CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218037Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	218037		
Applicant Name	Alexion Pharmaceuticals, Inc.		
Drug Product Name	Voydeya (danicopan)		
Dosage Form.	Tablet		
Proposed Strength(s)	50 mg and 100 mg		
Route of Administration	Oral		
Maximum Daily Dose	600 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	• VOYDEYA is a complement inhibitor indicated as an add-on to ravulizumab or eculizumab for the treatment of (b) (4) extravascular hemolysis (EVH) in adult (b) (4) with paroxysmal nocturnal hemoglobinuria (PNH).		
Drug Product Description	• 50 or 100 mg tablets packaged in an HDPE bottle with desiccant and child resistant seal in a carton. • 50 or 100 mg tablets packaged in 7-day blister packs sealed into a (b) (4) card, with four (b) (4) cards per carton.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Jansen ONDP/DNDAPI/NDB3	Zhengfu Wang ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Rao Kambhampati ONDP/DNDPIII/NDPB5	Theodore Carver ONDP/DNDPIII/NDPB5

	Manufacturing	Lixia Cai OPMA/DPMAIII/PMB7	Alexander Gontcharov OPMA/DPMAIII/PMB7
	Biopharmaceutics	Rebecca Moody ONDP/DB/BB3	Haritha Mandula ONDP/DB/BB3
	Microbiology	N/A	
	Other (specify):	N/A	
	RBPM	Musse Olani OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life 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, Alexion Pharmaceuticals, has submitted a 505(b)(1) application seeking marketing approval for danicopan tablets as an add-on to ravulizumab or eculizumab for the treatment of (b) (4) extravascular hemolysis (EVH) in adult (b) (4) with paroxysmal nocturnal hemoglobinuria. This application relies upon clinical studies including one pivotal Phase 3 study. The application was submitted as a rolling submission, and Part 2 of the submission (eCTD Sequence 0003) contains Module 3. Danicopan has received orphan drug and breakthrough therapy designations.

2.) Drug Substance (danicopan)

The drug substance, danicopan, is manufactured [redacted] The drug substance review determined [redacted] were adequately controlled. [redacted] The drug substance [redacted] was found to be thermodynamically stable, with no other forms identified, and polymorphic form is controlled in the drug substance specification. Polymorphic form and particle size are not critical quality attributes with respect to the drug product because the drug substance [redacted] The DS specification was found to include appropriate tests with adequate data to qualify impurities, and diastereomeric impurities are adequately controlled. Stability data support a retest date of [redacted] months for the drug substance stored [redacted]

3.) Drug Product (Danicopan tablets)

The drug product is film-coated, debossed tablets manufactured in two strengths, 50 mg and 100 mg. All excipients are compendial grade and the levels of excipients were confirmed to be acceptable during the review, based on products approved in the inactive ingredient database. Based on formulation development the commercial process includes manufacturing [redacted]. The specification was found to include appropriate tests and acceptance criteria. A process impurity and degradant of danicopan, [redacted] In response to information requests, the Applicant provided [redacted] test data for aged lots, in both bottle and blister packaging configurations, to support safe levels of this impurity through the proposed shelf life, based upon the FDA-determined acceptable intake limit. The Applicant has included the test for this [redacted] in the release and stability specifications. The long term and accelerated stability data support a shelf life of 24 months for the drug product when stored in the bottles and blister packaging at 20ºC to 25ºC.

4.) Manufacturing

Process – After several rounds of information requests, the manufacturing review determined that the Applicant established adequate in process

[redacted]

controls and tests to ensure consistent manufacturing of the drug product. The manufacturing process was determined to be adequate.
Facilities – All proposed manufacturing and testing facilities were determined to be acceptable based on their compliance status and inspection history.

5.) Biopharmaceutics
The Biopharmaceutics review was focused on the evaluation and acceptability of the proposed quality control dissolution method and acceptance criterion. After several information requests to the Applicant, the Biopharmaceutics review concluded that the dissolution method is sufficiently discriminating with respect to critical quality attributes of the drug product (b) (4) and that the dissolution method is adequate to support the quality of the drug product.

6.) Quality Labeling
The review of the quality labeling concluded that the labeling is adequate after minor revisions to the labeling, which were communicated to the Applicant and will be included in the final labeling revisions.

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:
None

Comparability Protocols (PACMP): No
Comments:
None

Additional Lifecycle Comments: None.

Theodore Carver

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(b) (4)

R REGIONAL INFORMATION

Environmental
Alexion requested a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31 (b). To the best of the sponsor's knowledge, no extraordinary circumstances, as referenced in 21 CFR 25.21, exist relative to this action.

The calculations to support the categorical exclusion from the need to prepare an environmental assessment are outlined below.

(b) (4)
the EIC for ALXN2040 is significantly below the 1ppb trigger for full EA. Therefore, it can be concluded that an EA for ALXN2040 is not required.

(b) (4)

Assessment: *Adequate*
In the initial NDA submission, the applicant did not provide EIC for danicopan substance, however, upon comment, the information was provided in the Amendment #0031 dated 12/22/2023 to the NDA. The EIC is much lower than 1 ppb.

Methods Validation or Verification Package
In the NDA, Section 3.2R Regional Information section, the applicant provided method validation reports for all the analytical methods used for the drug product tablet testing.

Assessment: *Adequate*
The reports contain all the information required for method verification.

Comparability Protocols

Assessment: ***N/A***

Post-Approval Commitments

Assessment: ***N/A***

Lifecycle Management Considerations

None

DRUG PRODUCT LIST OF DEFICIENCIES: None

All the deficiencies that were communicated during the course of the NDA review were adequately addressed by the applicant, therefore, no deficiencies are pending.

Primary Drug Product Assessor Name and Date: Rao V. Kambhampati, Ph.D. 12/22/2023.

CHAPTER IV: LABELING
NDA 218037

NDA Number	218037
Assessment Cycle Number	1
Drug Product Name	Danicopan Tablets

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate after recommended changes are made.	
Patient Information	Adequate after recommended changes are made.	
Instruction for Use (IFU)	N/A	
Container Labels	Adequate after recommended changes are made.	
Carton Labeling	Adequate after recommended changes are made.	

Brief Description of Outstanding Issues: All the comments in this review were incorporated into the USPI and Medication Guide documents in the sharepoint and they were communicated to the applicant. The revised USPI, Medication Guide, container and carton labels will reflect the recommended changes.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
Rolling NDA Part 1 eNDA Seq# 0001	1/13/2023	Full Module 3 (CMC) was submitted
Rolling NDA Part 2 eNDA Seq.# 0003	3/30/2023	Container and carton labels. Propreitary name was proposed.
Amendment eNDA Seq.# 0025	10/30/2023	Revised USPI and new Medication guide

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Item 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[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	Danicopan Tablets
Route(s) of administration	Adequate	Oral
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	Danicopan Tablets
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).[6]	N/A	

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1

Item	Item 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)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral 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.[8]	N/A	

Assessment: *Adequate*

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(*copy of proposed text*)

Item	Item 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 and/or soft food[10], storage	N/A	

[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>
[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)
[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

Item	Item 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)
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).	N/A	
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Adequate*

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

Item	Item 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	Film-coated tablets
Strength(s) in metric system	Adequate	50 mg and 100 mg
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 (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	This information was provided in 16. How Supplied/Storage and Handling section of the USPI
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 parenteral 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 (see USP <659>).	N/A	

Assessment: *Adequate*

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

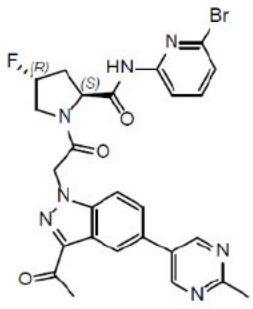
1.2.3 Section 11 (DESCRIPTION)[14]

Item	Item 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)[15] [§ 201.57(c)(12)(i)(A)].	Inadequate	Proprietary name, (b) (4) should be included. Established name, danicopan, was included.
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Tablets. For oral administration.
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)" [§ 201.57(c)(12)(i)(C)].	Adequate	
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Inadequate	Presently shown as: The tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and hypromellose acetate succinate. The tablet coating components are: polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc.

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item 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)
		Comment: Ingredients should be listed in alphabetical order.
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. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	Danicopan is a small molecule complement factor D (FD) inhibitor (b) (4)
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	(2*S*,4*R*)-1-{[3-acetyl-5-(2-methylpyrimidin-5-yl)-1*H*-indazol-1-yl] acetyl}-*N*-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide.  580.4

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

Item	Item 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)
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	N/A	
For oral prescription drug products, include gluten statement[19] (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	

Assessment: *Adequate*
Adequate after the above recommended changes are made. All comments in the above tables were incorporated into the sharepoint USPI document, which was communicated to the applicant by the clinical division. The revised document will reflect the above recommended changes.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

Item	Item 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) [§ 201.57(c)(17)].	Adequate	Tablets

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)
[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item 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)
Strength(s) in metric system. [§ 201.57(c)(17)(i)] 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. No equivalency statement.	Adequate	50 mg and 100 mg
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	1) Packed inside a carton: One 90 count bottle of 50 mg tablets. One 90 count bottle of 100 mg tablets. 2) Packed inside a carton: Two 90 count bottles of 100 mg tablets. 3) Packed inside a carton: Four blister (b) (4) cards of twenty-one 50 mg tablets and twenty-one 100 mg tablets. 4) Packed inside a carton: Four blister (b) (4) cards of forty-two 100 mg tablets per (b) (4)
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	1) White to off-white, round film-coated tablets. Debossed on one side with "DCN 50". 2) White to off-white, round film-coated tablets. Debossed on one side with "DCN 100". NDC numbers were included.
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 parenteral 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 (see USP <659>).	N/A	

Item	Item 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 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." [§ 201.57(c)(17)(iv)]	Adequate	Store in the original container.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (See USP <659>).	Inadequate	Presently shown as: (b) (4) [redacted] Comment: Above statement should be changed to "Store in original container 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."*[21]	N/A	

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)

Item	Item 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)
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Adequate	HDPE bottles with desiccant and child resistant seal, packed inside a carton.

Assessment: *Adequate*

Adequate after the above recommended changes are made. All comments in the above tables were incorporated into the sharepoint USPI document, which was communicated to the applicant by the clinical division. The revised document will reflect the above recommended changes.

1.2.5 Other Sections of Labeling: Not applicable

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	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	Manufactured for: Alexion Pharmaceuticals, Inc. 121 Seaport Boulevard Boston, MA 02210 USA

Assessment: *Adequate*

2.0 PATIENT LABELING

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

[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	Danicopan
Special preparation instructions (if applicable).	N/A	
Storage and handling information (if applicable).	Adequate	Store VOYDEYA in original container between 59°F and 86°F (15°C and 30°C).
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	Adequate	
Active ingredient(s) (if applicable).	Adequate	danicopan
Alphabetical listing of inactive ingredients (if applicable).	Inadequate	Inactive ingredients should be listed alphabetically
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	Manufactured for: Alexion Pharmaceuticals, Inc., 121 Seaport Boulevard, Boston, MA 02210 USA

Assessment: *Adequate*
Adequate after the above recommended changes are made. All comments in the above table were incorporated into the sharepoint Medication Guide document, which was communicated to the applicant by the clinical division. The revised document will contain the recommended changes.

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

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[24] Established name = [Drug] [Route of Administration] [Dosage Form]
[25] Carton and Container Labeling Resources
[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

(b) (4)

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency	N/A	Yes	

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

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].			
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	
For injectable drug products for parenteral 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. (See USP <659>).	N/A	Yes	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	Yes	

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	No	See Prescribing Information was included on the carton label only.
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	N/A	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Inadequate	Yes	A statement about dispensing a Medication Guide to each patient should be included.
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	
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.[31]	N/A	Yes	
And others if space is available.	N/A	Yes	

Assessment of Carton Labels and Container Labeling: *Adequate*
Adequate after the above recommended changes are made. The comments in the above tables were communicated to the applicant by the clinical division and the revised container and carton labels will reflect the above recommended changes.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

All the comments shown in the above tables were communicated to the applicant by the clinical division and the responses will be included in the final revised Prescribing Information (USPI), Medication Guide, and on container and carton labels.

Primary Labeling Assessor Name and Date: Rao V. Kambhampati, Ph.D. 12/22/2023.

[31] USP General Notices 3.20 Indicating Conformance

Rao Kambhampati

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Theodore Carver

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	505(b)(1); Type 1: New Molecular Entity
NDA Number	218037
Assessment Cycle Number	1
Drug Product Name/ Strength	VOYDEYA (danicopan) Tablets, 50 mg and 100 mg
Route of Administration	Oral
Applicant Name	Alexion Pharmaceuticals
Therapeutic Classification/ OND Division	Division of Non-Malignant Hematology (DNH)
RLD/RS Number	N/A
Proposed Indication	An add-on to ravulizumab or eculizumab in the treatment of adult (b) (4) with paroxysmal nocturnal hemoglobinuria (PNH) (b) (4) extravascular hemolysis (EVH)

Assessment Recommendation: **Adequate**

Assessment Summary:

Alexion Pharmaceuticals Inc., the Applicant, submitted a 505(b)(1) application for the proposed VOYDEYA (danicopan) Tablets, 50 mg and 100 mg, on March 30, 2023. Danicopan is a first-in-class small molecule, orally administered complement factor D (FD) inhibitor, developed as an add-on to ravulizumab or eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) (b) (4) of extravascular hemolysis (EVH). The tablet formulation development consisted of (b) (4)

The recommended starting dose of VOYDEYA for adult patients (≥ 18 years old) is 150 mg three times a day administered orally (b) (4) Depending on the clinical response, dose can be increased to 200 mg tid. In support of their NDA submission, the Applicant conducted 14 Phase 1 clinical pharmacology studies, 8 Phase 2 studies in several indications (PNH, complement 3 glomerulopathy [C3G]/immune-complex membranoproliferative glomerulonephritis [IC-MPGN], GA, and coronavirus disease 2019), and 1 pivotal Phase 3 study in PNH.

The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed quality control dissolution method and acceptance criterion.

Dissolution method and Acceptance Criterion: The FDA approved quality control dissolution method and acceptance criterion (finished drug product batch release and stability testing) for VOYDEYA (danicopan) Tablet; 50 mg and 100 mg are as follows:

Medium	pH 6.8 Sodium Phosphate Buffer with 0.3% SDS
Volume/Temp	900 mL; 37°C
USP Apparatus	2 (Paddle)
Rotational Speed	75 rpm
Acceptance Criterion	NLT (b)(4)% (Q) of the labeled amount of danicopan is dissolved in 30 minutes

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0003 (3) Original Submission	**March 30, 2023**
0015 (15) Quality IR Amendment	**August 18, 2023**
0022 (22) Quality IR Amendment	**October 10, 2023**

Highlight Key Issues from Last Cycle and Their Resolution: None
Concise Description of Outstanding Issues: None

B.1 BCS DESIGNATION

Solubility: The Applicant conducted solubility testing across the pH range of 1.2-6.8 and found that danicopan exhibits low solubility across the entire physiological pH range. Solubility of danicopan is provided below in Table 1.

Table 1. Solubility of Danicopan

Base Media	24 hr Average Concentration (µg/mL)	24 hr pH
SGF without enzymes	44.5	1.24
pH 4.5 Sodium Acetate	3.05	4.55
pH 6.8 Sodium Phosphate	5.26	6.77
FaSSIF	16.8	6.50
FeSSIF	65.2	5.03

SGF = Simulated gastric fluid, FaSSIF = Fasted State Simulated Intestinal Fluid, FeSSIF = Fed State Simulated Intestinal Fluid

Permeability: The permeability classification of danicopan is based on human absorption, distribution, metabolism, and excretion (ADME) study (ACH471-005). From the data, the Applicant surmised that danicopan is well absorbed (highly permeable).

Dissolution: See Assessment below.

Reviewer Comment: The Applicant did not request an official BCS claim. The Applicant concluded that danicopan is a BCS Class II drug substance (high solubility, low permeability). While danicopan exhibits low solubility (see Table 1), a definitive conclusion with respect to BCS classification cannot be drawn based on permeability data provided.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

The approved dissolution test method and acceptance criterion for VOYDEYA (danicopan) tablets, 50 mg and 100 mg are as follows:

Medium	pH 6.8 Phosphate Buffer with 0.3% w/v SDS
Volume/Temp	900 mL; 37°C
USP Apparatus	2 (paddle)
Rotational Speed	75 rpm
Acceptance Criterion	Q= (b) (4)% in 30 minutes

Figure 1. Dissolution for Danicopan 50 mg Film Coated Tablet Batch 4240799 used in Phase 3 study (ALXN2040-PNH-301)

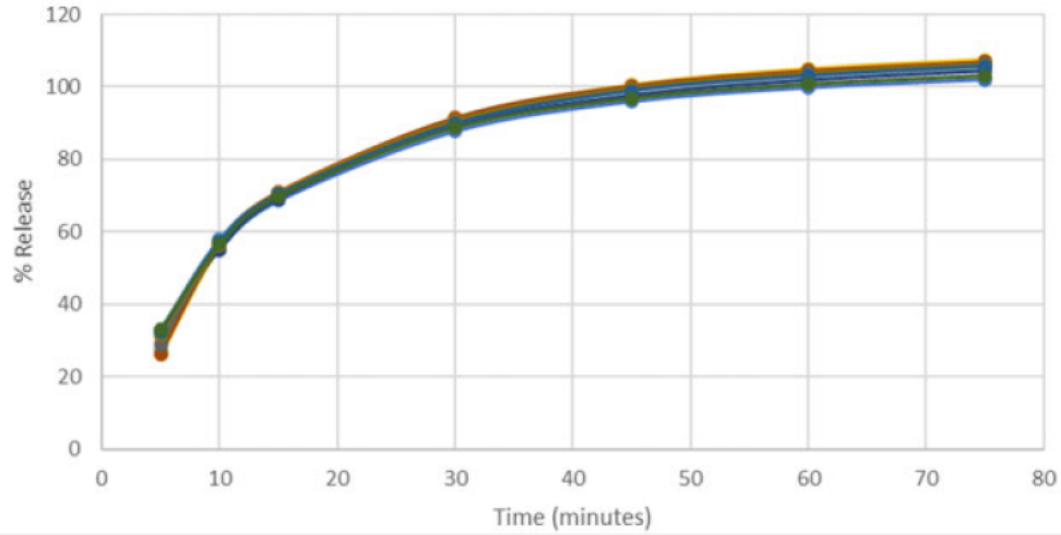
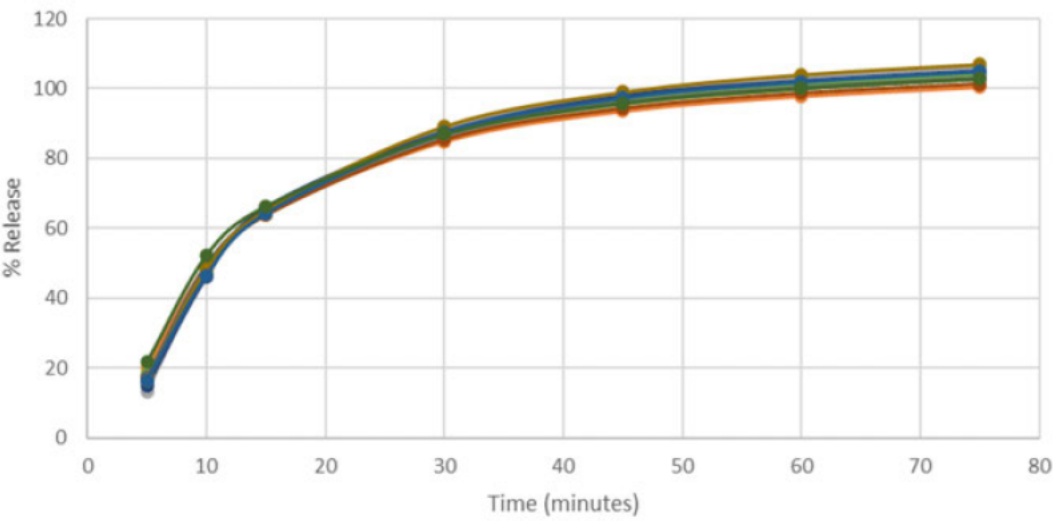


Figure 2. Dissolution for Danicopan 100 mg Film Coated Tablet Batch 4240817 used in Phase 3 study (ALXN2040-PNH-301)



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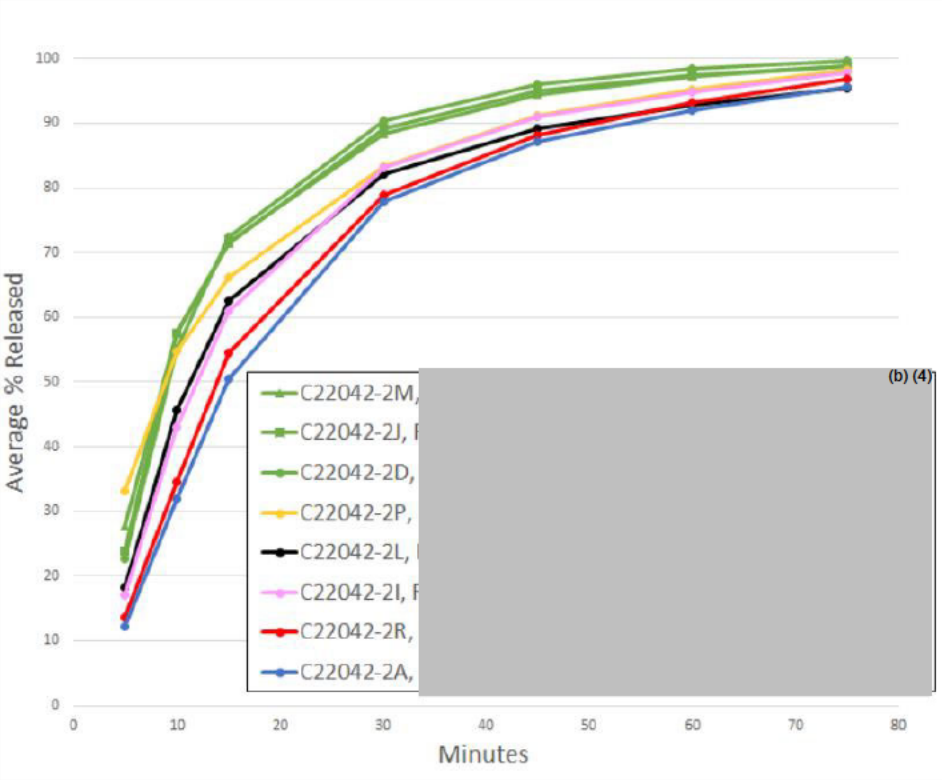
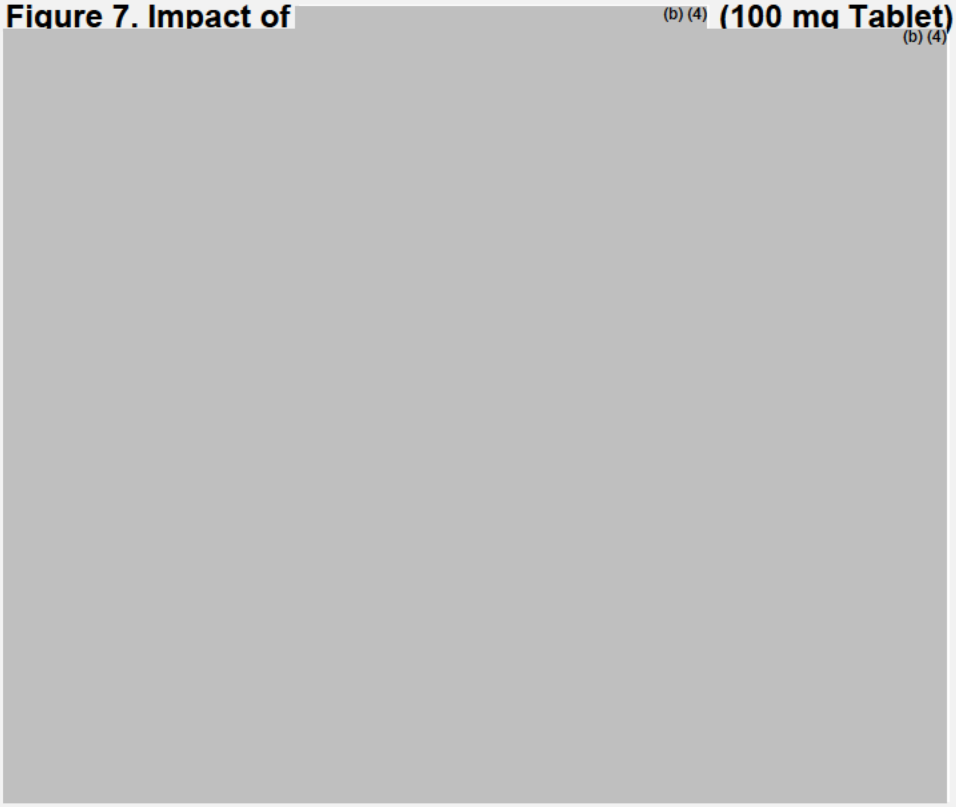
Discriminating Power of the Dissolution Method: The discriminating ability of the dissolution method was investigated by comparing the dissolution profiles of the formulation DoE batches, the process DoE batches, coating studies (coated vs uncoated tablet dissolution), and (b) (4). The amount of (b) (4) were varied in the formulation robustness study. (b) (4) As can be seen from Figures 6 and 7, the proposed dissolution method could detect differences in composition and process parameters of the core tablets.

Figure 6. Impact of (b) (4) vs Target Formulation (100 mg Tablet)



(b) (4)

Figure 7. Impact of (b) (4) (100 mg Tablet)



(b) (4) As shown in Figure 8, the proposed dissolution method was sensitive to changes in the aforementioned attributes.

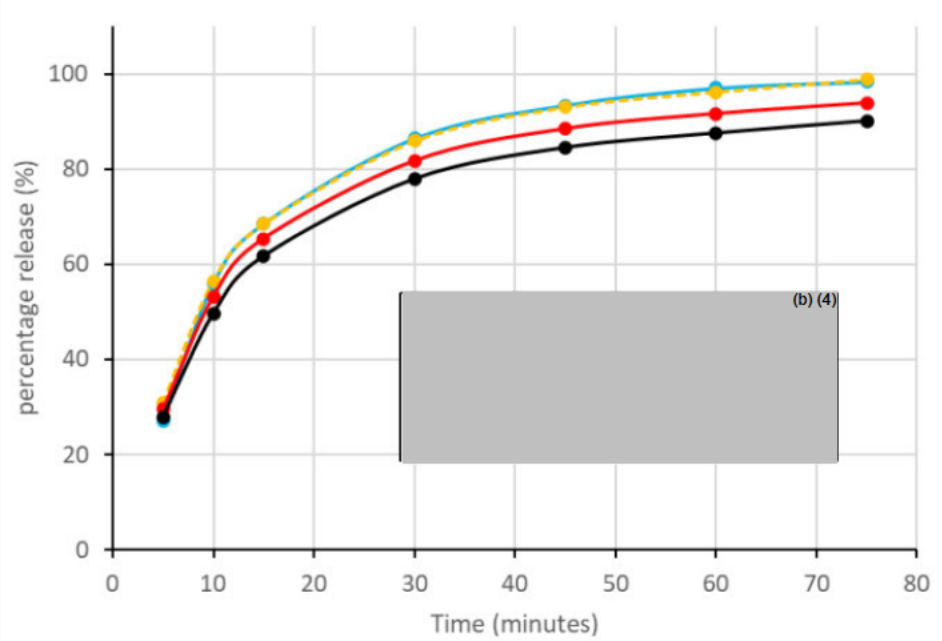
Figure 8. Impact of (b) (4) Product Attributes on Dissolution at 30 Minutes

In response to IR dated August 4, 2023, the Applicant stated they have also controlled the particle size of the (b) (4) (D90 (b) (4) µm) to ensure product quality.

Finally, as the product is an (b) (4), the Applicant investigated the ability of the dissolution method to discriminate against changes to the polymorphic form of danicopan (b) (4) As seen from Figure 9, (b) (4) . Nevertheless, to further mitigate risk, the Applicant has instated a

(b) (4)

Figure 9. Impact of Apparatus and Rotational Speed (100 mg Tablet)



Dissolution Acceptance Criterion[1]

The dissolution acceptance criterion was tightened from (b) (4) to "Q= (b) (4)% in 30 minutes" in response to the IR dated October 3, 2023.

Table 2. Summary of Dissolution Performance in pH 6.8 with 0.3% SDS for Clinical Batches of Danicopan Tablets used in Phase 3 study

Range	Time (minutes)	% release (Label claim: 50mg)	% release (Label claim: 100mg)
Range of individual dosage unit % release	15	(b) (4)	
	30		
	45		
	60		
Range of mean (batch) % release	15		
	30		
	45		
	60		

Note: Range of mean is reported based on 50 mg (n=4) and 100 mg (n=5)

Reviewer Comment: The proposed dissolution method can discriminate towards changes in formulation variables (b) (4) Tightening of the dissolution acceptance criterion from (b) (4) to "Q= (b) (4)% in 30 minutes" provides additional discriminating ability and can reject variant batches as illustrated in Figures 6-9. All batches meet the proposed acceptance criterion at release and on stability. Therefore, the proposed dissolution

[1] NDA 218037 Seq 0030 (30) Module 3.2.P.5.6 Justification of Specifications Pgs 3-10

method and acceptance criterion are adequate for the quality control of Danicopan Film-Coated Tablets, 50 mg and 100 mg.

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

Assessment: Adequate

The product is designed as an immediate release tablet

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: Adequate

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

B.12 BRIDGING OF FORMULATIONS

Assessment: N/A

The to-be-marketed tablet formulation is the same as that tested in the Phase 3 Pivotal Study (ALXN2040-PNH-301). Therefore, bridging of formulations (in vitro or in vivo) is not required.

B. 13 BIOWAIVER REQUEST

Assessment: N/A

Danicopan is supplied as 50 mg and 100 mg round film-coated tablets. Both strengths were evaluated in pivotal clinical trials.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Appendix

Biopharmaceutics Information Requests and Applicant's Responses

(b) (4)

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Haritha Mandula

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Rebecca Moody

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Theodore Carver

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THEODORE E CARVER
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