CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218276Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	218276		
Applicant Name	Novartis Pharmaceuticals Corp.		
Drug Product Name	FABHALTA (iptacopan)		
Dosage Form.	Capsule		
Proposed Strength(s)	200 mg		
Route of Administration	Oral		
Maximum Daily Dose	400 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Indicated for the treatment of (b) (4) paroxysmal nocturnal hemoglobinuria		
Drug Product Description	Capsules containing 200 mg iptacopan packaged in HDPE bottles with child-resistant closures.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20 to 25ºC		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Ben Zhang ONDP/DNDAPI/NDB3	Zhengfu Wang ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Charudharshini Srinivasan ONDP/DNDPIII/NDPB5	Theodore Carver ONDP/DNDPIII/NDPB5
	Manufacturing	Ke Ren OPMA/DPMAIII/PMB7	Alexander Gontcharov OPMA/DPMAIII/PMB7

	Biopharmaceutics	Zhuojun Zhao ONDP/DB/BB3	Haritha Mandula ONDP/DB/BB3
	Microbiology	N/A	
	Other (specify):	N/A	
	RBPM	Musse Olani OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver ONDP/DNDPIII/NDPB5	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

An expiry dating period of 24 months is granted for the drug product when stored at 20°C to 25°C.

b. Additional Comments for Action
None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1. Background

The Applicant, Novartis is seeking approval for marketing of this 505(b)(1) New Drug Application, which has orphan drug and breakthrough therapy designations for treatment of (b) (4) paroxysmal nocturnal hemoglobinuria. The NDA relying upon results of a pivotal Phase 3 study to support approval. The drug product consists of 200 mg of the iptacopan hydrochloride monohydrate drug substance filled into size 0 hard gelatin capsules with no added excipients. This Integrated Quality Assessment includes drug substance, drug product, manufacturing, and biopharmaceutics reviews.

2. Drug Substance (iptacopan hydrochloride monohydrate)

Iptacopan is a synthetic small molecule with two stereogenic centers. The drug substance is [redacted] (b) (4) slightly soluble in water. The drug substance review found that the starting materials and their specifications are adequately justified, and the manufacturing process and structural characterization studies are adequately described. In addition to identification, assay, and impurities, the specification contains appropriate test to control the quality of the drug substance, including water content, particle size, enantiomeric purity, residual solvents, [redacted] (b) (4) counterion content, and microbial enumeration tests. There are several potential genotoxic impurities that may be generated during drug substance manufacturing, which were found to be adequately controlled. [redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4) The stability data were found to support a [redacted] (b) (4) month retest date. Overall, the review concluded that the information is adequate to support the drug substance.

3. Drug Product (Iptacopan capsules)

The Iptacopan drug product consists of [redacted] (b) (4) gelatin capsules with no added excipients. The drug product specification contains appropriate tests for drug product critical quality attributes, including identification, assay, degradants, content uniformity, dissolution [redacted] (b) (4)

[redacted] (b) (4)

[redacted]

(b) (4)

(b) (4) The NDA included long-term (12 months), intermediate (12 months), and accelerated stability data (6 months) drug product stability data for three primary batches, which were reviewed and found to support the proposed 24-month shelf life for the drug product stored at 20ºC to 25ºC. Overall, the drug product review concluded that the information provided is adequate to support the drug product.

4. Manufacturing

Process – The review of the manufacturing process, which consists of filling the drug substance into the capsules, concluded that it is adequate.
Facilities – A preapproval inspection was conducted for the drug product manufacturing facility. The inspection concluded with a result of Voluntary Action Indicated (VAI). All other facilities requiring evaluation were approved based on previous history. The facilities are recommended for approval overall.

5. Biopharmaceutics

The proposed dissolution method and acceptance criteria were found to be acceptable with the proposed pH of 2.0 for testing, and adequate data were provided to bridge formulations employed during the clinical development program.

6. Quality Aspects of Product Labeling

The quality aspects of the drug product labeling were reviewed and found to be adequate overall, with minor revisions being negotiated with the Applicant during final review of the labeling.

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	**-**	**Adequate**
Microbiology	**-**	**N/A**

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

The Iptacopan drug substance and drug product (b) (4) (b) (4) in the specifications. (b) (4) (b) (4)

Theodore Carver

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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:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided	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)
Established name(s)[1]	Brandname® (iptacopan) capsules, for oral use	Adequate	
Route(s) of administration	Oral	Adequate	
Summary of the dosage form(s) and strength(s) in metric system	200 mg orally twice daily with or without food.	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".		N/A	

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

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).	(b) (4) capsules: 200 mg (3)	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: *Removed the word "hard" throughout the PI* " (b) (4) capsules: 200 mg (3) "

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided	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)
Special instructions for product preparation (e.g., reconstitution and resulting		N/A	

concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)			
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	"2.2 Dosage The recommended dose of Brandname is 200 mg orally twice daily. (b) (4) (b) (4) If a dose or doses are missed, advise patient to take one dose of Brandname as soon as possible (even if it is soon before the next scheduled dose) and then to resume the regular dosing schedule"	Adequate	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*		N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure		N/A	

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

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided	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)	Capsules	Adequate	
Strength(s) in metric system	200 mg hard capsules	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).	Brandname 200 mg (b) (4) capsules	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: • *Removed the word (b) (4) throughout the PI* "(b) (4) *Capsules: 200 mg of iptacopan in pale yellow, …"*
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	Brandname 200 mg (b) (4) capsules: pale yellow opaque hard gelatin capsules imprinted with "LNP200" on the body and "NVR" on the cap.	Adequate	• See above, *Removed the word (b) (4) throughout the PI*
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	Information Provided	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)	Brandname® (iptacopan) capsules	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: (b) (4) [redacted] <u>NOTE to the Applicant added on the PI</u>: ***To the Applicant:*** *Recommend that salt equivalence be included in the description of the drug product below, as indicated.*
Dosage form(s) and route(s) of administration	Brandname is supplied as 200 mg hard gelatin capsules for oral 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)"	Brandname® (iptacopan) capsules, for oral use	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: (b) (4) Iptacopan hydrochloride monohydrate is white or almost white to pale purplish-pink powder that is slightly soluble in water at 25°C. NOTE to the Applicant added on the PI: ***To Applicant:*** *Recommend adding a statement regarding pH of solutions.* Brandname is supplied as (b) (4) hard gelatin capsules for oral administration. The (b) (4) capsules are packaged in high density polyethylene (HDPE) bottles with induction seals and child resistant caps. Each Brandname (b) (4) capsule contains 200 mg iptacopan (provided as 225.8 mg iptacopan hydrochloride monohydrate) and the capsule shell contains the following inactive ingredients gelatin, red ferric oxide, titanium dioxide, yellow ferric oxide. The black printing ink contains ferrosoferric oxide, potassium hydroxide, propylene glycol, shellac, and strong ammonia solution.

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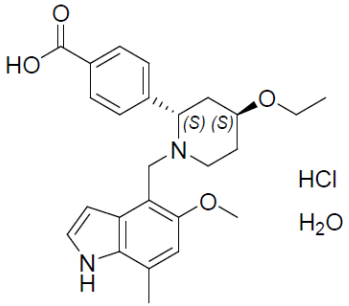
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Each Brandname 200 mg capsule contains 200 mg iptacopan (as 225.8 mg iptacopan hydrochloride monohydrate) (b) (4) (b) (4) (b) (4) gelatin, red ferric oxide, titanium dioxide, yellow ferric oxide. The black printing ink contains ferrosoferric oxide, potassium hydroxide, propylene glycol, shellac, and strong ammonia solution.	N/A	There are no inactive excipients in this product See above
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	Brandname contains iptacopan, (b) (4) (b) (4)	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: Deleted (b) (4) to match the statement in Highlights of Prescribing Information section.

Chemical name, structural formula, molecular weight	(b) (4) The chemical name is (2S,4S)-2-(4-Carboxyphenyl)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl) methylpiperidin-1-ium chloride—water (1/1). The molecular formula is C25H30N2O4·HCl H2O. The structure is shown below  	Adequate	
If radioactive, statement of important nuclear characteristics.		N/A	
Other important chemical or physical properties (such as pKa or pH)		N/A	

2. Section 11 (DESCRIPTION) Continued

Item	Information Provided	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)

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Item	Information Provided	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			
Available dosage form(s)	Capsules	Adequate	
Strength(s) in metric system	200 mg	Adequate	
Available units (e.g., bottles of 100 tablets)	200 mg hard capsules: pale yellow opaque, (b) (4)	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: 200 mg (b) (4) capsules: pale yellow opaque hard capsules, imprinted with "LNP200" on (b) (4) one half and "NVR" on the (b) (4) other half, packaged in a high density polyethylene (HDPE) bottle with induction seal and child-resistant cap. Each bottle contains (b) (4) 60 capsules (NDC xxxx-xxxx-xx). Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

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."		N/A	Forced degradation photostability study on the drug product revealed that results of unpacked and packed product met the acceptance criteria for all the tests. Hence no special handling about the supplied product is provided. A note is added to the Applicant in the PI: *"To ensure appropriate storage of the medication, we recommend adding the statement "Store and dispense in the original container." after the storage statement."*

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

Item	Information Provided	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.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: Revised the storage statement: "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). [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	Not provided	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: In Section 16 added "with induction seal and child-resistant caps" to match Section 11. See above.

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	Information Provided	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	Distributed by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936 For more information, visit www.xxxx.com or call x-xxx-xxx-xxxx.	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Information Provided	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)
Patient Labeling			
Established name[2]	BRANDNAME® (phonetic spelling) (iptacopan) capsules, for oral use	Adequate	
Special preparation instructions (if applicable)		N/A	
Storage and handling information (if applicable)	(b) (4)	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)	Iptacopan	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: See above. Refer to Section 11 in this review.

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

Alphabetical listing of inactive ingredients (if applicable)	(b) (4)	Adequate	**Active ingredient:** iptacopan **Inactive ingredients:** the capsule shell contains gelatin, red ferric oxide, titanium dioxide, yellow ferric oxide. The black printing ink contains ferrosoferric oxide, potassium hydroxide, propylene glycol, shellac, and strong ammonia solution. (b) (4)
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Distributed by: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936 © Novartis	Adequate	

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

3.0 CONTAINER AND CARTON LABELING

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container 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	

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

If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	***Labeling IRs communicated to the Applicant: See under "Assessment of Carton and Container Labeling" list of IRs sent at the end of this review.*** *1) We recommend removing the asterisk from the strength listed on the main panel and revising the equivalency statement in the side panel to read: "Each capsule contains 200 mg iptacopan provided as 225.8 mg Iptacopan monohydrate hydrochloride."* *2) We recommend adding the following statement after storage statement on the container label" "[See USP Controlled Room Temperature]"*
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	*See Above*
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	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container 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.	Adequate	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *{Adequate}*

Carton labeling: *Not provided. Not applicable for this drug product.*

Container labeling:

Information Request for Container labeling, communicated with the Applicant

Round 1: (IR sent to the Applicant on 10/02/2023)

1) *We recommend removing the asterisk from the strength listed on the main panel and revising the equivalency statement in the side panel to read: "Each capsule contains 200 mg iptacopan provided as 225.8 mg Iptacopan monohydrate hydrochloride."*

2) *We recommend adding the following statement after storage statement on the container label" "[See USP Controlled Room Temperature]"*

IR Response received from the Applicant on 10/12/2023, eCTD Sequence#0040, SDN#41:

*Response is **Adequate**. Applicant has revised the label as shown below:*

3. 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.

N/A

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Charudharshini Srinivasan, Ph.D., 10/17/2023

Secondary Assessor Name and Date (and Secondary Summary, as needed): Theodore Carver, Ph. D., 10/20/23

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Charudharshini Srinivasan

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CHAPTER III: ENVIRONMENTAL

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

R REGIONAL INFORMATION

Environmental

Novartis has claimed a categorical exclusion from the requirements of an Environmental Impact analysis Statement (EIS) or Environmental Assessment (EA) under 21 CFR § 25.31(b). They provided statement that "*It certifies that this NDA submission for Iptacopan qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as the estimated environmental intake concentration of the active moiety, Iptacopan, will be significantly less than 1 ppb, based on the peak production estimates within the next five years.*"

Applicant provided calculation justifying that the proposed Iptacopan would not be reasonably anticipated to increase amounts of active moiety available for use. Applicant also claims that no extraordinary circumstances exist that would warrant the preparation of an Environmental Assessment for Iptacopan under 21 CFR § 25.21.

Assessment: *{Adequate}*
Novartis's claims for categorical exclusion per 21 CFR 25.31(b) and extraordinary circumstances per 21 CFR 25.21 are acceptable. Even though Iptacopan could fall under the scope of the FDA Guidance Document (2016) on Environmental Assessment[4], the applicant further noted that "per Type B Content Format Briefing Document submitted to IND 134655 on April 20, 2022 (SN-0049) information shared and in the [FDA Type B Written Responses Only dated May 18, 2022], FDA indicated agreement that this information and analysis were reasonable to justify that no extraordinary circumstances exist (as per 21 CFR 25.21) and support a claim for categorical exclusion under 21 CFR 25.31(b) (Question 12)".
This is acceptable.

Primary Environmental Assessor Name and Date: Charudharshini Srinivasan, Ph.D., 10/18/2023

Secondary Assessor Name and Date (and Secondary Summary, as needed): Theodore Carver, Ph. D., 10/20/2023

[4] Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity Guidance for Industry, March 2016

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

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

Product Information	
NDA Number	218276
Assessment Cycle Number	001
Drug Product Name/ Strength	Iptacopan Capsules, 200 mg
Route of Administration	Oral
Applicant Name	Novartis Pharmaceutical Corp.
Therapeutic Classification/ OND Division	Division of Non-Malignant Hematology (DNH)
Proposed Indication	Treatment of paroxysmal nocturnal hemoglobinuria (PNH)

Assessment Recommendation: **Adequate**

Assessment Summary:
Novartis Pharmaceutical Corp. submitted a 505(b) (1) application for the proposed Iptacopan Capsules, 200 mg for treatment of paroxysmal nocturnal hemoglobinuria (PNH).

The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed quality control dissolution method and acceptance criterion as well as the in vitro formulation bridging study.

Dissolution method and Acceptance Criterion:
Based on the provided information, the proposed Iptacopan Capsules, 200 mg is deemed as an eligible drug product for standard dissolution testing condition according to *Guidance for Industry Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances*. The Applicant also provided adequate justification for dissolution medium of 0.01 N HCl (pH 2.0) (b) (4) Therefore, the proposed dissolution method and dissolution acceptance criterion are found acceptable:

Dissolution Method and Acceptance Criterion	
Medium	0.01 N HCl
Apparatus	USP I (Basket)
Volume	500 mL
Rotation Speed	100 RPM
Temperature	37°C
% Drug Release	NLT (b) (4)% (Q) in 30 minutes

Bridging Formulations:
The Applicant also provided adequate in vitro dissolution data to bridge the formulations, DS substance sources and drug product manufacturers for the proposed Iptacopan Capsules, 200 mg.

List Submissions Being Assessed:

Document Assessed	Date Received
Original Submission (0001)	April 5, 2023

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues: None

B.1 BCS DESIGNATION

Solubility:
The Applicant provided solubilities of the drug substance, Iptacopan hydrochloride monohydrate, at 25°C (Table 1) and 37°C (Table 2) in aqueous media at pH values across the range from 1.0 to 6.8 and in bio-relevant media.

Table 1: Drug substance solubility at 25 ± 0.2 °C

Solvent	Solubility in mg/ml of solution	Solubility (g/100 ml)	Description term [1]
Water	8.63	0.9	Slightly soluble
Hydrochloric acid 0.1N, pH 1.0	0.80	<0.1	Very slightly soluble
Hydrochloric acid 0.01N, pH 2.0	4.39	0.4	Slightly soluble
Phosphoric acid, pH 2.0	8.14	0.8	Slightly soluble
Acetate buffer, pH 4.5	27.72	2.8	Sparingly soluble
Phosphate buffer, pH 6.8	28.82	2.9	Sparingly soluble
Acetonitrile / water 2/8 v/v	49.63	5.0	Soluble
Acetonitrile / water 1/1 v/v	-	>10	Freely soluble
Methanol	-	>10	Freely soluble
1-Methyl-2-pyrrolidone	-	>10	Freely soluble
Dimethyl sulfoxide	-	>10	Freely soluble

Table 2: Drug substance solubility at 37 ± 0.5 °C

Solvent	Solubility (mg/ml)	Solubility (g/100 ml)	Description term [1]
Water	10.78	1.1	Sparingly soluble
Hydrochloric acid 0.1N, pH 1.0	1.09	0.1	Slightly soluble
Hydrochloric acid 0.01N, pH 2.0	4.38	0.4	Slightly soluble
Simulated gastric fluid, pH 1.2	1.22	0.1	Slightly soluble
Acetate buffer, pH 4.5	21.35	2.1	Sparingly soluble
Phosphate buffer, pH 6.8	18.61	1.9	Sparingly soluble
Fasted state simulated intestinal fluid (FaSSIF pH 6.5)	11.80	1.2	Sparingly soluble
Fed state simulated intestinal fluid (FeSSIF pH 5.8)	12.52	1.3	Sparingly soluble

[1] According to USP, Pharm. Eur., J.P.

The sponsor states that the drug substance is highly soluble as the proposed single therapeutic dose of 200 mg[1] is completely soluble in 250 ml aqueous media (i.e., 0.8 mg/ml) over the pH range of 1.2–6.8 at 37°C.

[1] The proposed dosage regimen is 200 mg orally twice daily taken with or without food (daft labeling).

Permeability:
The Applicant states that Iptacopan permeability is low to moderate which is modulated by efflux transporter (P-glycoprotein) based on Caco-2 cell line permeability which was calculated to be 1.33 x 10^{-6} cm/s (at nominal concentration of 0.5 µM) in Report DMPK R1500730.

Assessment: ***{Adequate}***
The Applicant did not request an official BCS designation. Based on the provided information, the Applicant reported the drug substance to be a high soluble and low permeable substance according to regulatory criteria.

B.2 FORMULATION

The proposed Iptacopan hard capsules, 200 mg are an immediate release dosage form for oral administration and the composition is shown in Table 3.

Table 3: Composition of Iptacopan 200 mg Hard Capsules

Ingredient	Amount per Capsule (mg)	Function	Reference to standards
Iptacopan hydrochloride monohydrate (corresponding to Iptacopan free base)	225.800 (200.000)	Active ingredient	Novartis specification
Gelatin[a]			Ph. Eur., USP/NF, JP
Titanium dioxide			Ph. Eur., Regulation (EU) 231/2012[a], USP/NF, JP
			Regulation (EU) 231/2012[a], USP/NF, JPE
Yellow ferric oxide[a]			Regulation (EU) 231/2012[a], USP/NF, JPE
Red ferric oxide[a]			Ph. Eur., USP/NF
Shellac			Regulation (EU) 231/2012[a], USP/NF
Ferrosoferric oxide			Ph. Eur., USP/NF
Propylene glycol			Ph. Eur., USP/NF
Strong ammonia solution			Ph. Eur., USP/NF
Potassium hydroxide			
Total capsule weight			

(b) (4)

B.3 DISSOLUTION METHOD

The Applicant proposes the following standard dissolution method for the proposed Iptacopan hard capsules, 200 mg according to Option A in section IV in FDA Guidance *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances* with one exception: 0.01 N HCl (pH 2.0) is used as dissolution medium (b) (4)

Dissolution Method	
Medium	0.01 N HCl
Apparatus	USP I (Basket)
Volume	500 mL
Rotation Speed	100 RPM
Temperature	37°C

No extensive method development study or discriminating ability study is provided in the submission. The Applicant provided the following data in support of 0.01 N HCl (pH 2.0) as the dissolution medium (b) (4)

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Therefore, the proposed dissolution method is found acceptable for the QC of the proposed Iptacopan hard capsule 200 mg.

B.4 DISSOLUTION METHOD ACCEPTANCE CRITERION

The Applicant proposes an acceptance criterion of NLT (b) (4)% (Q) in 30 minutes for the proposed Iptacopan hard capsule 200 mg. The Applicant provided the dissolution results observed during release and stability testing of Iptacopan 200 mg hard capsules[2 & 3], which demonstrated the drug product meeting the proposed acceptance criterion.

Assessment: ***{Adequate}***

The proposed acceptance criterion of Q= (b) (4)% in 30 minutes is found acceptable based on *Guidance for Industry Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances.*

B.5 B.6 BRIDGING OF FORMULATIONS

The proposed commercial capsule is different in the capsule color, imprint and the manufacturing site from Iptacopan 200 mg hard capsules used in phase 3 studies (A2301, B12301, CLNP023C12301-24W and CLNP023C12302-24W), as shown in Table 7, Table 8 & Table 9.

Table 7: Compositions of Iptacopan Hard Capsules, 200 mg

Ingredient	Amount per unit dose [mg]	
	Pivotal formulation	Commercial formulation
	200 mg	200 mg
(b) (4)	225.800	225.800
Hard gelatin capsule	(b) (4)	Pale yellow opaque with imprint
Capsule weight		(b) (4)
Capsule size		
Total weight		

[1] Amount of salt as monohydrate per unit dose equivalent to 200 mg free form

Table 8: Iptacopan Hydrochloride Monohydrate Drug Substance Batches

Batch	Batch type	Description
1010024988	Pivotal clinical/ Pilot	Manufactured at Novartis Basel (b) (4)
1010025563	Registration stability /Clinical/ Pilot	Manufactured at Novartis Basel
1010025454	Registration stability /Pilot	Manufactured at Novartis Basel
C0001	Proposed commercial	Manufactured at Novartis Schweizerhalle (b) (4)
C0003	Proposed commercial	Manufactured at Novartis Schweizerhalle
C0004	Proposed commercial	Manufactured at Novartis Schweizerhalle

[2] \\CDSESUB1\EVSPROD\nda218276\0000\m3\32-body-data\32p-drug-prod\lnp023-hard-capsule\32p5-contr-drug-prod\32p54-batch-analys\batch-analyses.pdf

[3] \\CDSESUB1\EVSPROD\nda218276\0000\m3\32-body-data\32p-drug-prod\lnp023-hard-capsule\32p8-stab\stability-data-registration.pdf

Table 9: Iptacopan Hydrochloride Monohydrate Drug Product Batches

Strength	Batch	Batch type	Manufacturing date	Drug substance batch	Description
200 mg	1010025352	Pivotal clinical/ Pilot	Dec 2019	1010024988	Manufactured at Novartis TRD Basel in size 0 (b) (4) opaque hard capsule
200 mg	1010026523	Registration stability/ Proposed commercial	Feb 2021	1010025454	Manufactured at Novartis Wehr in size 0 pale yellow opaque hard capsule with imprint
200 mg	1010026525	Registration stability/ Proposed commercial	Feb 2021	1010029867	Manufactured at Novartis Wehr in size 0 pale yellow opaque hard capsule with imprint
200 mg	1010034620	Clinical/ Proposed commercial scale	May 2021	C0003	Manufactured at Novartis Wehr in size 0 (b) (4) opaque hard capsule

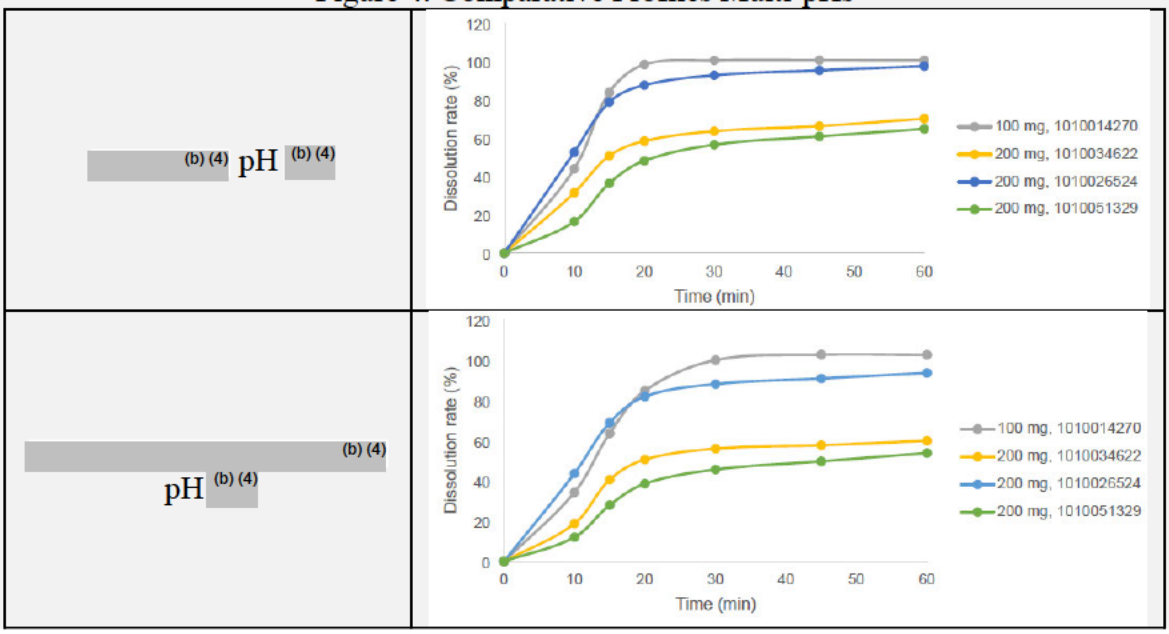
The Applicant provided comparative dissolution study on LNP023 100 mg hard Gelatin Capsule (used in Clinical PK study), Phase 3 200 mg Hard Gelatin Capsules and registration bathes of 200 mg Hard Gelatin Capsules (Table 10) in 500 mL (b) (4) (pH (b) (4)), (b) (4) (pH (b) (4)), HCl 0.01N (pH 2.0, QC method), (b) (4) (pH (b) (4)) and (b) (4) (pH (b) (4)) using USP Apparatus 1 at 100 rpm[4].

Table 10: Batches used for comparative dissolution testing

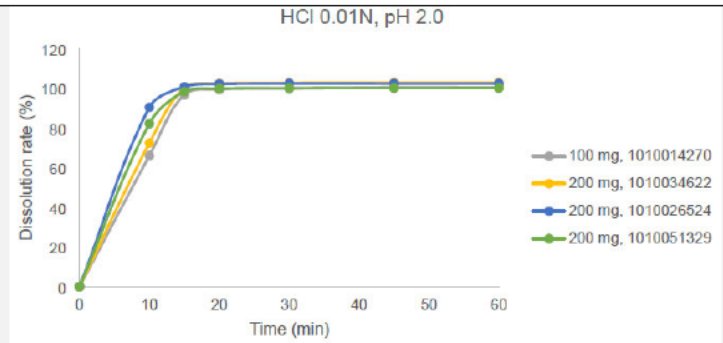
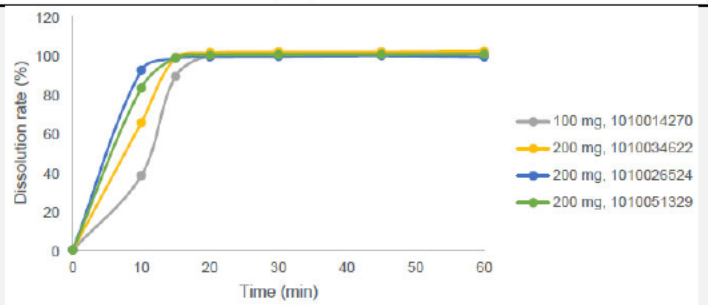
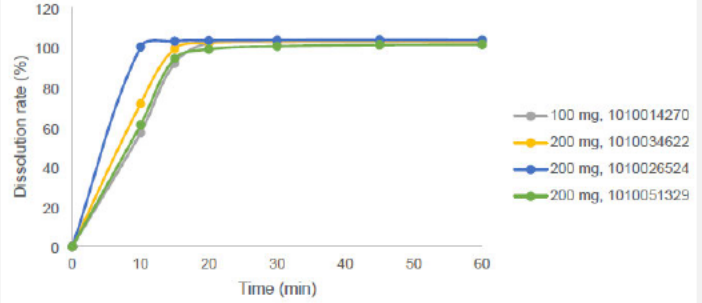
Dosage strength	Product code [1] Basis No.	Product code [1] Variant No.	Material No.	Batch No.	Batch type	Batch size [units]	Manufacturing site	Manufacturing date	DS batch	Batch description
100 mg	(b) (4)		860981	1010014270	Pilot scale	(b) (4)	Novartis Pharma, Switzerland	10-Apr-2017	1010013097	Clinical PK study
200 mg			863852	1010034622	Production scale		Novartis Wehr, Germany	25-May-2021	C0004 / 833709	Phase 3 clinical study
200 mg			863007	1010026524	Production scale		Novartis Wehr, Germany	26-Feb-2021	1010025563	Registration stability
200 mg			864351	1010051329 / WXL58	Production scale		Novartis Wehr, Germany	15-JUL-2022	C0007 / 833709	Process validation, Biobatch

[1] Novartis internal reference system
[2] Batch size reported from SAP

Figure 4. Comparative Profiles Multi-pHs



[4] \\CDSESUB1\EVSPROD\nda218276\0000\m3\32-body-data\32p-drug-prod\lnp023-hard-capsule\32p2-pharm-dev\pharmaceutical-development-comp-dissolution-100mg-200mg.pdf

0.01 N HCl, pH 2.0	
[(b) (4)] pH [(b) (4)]	
[(b) (4)] pH [(b) (4)]	

Rapid release, i.e., above 85% released after 15 minutes (no *f*2 was calculated) for all tested batches in QC method, pH [(b) (4)] and pH [(b) (4)] Incomplete release was observed using [(b) (4)] [(b) (4)] (pH [(b) (4)]) and [(b) (4)] (pH [(b) (4)]), which agreed with the Applicant's discussion on dissolution medium in the previous section [(b) (4)] [(b) (4)]

Assessment: ***{Adequate}***

Based on the comparative dissolution data using the proposed QC method (pH 2.0), the Applicant's bridging results for the formulations, DS substance source and drug product manufacturers are found acceptable.

B.6 BIOWAIVER REQUEST

Assessment: N/A

A biowaiver is not submitted nor required for this NDA.

Primary Biopharmaceutics Assessor's Name and Date: Zhuojun Zhao, Ph.D., 9/7/2023

Secondary Assessor Name and Date: Haritha Mandula, Ph.D., 10/8/2023

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Theodore Carver

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