CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216386Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number	216386		
Applicant Name	Biohaven Pharmaceutical Holding Company, Ltd.		
Drug Product Name	Zavegepant nasal spray		
Dosage Form	Spray		
Proposed Strength(s)	10 mg		
Route of Administration	Nasal		
Maximum Daily Dose	10 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Acute treatment of migraine with or without aura in adults		
Drug Product Description	Unit dose disposable system delivers 10 mg zavegepant in in a buffered aqueous solution containing succinic acid, dextrose (b) (4) sodium hydroxide and hydrochloric acid.		
Co-packaged product information	N/A		
Device information	(b) (4)		
Storage Temperature/ Conditions	20°C – 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katherine Duncan	Gaetan Ladouceur
	Drug Product/ Labeling	Mariappan Chelliah	Julia Pinto

	Manufacturing	Tarun Mehta	Jingbo Xiao
	Biopharmaceutics	N/A	N/A
	Microbiology	Gouri Chattopadhyay	Elizabeth Bearr
	Other (specify):	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation – Approval

3. Action Letter Information

a. Expiration Dating:

24 months, when stored at 20°C to 25°C (controlled room temperature).

b. Additional Comments for Action

There are no additional comments for the action letter.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

Zavegepant is a novel calcitonin gene-related protein (CGRP) receptor antagonist developed for treatment of migraine. The Office of Pharmaceutical Quality (OPQ) The Office of Product Quality (OPQ) review team recommends APPROVAL of NDA 216386 for zavegepant nasal spray 10 mg. Based on our evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the drug product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments:

There are no lifecycle comments.

Martha Heimann

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U.S. FOOD & DRUG ADMINISTRATION

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	Inadequate	The package type is described as (b) (4) (b) (4) which is incorrect. The PI will be edited to replace it with "unit-dose".
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	

[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).	Adequate	
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	N/A	
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)"	Inadequate	The PI states that 10 mg of free base is equivalent to (b) (4) mg of salt – it should be10.6 mg. The PI will be edited accordingly.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inadequate	The ingredients not listed alphabetically. The PI will be edited to meet this requirement.
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	
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)	Inadequate	The PI will be edited to include pKa and pH.

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)	N/A	
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.	Inadequate	
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."	N/A	

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]	Adequate	
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.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Inadequate	The Patient Information will be edited to list the excipients alphabetically.
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

The front and back of the device label is shown below:

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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	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	
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]

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***

Some section of the PI needs to be edited to meet the appropriate USP/CFR requirement. This will be done once the PI becomes available for edit.

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor: Mariappan V. Chelliah

Secondary Assessor: Julia Pinto

Mariappan Chelliah

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Julia Pinto

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	The drug product is a nasal spray and indicated for the treatment of acute migraine
NDA Number	**216386**
Assessment Cycle Number	01
Drug Product Name/ Strength	Zavegepant, 10 mg
Route of Administration	Intranasal Spray
Applicant Name	Biohaven Pharmaceutical Holding Company, Ltd.
Therapeutic Classification/ OND Division	Nasal Spray/CDER/OND/ON/DN2
Manufacturing Site	(b) (4)
Method of Sterilization	N/A, Drug Product is non-sterile

Assessment Recommendation: Adequate

List Submissions being assessed (table):

Document(s) Assessed	Date Received
• Original NDA Submission (SEQ 0001)	• 03/09/2022
• Response to Information Request (Quality)	• 04/29/2022
• Response to Information Request (Quality)	• 08/05/2022

Assessment Summary: The drug product (10 mg) is supplied in a disposable single use unit dose (to one nostril) nasal spray drug – device combination product, using (b) (4) **spray device. The drug product is** (b) (4) (b) (4) **filled into** (b) (4) **glass vials** (b) (4) **and stoppered. The stoppered vials, actuator and vial holder are assembled to form the Zavegepant Nasal Spray drug product** (b) (4) (b) (4)

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

Remarks: N/A

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

Supporting Documents:

(b) (4)

S DRUG SUBSTANCE

No review was conducted on the drug substance as the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product-** Zavegepant nasal spray is formulated at (b) (4) mg/mL, ready-to-use unit dose and filled into a (b) (4) spray device; so that 10 mg of Zavegepant can be delivered on actuation from the (b) (4) device that is pre-set to deliver a volume of (b) (4) µL. The drug product is delivered as a single dose into one nostril and used for acute treatment of migraine.
- **Drug product composition** –

Component	Quality Standard	Function	Quantity per (b) (4) dose	
			% (w/v)	mg
Zavegepant Hydrochloride	In-house Specification**	API	(b) (4)	10.00 mg***
Succinic Acid	NF			(b) (4)
Dextrose, (b) (4)	USP			
Hydrochloric Acid****	NF/Ph. Eur.			
Sodium Hydroxide****	NF/Ph. Eur.			
Water For Injection	USP/Ph. Eur.			
(b) (4) Device	Not Applicable	Drug Delivery	1 Unit	

(b) (4)

- **Description of container closure system-** The drug product is packaged in a glass vial, stoppered with a rubber plunger (primary packaging) and assembled with a (b) (4) delivery device. The (b) (4) delivery device is comprised of a vial/container holder and actuator (secondary packaging). Each device is packaged in a blister with peel off lid.

Container Closure Component	Packaging Designation	Description	DMF Number	Supplier
Vial	Primary	Unit-Dose, Clear, USP (b) (4) Glass Vial	Type III DMF# (b) (4)	(b) (4)
			Type III DMF # (b) (4)	
Stopper (Plunger)		Grey (b) (4) stopper, (b) (4)	Type III DMF# (b) (4)	
Actuator (b) (4)	Secondary	(b) (4)	Type III DMF # (b) (4)	
Vial Holder (Container Holder)			Type III DMF # (b) (4)	

(b) (4)

(b) (4)

Reviewer's Assessment: Adequate
The applicant has provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT
P.2.5 MICROBIOLOGICAL ATTRIBUTES
Container/Closure and Package Integrity- N/A. Nonsterile drug product.
Antimicrobial Effectiveness Testing- N/A, single dose vial

P.3 MANUFACTURE
P.3.1 MANUFACTURERS
(3.2.P.3.1)
(b) (4)

FEI Number - (b) (4)
Responsibility: Manufacturing (Drug Product), Quality Control Testing, Packaging, Labeling and Batch Release and Stability testing of Drug Product

(b) (4)

Responsibility: Quality Control Testing of DP

P.3.3 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS
Overall Manufacturing Operation
(3.2.P.3.3/*manuf-process-and-controls.pdf*)
(b) (4)

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2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

The drug product should be stored at room temperature between 68°F to 77°F (20°C to 25°C) and is a ready-to-use, single dose, nasal spray (10 mg); the recommended dose is 10 mg given as a single spray (pre-set to deliver a volume of (b) (4) µL) in one nostril in a 24-hour time.

Reviewer's Assessment: Adequate
The labeling provides adequate instructions to maintain the microbiological quality of the subject drug product during storage and use.

Post-Approval Commitments- N/A

MICROBIOLOGY LIST OF DEFICIENCIES

The following deficiencies are considered: ☐ Major ☐ Minor

Primary Microbiology Assessor Name and Date: Gouri Chattopadhyay, Ph.D. 08/24/2022
Secondary Assessor Name and Date: Elizabeth Bearr, Ph.D., 08/24/2022

Elizabeth Bearr

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Gouri Chattopadhyay

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