviewer concludes that the proposed dissolution method and acceptance criterion for quality control (QC) testing of Aprocitentan tablets at release and on stability is adequate. Note that the commercial drug product differs from the phase III clinical tablets with respect to identification such as debossing and film-coating color. The biopharmaceutics reviewer concludes that such differences are considered minor and are unlikely to impact drug product performance in vivo which is supported by adequate in vitro drug release similarity data. Therefore, the bridging between the pivotal phase 3 clinical batches and the to-be-marketed product is adequate. During the review process, the biopharmaceutics reviewer identified that the drug substance particle size distribution (PSD) is critical because of its low solubility characteristics. To mitigate the risk of incomplete dissolution, the biopharmaceutics reviewer (along with the drug substance reviewer) negotiated with the Applicant (through information request) to establish an appropriate PSD limit in the specification.

Microbiology (if applicable): Adequate

The manufacturing process reviewer concludes that the Applicant's proposal of (b) (4) testing of microbial limits for the drug product release- test at least (b) (4) per year is acceptable. The result of the microbial limits from the exhibit batches at release and stability shows that the risk of microbial contamination in this solid oral dosage form is very low.

Manufacturing Facilities: Adequate

Based on the inspection history, manufacturing experience and acceptable compliant status, the Office of Pharmaceutical Manufacturing Assessment (OPMA) has recommended an overall approval for all the currently listed manufacturing and testing facilities concerning this NDA.

Environmental Assessment: Adequate

Based on the Agency's environmental assessment (EA) for Aprocitentan, the estimated concentration at the point of entry (EIC) of the drug substance is found to be less than 1 ppb per 21 CFR 25.31(b). Therefore, the reviewer concludes that there is an absence of extraordinary circumstances which fulfills the requirement as per the 21 CFR 15.15(a).

B. Risk Assessment

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Assay, stability	Low	The NDA contains 24-month of long-term and accelerated stability data from 6 registration batches (3 batches per strength). the Applicant is seeking 24-month expiry; therefore, the risk is low.	Low	Stability data indicates no sign of degradation trending and thus the risk is low.
Physical (solid-state) stability	Medium	(b) (4)	Low	(b) (4)
Degradation impurities	Low	Controlled as per the specification. (b) (4) and (b) (4) are the two major impurities. They were qualified by a 39-week toxicological study in dogs. Qualification level claimed are (b) (4)% and (b) (4)%, respectively. The risk is low.	Low	During review, the impurity qualification data was further confirmed with the non-clinical reviewer and found to be a low risk factor. All stability data indicates that the impurity level does not exceed the specified limit in specification.
Content Uniformity	Low	Controlled as per the specification. Therefore, the risk is low.	Low	No change in risk level after review.
Microbial Limits	Low	Controlled as per the specification. Additionally, the dosage form is a solid oral tablet. Therefore, the risk is low.	Low	No change in risk level after review.
(b) (4)	Low	Controlled as per the specification. Therefore, the risk is low.	Low	No change in risk level after review.
Dissolution	Medium	The drug substance is a poorly soluble compound. Dissolution could be the rate limiting step. Therefore, dissolution is a critical quality attribute and its testing methodology need to be carefully reviewed.	Low	During the review, both the drug substance and biopharmaceutics reviewers engaged through a collaborative discussion to establish appropriate particle size distribution for the drug substance. After sending multiple IRs, the Applicant finally has established an appropriate (b) (4). The dissolution method and their limits are found to be adequate for routine quality control by the biopharmaceutics reviewer. Therefore, the risk is now low.

C. List of Deficiencies for Complete Response: N/A

Application Technical Lead Name and Date:

Akm Khairuzzaman, Ph.D. 8/11/2023 Akm Khairuzzaman

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

This assessment is based on labeling info in module 1.14.1 in sequence 0001(1).

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[1]	Adequate	TRADENAMETM (aprocitentan) tablets
Route(s) of administration	Adequate	for oral use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Tablets: 12.5 mg (b) (4)
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.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

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

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)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	TRADENAME may be taken with or without food. **Clinical revision:** **Added: swallow tablets whole** **Deleted:** (b) (4) [redacted]
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"*	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 11).	N/A	

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.*	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	Tablet
Strength(s) in metric system	Adequate	12.5 mg (b) (4)
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	• 12.5 mg: yellow to orange round, film-coated tablet, debossed with "AN" on one side and plain on the other side. (b) (4)
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.	N/A	

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	TRADENAME™ (aprocitentan)
Dosage form(s) and route(s) of administration	Adequate	[redacted] (b) (4) for oral administration.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	The inactive ingredients are croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. [redacted] (b) (4) the film coating contains the following inactive ingredients: hydroxypropyl cellulose, iron oxide black, iron oxide red, iron oxide yellow, polyvinyl alcohol, silica colloidal hydrated, talc, titanium dioxide, and triethyl citrate.
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.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	**Non-clinical revision:** **Deleted: [redacted] (b) (4) ERA** **Added: endothelin receptor antagonist**

Chemical name, structural formula, molecular weight	Adequate	The chemical name of aprocitentan is N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-sulfamide. It has a molecular formula of C16H14Br2N6O4S and a molecular weight of 546.2 g/mol.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	Aprocitentan is a white to off-white powder that is insoluble in water.

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	

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	Tablet
Strength(s) in metric system	Adequate	12.5 mg (b) (4)
Available units (e.g., bottles of 100 tablets)	Adequate	**CMC revision:** **Deleted:** - (b) (4) - (b) (4) **child-resistant closure** **Added:** - **Each blister contains 10 tablets** - **Each bottle contains 30 tablets and has a child-resistant closure**
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	12.5 mg: yellow to orange round, film-coated tablet, debossed with "AN" on one side and plain on the other side. – NDC 80491-125-10 – NDC 80491-125-30 (b) (4)
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.	N/A	
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	Store in the original package. Protect from light and moisture. **DMEPA revision:** **Added: Dispense to patient in original container only. Replace cap securely each time after opening. Do not discard desiccant**

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	Store at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature].
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	Adequate	child-resistant closure

1.2.5 Other Sections of Labeling

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	**CMC revision:** **Added:** **Distributed by:** **Idorsia Pharmaceuticals US Inc.** **Radnor, PA 19087**

2.0 PATIENT LABELING

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]	Adequate	TRADENAME [phonetic spelling] (aprocitentan) Tablets, for oral use
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	Store TRADENAME tablets at room temperature, between 68°F and 77°F (20°C and 25°C).
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	Adequate	**DMEPA revision:** **Added: TRADENAME bottle contains a desiccant packet to help keep your tablets dry (protect them from moisture).** (b) (4) **Tightly close the TRADENAME bottle each time after opening.**
Active ingredient(s) (if applicable)	Adequate	aprocitentan
Alphabetical listing of inactive ingredients (if applicable)	Adequate	croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. (b) (4) hydroxypropyl cellulose, iron oxide black, iron oxide red, iron oxide yellow, polyvinyl alcohol, silica colloidal hydrated, talc, titanium dioxide, and triethyl citrate.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Distributed by: Idorsia Pharmaceuticals US Inc. Radnor, PA 19087

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(b) (4)

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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[3], (font size and prominence)	Adequate	Container: (b) (4) Carton: (b) (4)
Strength(s) in metric system	Adequate	12.5 mg (b) (4)
Route(s) of administration	N/A	
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)	Adequate	Bottle presentation: (b) (4) Blister presentation: (b) (4)
"Rx only" displayed on the principal display	Adequate	It is present in both presentations (bottle and blister) for both carton and container labels
NDC	Adequate	It is present in both presentations (bottle and blister) for both carton and container labels
Lot number and expiration date	Adequate	It is present in both presentations (bottle and blister) for both carton and container labels
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	(b) (4)
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.	N/A	

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

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.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	It is present in both presentations (bottle and blister) for both carton and container labels

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	(b) (4)
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	(b) (4)
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
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: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date:

Ali Mohamadi, Ph.D., 7/12/2023

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Akm Khairuzzaman

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Date: 7/12/2023 02:18:59PM
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Ali Mohamadi

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Date: 7/12/2023 01:49:31PM
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CHAPTER VI: BIOPHARMACEUTICS

Product Information	505(b)(1); Type 1: New Molecular Entity- Aprocitentan Tablet
NDA Number	217686
Assessment Cycle Number	1
Drug Product Name/ Strength	Aprocitentan Tablets; 12.5 mg (b) (4)
Route of Administration	Oral
Applicant Name	Idorsia Pharmaceuticals Ltd
Therapeutic Classification/ OND Division	Anti-hypertensive agent/Division of Cardiology and Nephrology (DCN)
RLD/RS Number	N/A
Proposed Indication	In combination with other antihypertensive drugs, indicated for the treatment of hypertension to lower blood pressure (BP) in patients who are not adequately controlled on other drugs.

Assessment Recommendation: **Adequate**

Assessment Summary:

On 12/19/2022, the Applicant, Idorsia Pharmaceuticals Ltd., submitted an NDA under 505(b)(1) seeking marketing approval for TRYVIO (aprocitentan) Tablets, 12.5 mg (b) (4)

Aprocitentan is a dual endothelin receptor antagonist (ERA) indicated for the treatment of hypertension, to lower blood pressure in patients who are not adequately controlled on other drugs. It is noted that aprocitentan has the same chemical structure of the active metabolite of macitentan (Opsumit®; NDA 204410; approved 10/18/2013), which is indicated for the treatment of pulmonary arterial hypertension.

The proposed drug product is formulated as round film-coated tablets containing 12.5 mg (b) (4) of aprocitentan and manufactured by (b) (4) . The final 12.5 mg (b) (4) film-coated tablets proposed for commercialization only differ from the pivotal Phase 3 formulation in the debossing and the film-coat color. No changes were made to the process site, equipment, or batch size.

The recommended dose is 12.5 mg taken orally once daily, with or without food. (b) (4)

In support of this submission, the Applicant provided efficacy and safety data from a single pivotal Phase 3 study (ID-080A301 PRECISION) supplemented by data from a Phase 2 dose-finding study (AC-080A201). The clinical studies showed dose proportional PK in tested range of 5 mg-100 mg aprocitentan once daily with Tmax achieved 3-5 hr after single doses up to 50 mg.

This Biopharmaceutics assessment is focused on the assessment of the proposed dissolution method and acceptance criterion for quality control (QC) testing of aprocitentan tablets at release and on stability as well as formulation bridging between the pivotal Phase 3 clinical batches and the to-be-marketed product.

The FDA approved quality control dissolution method and acceptance criterion (finished drug product batch release and stability testing) for 12.5 mg (b) (4) are as follows:

Medium	pH 6.8 Phosphate Buffer with 0.05% (w/v) CTAB and 0.5% (w/v) Tween® 20
Volume/Temp	900 mL; 37°C
USP Apparatus	2 (paddle)
Rotational Speed	50 rpm
Acceptance Criterion	NLT (b) (4) % (Q) of the labeled amount of aprocitentan is dissolved in 30 minutes

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Medium	Aprocitentan is a low solubility drug substance.	Low	To mitigate risk for slow or incomplete dissolution, the Applicant instituted a (b) (4) . Further, the proposed dissolution method was discriminatory towards drug substance particle size distribution (f2 < 50 for drug product batches produced with (b) (4) API).

Overall Recommendation: From the Biopharmaceutics perspective, NDA 217686 for the proposed Aprocitentan Tablets, 12.5 mg (b) (4), is **Adequate** and recommended for **Approval.**

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0001(1) Original Submission	12/19/2022
0018(18) Quality IR Response	5/12/2023
0022(22) Quality IR Response	5/26/2023

Highlight Key Issues from Last Cycle and Their Resolution: None

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

B.1 BCS DESIGNATION

Assessment: Not applicable. The Applicant did not request an official BCS claim. Therefore, no assessment is necessary. The Applicant reported aprocitentan drug substance exhibits low aqueous solubility and high permeability across cell membranes.

Solubility: *Low.* The Applicant conducted solubility testing across the pH range of 1.2-6.8 and found that aprocitentan exhibits low solubility across the entire physiological pH range. The solubility of aprocitentan increases in FaSSIF and FeSSIF media due to the presence of bile salts. Solubility of aprocitentan in aqueous media is provided below in Table 1 and solubility of aprocitentan in biorelevant media is provided in Table 2.

Table 1. Equilibrium Solubility of Aprocitentan in Aqueous Medium as a function of pH

Aqueous media	pH	Solubility [µg/mL]	USP definition
Water	6.29	2.6	Practically insoluble, or Insoluble
0.1N HCl	1.13	1.2	Practically insoluble, or Insoluble
0.01N HCl	2.10	1.2	Practically insoluble, or Insoluble
Citric acid – NaOH – HCl buffer pH 2	2.02	1.2	Practically insoluble, or Insoluble
Citric acid – NaOH pH 5	4.97	1.2	Practically insoluble, or Insoluble
KH_2PO_4 – $Na_2HPO_4.2H_2O$ buffer pH 7	6.95	10.5	Practically insoluble, or Insoluble
Boric acid – NaOH – KCl buffer pH 9	8.92	778	Very slightly soluble
$Na_2HPO_4.2H_2O$ – NaOH buffer pH 12	9.72	11,520	Sparingly soluble
0.1N NaOH	9.77	50,880	Soluble

Table 2. Equilibrium Solubility of Aprocitentan in Biorelevant Media

Aqueous media	pH	Solubility [µg/mL]	USP definition
SGF pH 1.3	1.20	2.2	Practically insoluble, or Insoluble
FaSSIF	6.47	18.2	Practically insoluble, or Insoluble
FeSSIF	4.95	16.4	Practically insoluble, or Insoluble

FaSSIF = fasted state simulated intestinal fluid; FeSSIF = fed state simulated intestinal fluid; SGF = simulated gastric fluid; USP = United States Pharmacopeia.

Permeability: ***High.*** The Applicant conducted an in vitro study to determine the bidirectional permeability of aprocitentan in MDCKII wild-type cells. The Applicant used propranolol and metoprolol as highly permeable reference compounds, while atenolol and mannitol were used as intermediate and low permeable reference compounds, respectively. In the A-B (i.e., absorption) direction, the P_{app} value of aprocitentan was 13.6×10^{-6} ±1.5 cm/s. This value was in the range found for metoprolol (which had a P_{app} value of 17×10^{-6} ± 2.5 cm/s), indicating aprocitentan has high permeability across cell membranes.

Dissolution: See Assessment below.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

- ***Proposed Dissolution Method***

Apparatus	Speed	Medium/Temperature	Volume	Acceptance Criterion
USP Type II (Paddle)	50 RPM	pH 6.8 Phosphate Buffer with 0.05% (w/v) CTAB and 0.5% (w/v) Tween® 20 37 ± 0.5°C	900 mL	Q= (b) (4)% in 30 minutes

- ***Dissolution Method Development***

(b) (4)

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(b) (4)

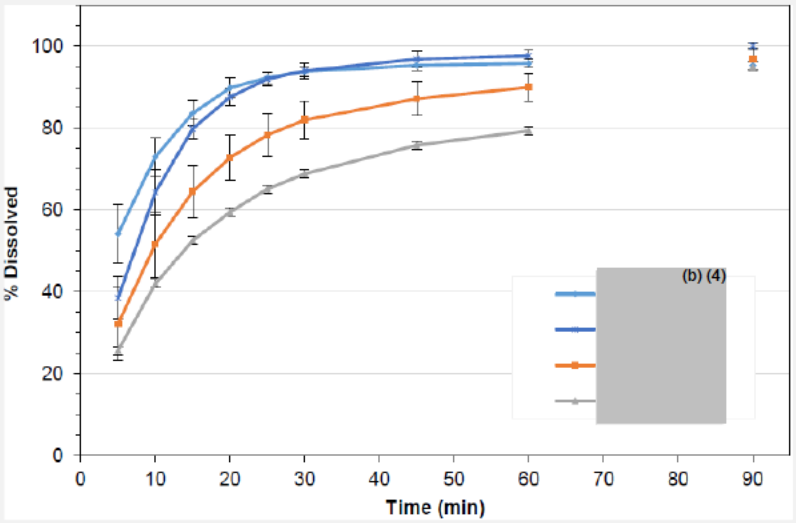
[redacted]

- ***Discriminating Ability of the Dissolution Method:*** The Applicant investigated the proposed dissolution method's capability to discriminate towards 1) drug product batches produced using drug substances of different particle sizes, 2) process changes, 3) changes on stability, and 4) formulation changes.
  - ***Effect of Drug Substance Particle Size:***

    The dissolution rate of aprocitentan, as a low soluble drug substance, is affected by particle size. [redacted] (b) (4) [redacted]. The proposed dissolution method was able to distinguish batches with aberrant PSDs. Specifically, batches manufactured with [redacted] (b) (4) (i.e., D90= [redacted] (b) (4) µm) would pass the proposed specification at Stage 2, while batches manufactured with [redacted] (b) (4) drug substance (i.e., D90= [redacted] (b) (4) µm) would not meet the proposed specification.

Nevertheless, in response to an IR, the Applicant implemented (b) (4) to further mitigate risk.

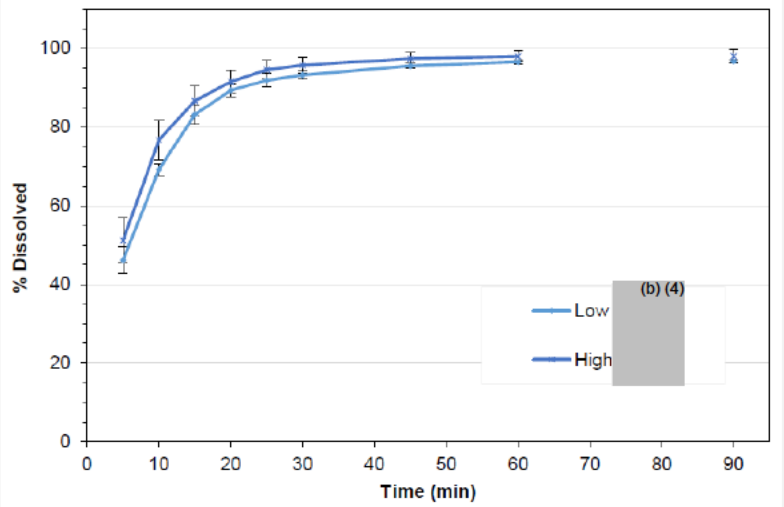
Figure 2. Dissolution Profiles of Batches Manufactured with Different API particle sizes



- ***Changes to the Amount of (b) (4):***

The Applicant investigated the discriminatory nature of the proposed dissolution method with respect to the amount of (b) (4) as the amount of (b) (4) and thus, dissolution. Drug product batches were manufactured with different amounts of (b) (4) (i.e., ±(b) (4)% target level of (b) (4)). The dissolution method was sensitive to changes in level of (b) (4), but it is not considered discriminatory.

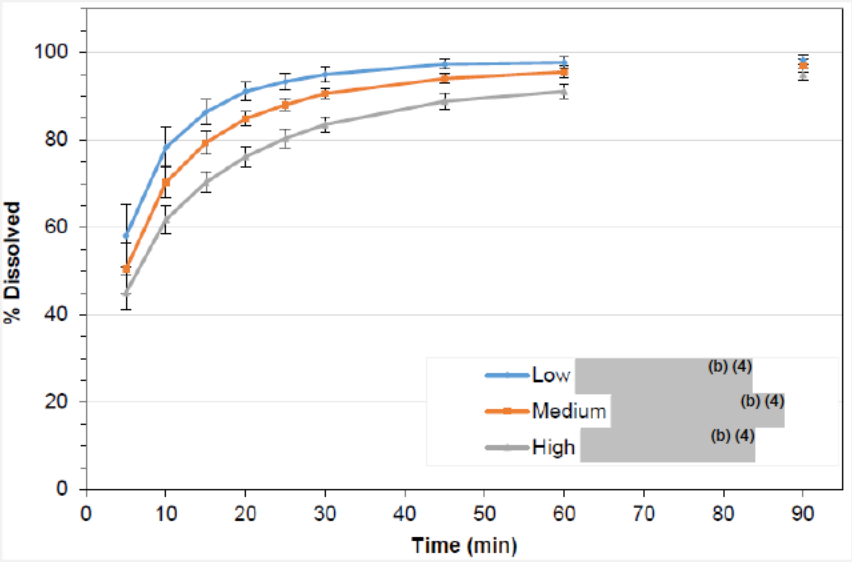
Figure 3. Dissolution Profiles of Batches Manufactured with Different Levels of (b) (4)



- ***Changes to (b) (4) Parameters:***

To study the discriminating capability of the dissolution method towards changes in drug product manufacturing process parameters, the Applicant produced batches that used different amounts of (b) (4). Batches produced with different amounts of (b) (4) were significantly different from each other with the dissolution rate increasing as amount of (b) (4) decreased.

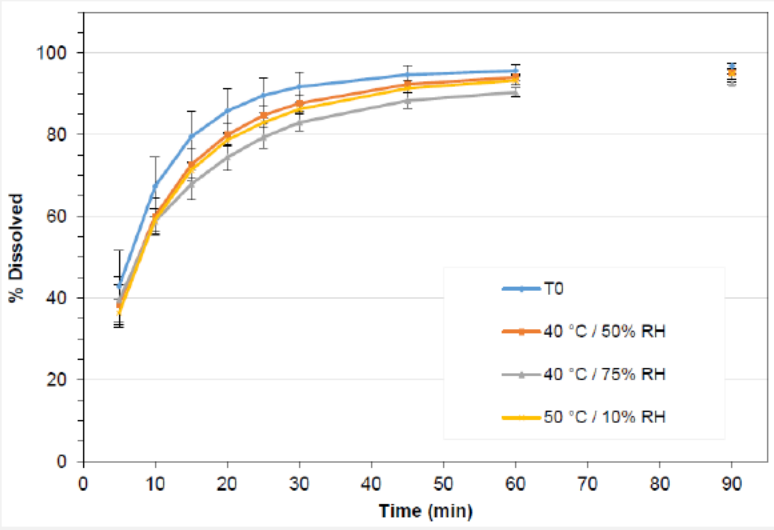
Figure 4. Dissolution Profiles of Batches Manufactured with Different Amounts of (b) (4)



- ***Drug Product Stability Changes:***

  As storage conditions can induce chemical and physical changes in the drug product, the Applicant assessed whether the proposed dissolution method was discriminatory towards drug product changes during storage. The same drug product batch was exposed to different temperature and humidity stress conditions.

Figure 5. Dissolution Profiles of Drug Product Batch 2010217 (25 mg) Exposed to Different Storage Conditions



The proposed dissolution method was sensitive to changes in the drug product upon stability with differing dissolution profiles of drug product exposed to high humidity and temperature changes. Therefore, the proposed dissolution method was considered as stability indicating per the Applicant.

- ***Dissolution Acceptance Criterion:*** The Applicant provided full profile dissolution data for 25 mg Clinical Trial Batches 1711993, 2010217, and 211887; 12.5 mg Clinical Trial Batch 11711985; and 25 mg Exhibit Batch 1915877. It is noted that all batches meet the proposed acceptance criterion of "NLT(b) (4)% (Q) of the labeled amount of aprocitentan dissolved in 30 minutes." Further, all exhibit batches are meeting at release and on stability.

Figure 6. Average Dissolution Profiles of 25 mg Clinical Batches (2010217 and 2111887) and Representative Registration Batch (1915877)

Table 5. Mean Dissolution Profile Data of Pivotal Clinical Batches

Batch Number/Time (min)	5	10	15	20	25	30	45	60	90
1711993 (25 mg)	39	62	75	82	87	90	95	97	99
2010217 (25 mg)	58	78	86	91	93	95	97	98	98
2111887 (25 mg-(b) (4))	46	72	84	91	94	96	98	98	99
1711985 (12.5 mg)	56	77	87	91	94	95	97	97	98

Reviewer comment: 25 mg strength batches 1711993, 1815781, and 2010217 and 12.5 mg strength batches 1711985, 1815788, 2010225 were tested in the pivotal Phase 3 clinical trial. All batches would meet an acceptance criterion of "NLT(b) (4)% (Q) in(b) (4) minutes;" however, batch 1711993 (25 mg strength) would need stage 2 level of testing (see highlight in Table 5). The Applicant optimized the dissolution method mainly via optimizing the dissolution medium, but the method was discriminating against changes to drug substance particle size, changes to manufacturing process ((b) (4)), and to drug product changes upon stability. Further, the Applicant has instituted

control strategies (e.g., [redacted] (b) (4)) that will help ensure the quality of the drug product. Considering the dissolution data for the pivotal Phase 3 clinical trial batches (see Table 5), the similar formulation for 12.5 mg and 25 mg tablets ([redacted] (b) (4)), and the in vivo Tmax of 3-5 hours, the proposed dissolution criterion of "Q= [redacted] (b) (4) % in 30 minutes" is acceptable [redacted] (b) (4) .

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

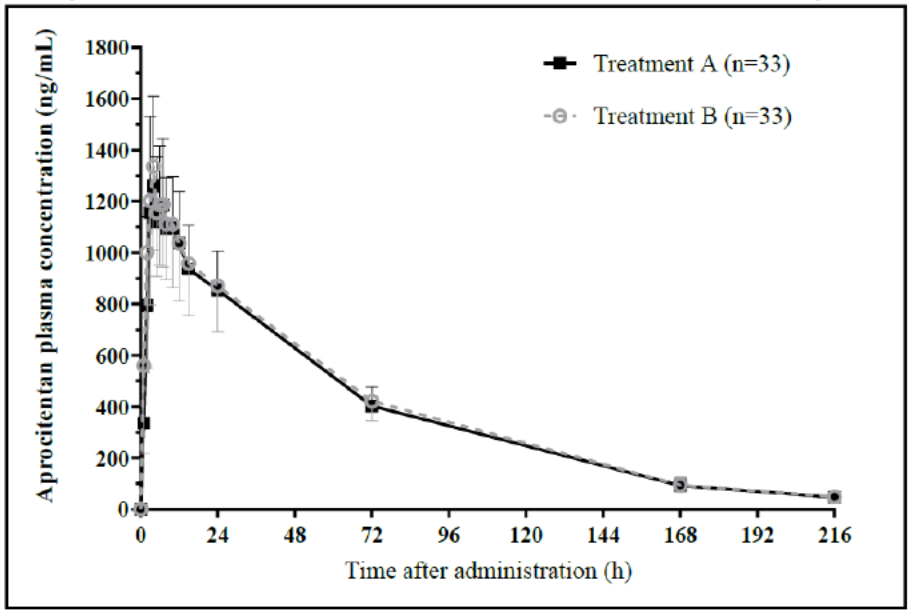
Assessment: Adequate

The Applicant established the clinical relevance of the proposed dissolution method by evaluating the bioequivalence of two drug product batches manufactured using drug substance batches with [redacted] (b) (4) .

Formulation	DP batch	Clinical treatment	Drug substance batch number	Drug substance [redacted] (b) (4)	Manufacturing Site	Study number
25 mg aprocitentan film-coated tablets	2010217	A	1915532	[redacted] (b) (4)		2021-005090-11
25 mg aprocitentan film-coated tablets	2111887	B	2105479	[redacted] (b) (4)		2021-005090-11

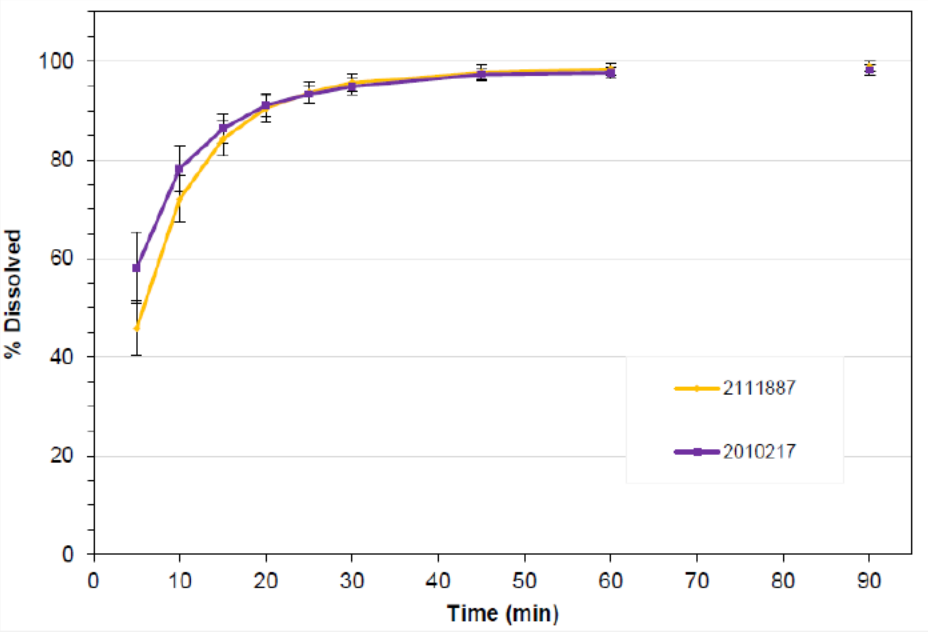
DP = drug product; DS = drug Substance

Figure 7. Mean Aprocitentan Plasma Concentration-Time Profiles (Treatment A vs B).



The Applicant noted that bioequivalence criteria were met for Cmax, AUC_{last}, and AUC_{∞} (90% CI of geometric mean ratio falls within 0.8-1.25). The Applicant stated the proposed dissolution method was supportive of in vivo bioavailability between drug product batches manufactured with differing (b) (4). Further, the Applicant instituted a (b) (4) for aprocitentan based on batches used in clinical trials. (b) (4), whereas batch 2111887 (Treatment B in the aforementioned BE study) had (b) (4). As batch 2111887 was BE to the Phase 3 Pivotal Clinical Trial batch (2010217), (b) (4) is clinically relevant and within the safe space for (b) (4).

Figure 8. Dissolution Profiles of Treatment A- 2111887 and Treatment B- 2010217



B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: Adequate

The Applicant used dissolution testing throughout drug product development and to evaluate robustness of final formulation.

B.12 BRIDGING OF FORMULATIONS

Assessment: Adequate

(b) (4) strengths, 12. 5 mg (b) (4), were evaluated in a Phase 3 Clinical Trial (ID-080A301 PRECISION). The final 12.5 mg (b) (4) film-coated tablets proposed for commercialization only differ from the pivotal Phase 3 formulation in the debossing and the film-coat color. The Applicant provided comparative multi-point dissolution profiles using the proposed quality control method to bridge the formulations.

Table 6. Dissolution Similarity Factors (*f2*)

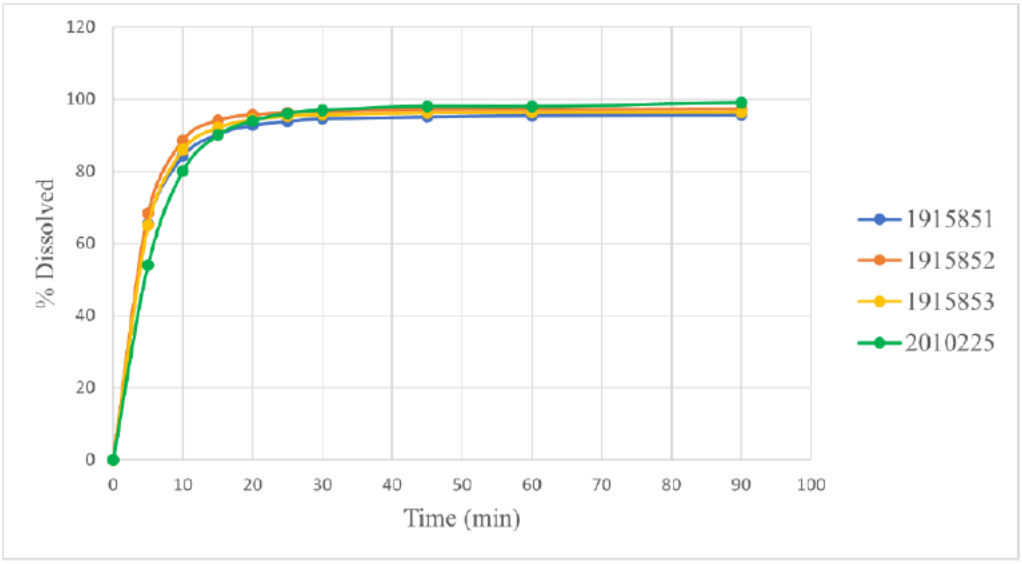
	Primary Stability Batch	*f2*
12.5 mg	1915851	N/A*

Phase 3 Batch 2010225	1915852	N/A*
	1915853	N/A*

(b) (4)

f2 calculation not necessary for drug products that dissolve very rapidly (≥85% dissolution in 15 minutes)

Figure 9. Dissolution Profiles of Primary Stability Batches and Representative Clinical Batch (12.5 mg tablets)



(b) (4)

Reviewer comment: The changes proposed to the formulation used in Phase 3 Clinical Trials vs the proposed formulation for commercialization (i.e., change in film-coat color and debossing) are considered minor and are unlikely to impact drug product performance in vivo. Therefore, the submitted comparative dissolution profiles in the proposed QC medium are adequate to bridge the 12.5 mg (b) (4) tablets used for Phase 3 Clinical Trials with intended commercial product. (b) (4) ; for the 12.5 mg tablet, f2 calculation was not necessary to demonstrate similarity as greater than 85% aprocitentan dissolved in 15 minutes.

B. 13 BIOWAIVER REQUEST

Assessment: N/A.

(b) (4) were tested in Phase 3 Pivotal Clinical Trials.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

(b) (4)

(b) (4)

Applicant's Response to Biopharmaceutics IR: The Applicant's response is adequate.

Reviewer's Assessment: The Applicant's response is acceptable.

Primary Biopharmaceutics Assessor's Name and Date: Rebecca R. Moody, Ph.D. 08/02/2023

Secondary Assessor Name and Date (and Secondary Summary, as needed): Haritha Mandula 08/04/2023

Rebecca Moody

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Haritha Mandula

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Date: 8/04/2023 10:51:46AM
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/s/

AKM KHAIRUZZAMAN
08/11/2023 10:20:01 AM
This NDA is Recommended for Approval by the OPQ Review Team