CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215206Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR EVALUATION OF DRUGS

Memorandum

DATE: September 17, 2021

TO: Division of Neurology 2

FROM: Martha R. Heimann, Ph.D.
Senior Pharmaceutical Quality Assessor, Office of New Drug Products

SUBJECT: Updated approval recommendation for Qulipta (atogepant) tablets

APPLICATION/DRUG: NDA 215206

The Office of Pharmaceutical Quality (OPQ) initially recommended approval for NDA 215206 on June 30, 2021, based on adequate information in the application to ensure product and acceptable compliance status for all manufacturing facilities involved in manufacturing

After the June 30, 2021 recommendation, the proposed packaging facility for Qulipta tablets, Allergan Sales, Inc. (FEI # 1523957), was placed on potential official action indicated (pOAI) status due to recent inspection findings primarily related to another product. The compliance status of this facility would have precluded approval of this NDA. Subsequently, on September 14, 2021, CDER Office of Manufacturing Quality (OMQ) reclassified the facility status from pOAI voluntary action indicated (VAI). Hence, based on the firm's experience with packaging and relabeling, the previous inspection history which included coverage of these operations, and the firm's continual acceptable compliance history, the facility is considered acceptable for blister packaging and bottle packaging of drug product in support of the NDA.

Based on the final compliant status for the Allergan Sales, Inc. facility, manufacturing/facility review and overall manufacturing inspection recommendation (OMIR) have been updated. OPQ recommends an **APPROVAL** action for NDA 215206.

Martha Heimann

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Comments: Updated approval recommendation.

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 215206
Review 1

Drug Product Name	Atogepant
Dosage Form	Tablet
Strength	10 mg, 30 mg, 60 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	AbbVie Inc.
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sharon Kelly	Donna Christner
Drug Product	Eric Bow	Julia Pinto
Manufacturing	Pratibha Bhat	Shujun Chen
Microbiology	N/A	
Biopharmaceutics	Jia Yin	Ta-Chen Wu
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	
Environmental	N/A	

Submission(s)	Document Date	Discipline(s) Affected
SD-1, Original NDA	1/28/2021	All
SD-12, Response to IR	4/23/2021	Manufacturing
SD-18, Labeling/container	5/25/2021	Drug product
SD-20, Response to IR	6/17/2021	Biopharmaceutics, Manufacturing

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed [1]	Comments
(b) (4)	III		(b) (4)	--	--	Adequate information in NDA
	III			--	--	
	III			--	--	
	III			--	--	
	III			--	--	
	III			--	--	

[1] Type III DMFs were not reviewed as the applicant provided adequate information in the NDA.

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
IND	114780	Development of atogepant (b) (4)
NDA	211765	Approved Allergan application for UBRELVY (ubrogepant), analog of atogepant

2. CONSULTS

None

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The OPQ review team recommends **APPROVAL** of NDA 215206 for atogepant tablets. The application, as amended in response to information requests, is adequate, from a product quality perspective, to ensure the safety and efficacy of the product for the intended patient population.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Atogepant, a new molecular entity, small molecule calcitonin gene-related peptide (CGRP) receptor antagonist [redacted (b) (4)]. It is one of several structurally similar CGRP receptor antagonists, that were originally developed by Merck Sharp & Dohme for treatment of migraine. A previous member of this structural class, ubrogepant, was acquired by Allergan and is marketed under approved NDA 211769 for acute treatment of migraine. [redacted (b) (4)]

The applicant, AbbVie, has acquired the rights to atogepant and proposes to market it as 10 mg, 30 mg, and 60 mg tablets for migraine prophylaxis [redacted (b) (4)] The recommended dose is 30 mg or 60 mg once daily; the 10 mg strength is recommended for patients with severe or end stage renal impairment.

Proposed indication(s) including intended patient population	Preventive treatment of migraine in adults with < 15 migraine days per month.
Duration of treatment	Chronic
Maximum daily dose	60 mg
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Atogepant is a synthetic, [redacted (b) (4)], [redacted (b) (4)] The applicant has established the chemical structure of atogepant by [redacted (b) (4)] Physicochemical properties

of atogepant, e.g., solubility, hygroscopicity, chemical reactivity, etc., are adequately characterized to evaluate the potential impact of the drug substance on the manufacture and performance of the product.

(b) (4) The manufacturing process detail is sufficiently described in the NDA. Controls for (b) (4) are sufficient to ensure the quality of the API. Process parameters, proven acceptable ranges (PARs), and normal operating ranges (NORs), and in-process controls are identified and are deemed acceptable.

The API specification includes appropriate test parameters to ensure quality. Analytical methods are described in detail and have been validated. Proposed limits for specified and unspecified impurities are acceptable.

Based on stability data provided, the proposed retest period of (b) (4) months is granted for atogepant (b) (4) API when stored at (b) (4) C, excursions permitted to (b) (4) C, in the proposed container closure system.

Drug Product: Adequate

The proposed drug products are white tablets containing 10 mg, 30 mg, or 60 mg atogepant. All inactive ingredients are compendial excipients that are commonly used in solid oral dosage forms and include polyvinylpyrrolidone/vinyl acetate copolymer, vitamin E polyethylene glycol succinate, mannitol, microcrystalline cellulose, sodium chloride, croscarmellose sodium, colloidal silicon dioxide, and sodium stearyl fumarate.

Two packaging configurations are proposed, a 30-count, 60 cc HDPE bottle (b) (4) (b) (4) and 4-count (b) (4) foil blister packs (physician samples).

The drug product specification includes test parameters that are typical for a solid oral product. All analytical procedures are adequately described and validated, as appropriate and acceptance criteria are justified.

Based on the stability data provided, an expiration dating period of **30 months for product stored at 20°C to 25°C** (controlled room temperature) in the original container, (b) (4) The applicant has provided release data for 14 batches, and 18 months of stability data for 19 batches. All of the release and stability data met the set release and stability specifications for all tested parameters. An expiry of 30 months has been granted based on the provided stability data.

Labeling: Adequate

No labeling issues were identified during the review.

Manufacturing: Adequate

The commercial manufacturing process for atogepant tablets comprises (b) (4)

(b) (4)

The drug product manufacturing process is designed to consistently produce drug product meeting the criteria of the target product profile and drug product quality attributes of appearance, content uniformity, assay, impurities/degradation products, (b) (4) finished product physical and chemical stability, identity, and dissolution. The relationships between the input materials and manufacturing process parameters that impact the drug product quality attributes were identified, and appropriate controls were instituted during major unit operations accordingly.

The proposed commercial batch formula is same as that of Phase 3 clinical and primary stability batches. The applicant proposes two batch sizes, i.e., (b) (4) kg and (b) (4) kg for each strength. The proposed batch sizes are the same as for phase 3 and primary stability batches. However, during manufacture of Phase 3 clinical and primary stability batches, (b) (4) (b) (4) The batch sizes and manufacturing equipment used for clinical, primary stability, and process evaluation batches are representative of commercial manufacture.

All the facilities listed in the application are acceptable. The drug product and drug substance manufacturing, packaging, and testing facilities are approved based on the firm's inspection history and manufacturing experience. There is no major GMP issue raised based on the review of the submitted batches.

Biopharmaceutics: Adequate

The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting **1)** formulation bridging between the pivotal clinical batch and the commercial batch, and **2)** the proposed dissolution method and acceptance criterion.

As the formulation used in Phase 2/3 studies is the proposed commercial formulation, no in vivo formulation bridging study is needed. In vitro drug release profiles across all proposed strengths show very rapid and overlapping.

Based on provided data, the selection of dissolution medium (0.1N HCl), apparatus (USP apparatus II, paddle), and rotation speed (75 rpm) is reasonable. However, [redacted]

The Applicant evaluated the discriminating ability of the proposed dissolution method against six critical quality attributes ([redacted] tablet hardness, [redacted] however, the discriminating ability of the proposed dissolution method cannot be determined based on the available data. As the drug product is an immediate release tablet with very rapid dissolution [redacted] the risk of dissolution is low, and the lack of discriminating ability is considered acceptable.

Based on dissolution data for pivotal clinical and primary stability batches and the dissolution data supporting the discriminating ability of the dissolution method, a dissolution acceptance criterion of Q = [redacted]% in [redacted] minutes could be considered as [redacted] Therefore, the proposed dissolution acceptance criterion of Q = [redacted]% in 20 minutes for all strengths of atogepant tablet was accepted.

Recommended and Agreed-upon interim Dissolution Method and Acceptance Criterion for the proposed Atogepant Tablet 10 mg, 30 mg, and 60 mg

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance Criteria
II (paddle)	75	0.1N HCl/ 37°C ± 0.5°C	500	Q = [redacted]% in 20 minutes

Environmental: Adequate

The applicant claimed a categorical exclusion from the requirement to prepare an environmental assessment atogepant in accordance with 21 CFR 25.31(b). The

estimated expected concentration (EEC) of atogepant into the aquatic environment (0.0599 ppb) is below the 1 ppb is threshold and there are no extraordinary circumstances.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay, stability	Formulation, container closure, (b) (4), process parameters, scale, equipment	**L**	(b) (4)	**Adequate**	
Physical stability (solid state)	Formulation, raw materials, (b) (4), container closure, manufacturing process and parameters, scale, equipment	**M**		**Adequate**	
Content uniformity	Formulation, manufacturing process and parameters, scale, equipment	**M**		**Adequate**	
Dissolution, BCS II & IV	Formulation, raw materials, (b) (4), process parameters, scale, equipment	**M**		**Adequate**	
Microbial limits	Formulation, raw materials, (b) (4), container closure, process parameters	**L**		**Adequate**	

D. List of Deficiencies for Complete Response

Not applicable

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
CMC Lead for Neurology Products
Office of New Drug Products

6/30/2021

Martha Heimann

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

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

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.	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	N/A	API is not a salt

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

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)	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)	N/A	
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	N/A	

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	API is not a salt
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.	N/A	

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	API is not a salt
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.	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	N/A	
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)	Adequate	

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	Only HDPE bottles marketed to patients. Blisters are physician samples.
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.	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	

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	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

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):

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]	N/A	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	
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	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(Copy/paste or refer to a representative example of a proposed container)

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

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	
Strength(s) in metric system	Adequate	
Route(s) of administration	N/A	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	API is not a salt
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"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.	N/A	
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	

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

QUALITY ASSESSMENT

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.	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***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

n/a

Overall Assessment and Recommendation:

The proposed labeling is adequate

Primary Labeling Assessor Name and Date: Eric Bow, PhD, 6/21/2021

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

Eric Bow

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Julia Pinto

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BIOPHARMACEUTICS

NDA: NDA 215206
Submission Type: 505(b)(1)
Drug Product Name / Strength: Atogepant Tablet / 10 mg, 30 mg, 60 mg
Dosage Form: Immediate-release (IR) Tablet
Route of Administration: Oral
Applicant: AbbVie Inc.
Indication: For the preventive treatment of migraine in adults with <15 migraine days per month
Submission Date: 1/28/2021
Primary Reviewer: Jia Yin, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

Background: The Applicant seeks approval for Atogepant Tablet under 505(b)(1) pathway for the preventive treatment of migraine in adults with <15 migraine days per month. Atogepant is considered as a new molecular entity (NME) and this NDA is granted priority review status. Atogepant tablet is an immediate-release (IR) tablet with three strengths: 10 mg, 30 mg, and 60 mg. The maximum recommended dose is 60 mg once daily. All three strengths were studied in Phase 2/3 clinical studies. No biowaiver request was submitted.

REVIEW SUMMARY

The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting **1)** formulation bridging between the pivotal clinical batch and the commercial batch, and **2)** the proposed dissolution method and acceptance criterion. The key review findings are summarized as follows:

Formulation Bridging: Adequate

As the formulation used in Phase 2/3 studies is the proposed commercial formulation, no in vivo formulation bridging study is needed. In vitro drug release profiles across all proposed strengths show very rapid and overlapping.

Dissolution Method: Interim Approval

Based on provided data, the selection of dissolution medium (0.1N HCl), apparatus (USP apparatus II, paddle), and rotation speed (75 rpm) is reasonable. However, justification for

(b) (4)

(b) (4)

The Applicant also evaluated the discriminating ability of the proposed dissolution method against six critical quality attributes ((b) (4) tablet hardness, (b) (4) (b) (4) (b) (4) However, either there is a lack of difference in dissolution between target and aberrant batches or the tested variable range is outside the Agency typically recommended target ±10–20%. Based on the provided data, the discriminating ability of the proposed dissolution method cannot be determined. As the drug product is an immediate release tablet with very rapid dissolution (b) (4) the risk of dissolution is low. The lack of discriminating ability of the dissolution method for this proposed drug product is considered acceptable.

Dissolution Acceptance Criterion: Acceptable

Based on the provided dissolution data of pivotal clinical and primary stability batches and the dissolution data supporting the discriminating ability of the dissolution method, a dissolution acceptance criterion of Q = (b) (4) % in (b) (4) minutes could be considered as (b) (4) (b) (4) (b) (4) Therefore, this reviewer accepts the proposed dissolution acceptance criterion of Q = (b) (4) % in 20 minutes for all strengths of atogepant tablet.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 215206 for Atogepant Immediate Release Tablet, 10 mg, 30 mg, and 60 mg, is recommended for interim approval.

Recommended and Agreed-upon interim Dissolution Method and Acceptance Criterion for the proposed Atogepant Tablet 10 mg, 30 mg, and 60 mg

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance Criteria
II (paddle)	75	0.1N HCl/ 37°C ± 0.5°C	500	Q = (b) (4) % in 20 minutes

BIOPHARMACEUTICS ASSESSMENT

List Submissions Being Reviewed

Received Date	Submission
1/28/2021	Original submission
6/17/2021	Response to Biopharmaceutics IR

BCS Designation

Reviewer's Assessment:

Based on the provided solubility and permeability data, the initial drug substance, (b) (4)

[redacted]

Drug Substance:

(b) (4)

[redacted]

(b) (4)

[redacted]

(b) (4)

[redacted]

Formulation Bridging

Reviewer's Assessment: ***Adequate***

As the formulation used in Phase 2/3 studies is the proposed commercial formulation, no in vivo formulation bridging study is needed. In vitro drug release profiles across all proposed strengths show very rapid and overlapping.

The tablet formulation used in phase 2/3 clinical studies (**Table 2**) is the same as the to-be-marketed commercial formulation. In addition, the composition of all three strengths is proportionally the same. No in vivo formulation bridging study is need. Results of in vitro studies, showing very rapid and overlapping dissolution profiles, further support the establishment of formulation bridging across all proposed strengths.

Table 2 Composition of Phase 2/3 tablet formulation

Component	Quality Standard	Function	%w/w	Unit Dose Composition (mg/tablet)		
				10 mg	30 mg	60 mg
(b) (4)						

Dissolution Method and Acceptance Criterion

Reviewer's Assessment:

Dissolution Method: ***Interim approval***

Based on the provided data, the selection of dissolution medium (0.1N HCl), apparatus (USP Apparatus II, paddle), and rotation speed (75 rpm) is reasonable. However, (b) (4) (b) (4) The Applicant was requested to implement 500 mL medium volume for all strengths of their product in an information request dated 6/14/2021. In response (6/17/2021), the Applicant accepted the Agency's recommendation. (b) (4)

The Applicant also evaluated the discriminating ability of the proposed dissolution method against six critical quality attributes ((b) (4) tablet hardness, (b) (4) (b) (4) (b) (4) However, either there is a lack of difference in dissolution between target and aberrant batches or the

tested variable range is outside the Agency typically recommended target ±10–20%. Based on the provided data, the discriminating ability of the proposed dissolution method cannot be determined. As the drug product is an immediate release tablet with very rapid dissolution [redacted] the risk of dissolution is low. The lack of discriminating ability of the dissolution method for this proposed drug product is considered acceptable.

Dissolution Acceptance Criterion: ***Acceptable***

Based on the provided dissolution data of pivotal clinical and primary stability batches and the dissolution data during the dissolution method development, a dissolution acceptance criterion of Q = [redacted]% in [redacted] minutes could be considered as [redacted] Therefore, this Reviewer accepts the proposed dissolution acceptance criterion of Q = [redacted]% in 20 minutes for all strengths of atogepant tablet.

Proposed Dissolution Method

Table 3 Proposed dissolution method

Dissolution Conditions:	
Apparatus	USP apparatus 2 (Paddles)
Paddle Rotation Speed	75 rpm
Media Volume	[redacted]
Dissolution Medium	0.1 N HCl
Temperature	37°C ± 0.5°C
Sampling Time Points	10, 15, 20, 30 and 60 min.

Proposed Dissolution Acceptance Criterion

NLT = [redacted]% in 20 minutes

Dissolution Method Development

[redacted]

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Ta-Chen Wu

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Jia Yin

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/s/

MARTHA R HEIMANN
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