CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214487Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) 214487

Integrated Quality Assessment

RECOMMENDATION

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

NDA 214487
Assessment #1

Drug Product Name	Avacopan capsules
Dosage Form	capsules
Strength	10 mg/capsule
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	ChemoCentryx, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	07-JUL-2020	All
Amendment	11-DEC-2020	Manufacturing/Biopharmaceutics
Amendment	05-MAR-2021	Drug Substance
Amendment	12-MAR-2021	Drug Substance
Amendment	19-MAR-2021	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sam Bain	Donna Christner
Drug Product	Caroline Strasinger	Wendy Wilson-Lee
Manufacturing	Ramesh Dandu	Yong Hu
Microbiology	N/A	
Biopharmaceutics	Kalpana Paudel	Haritha Mandula
Regulatory Business Process Manager	Florence Aisida/Oumou Barry	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
Environmental	Caroline Strasinger	Wendy Wilson-Lee

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

N/A – The application is recommended to be approved.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Avacopan Capsules are for oral administration and immediate release of a small molecule drug that inhibits the binding of complement 5a to the C5a receptor, providing a treatment for patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated Vasculitis (an orphan autoimmune disease). This disease, if left untreated, will lead to death for 80% of patients within 2 years. The drug has reasonable stability as formulated and room temperature storage is promoted. The formulation is (b) (4)

Proposed Indication(s) including Intended Patient Population	Treatment of ANCA-associated Vasculitis
Duration of Treatment	Chronic
Maximum Daily Dose	60 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance (DS): Adequate

The drug substance is manufactured (b) (4) All regulatory starting materials satisfy the ICH Q11 guidelines; and were acceptable to the Agency via a Type B CMC meeting on 12-SEP-2019. The drug

substance manufacturing process has been demonstrated to be satisfactory. The drug substance structure has been elucidated via multiple spectrometric techniques, including single crystal X-ray diffraction. The applicant has done extensive evaluations of potential impurities in the drug substance based upon the manufacturing process for the drug substance. The evaluations include starting materials, intermediates and the final drug substance, all of which are appropriately controlled. The applicant's specification for the drug substance meets the ICH Q6A, Q3C and Q3D guidelines. We note that the drug substance as well as the specified and potential impurities in it have the (b) (4) structural alert for mutagenicity. We asked the OND nonclinical review team for their evaluations of four toxicology reports on the impurities in the drug substance and of the applicant's limits of the impurities that are specified at above the ICH Q3A guidelines. After two information requests and the applicant's responses, the impurity limits are acceptable. The drug substance container closure system components are typical of what the Agency accepts, including the (b) (4) (b) (4) packaging material. The drug substance primary stability batches have been demonstrated to be stable over (b) (4) months under the shelf-life storage condition (b) (4) The supporting stability batches are stable over (b) (4) months at (b) (4) Thus, the proposed retest period of (b) (4) months for the drug substance is acceptable based upon ICH Q1E guidelines.

Drug Product (DP): Adequate

The drug product is a light orange and yellow opaque bicolor size 0 hard gelatin capsule with clear gelatin sealing band for oral administration. The capsule is printed with CCX168 in black ink and contains 10 mg avacopan. The drug formulation utilizes compendial (USP/NF) excipients and all are used at concentrations below that of other approved oral formulations. Gelatin capsules are manufactured by (b) (4) and a LOA to reference DMF (b) (4) has been provided (DMF (b) (4) deemed adequate for use in April 2020). The gelatin sealing band is non-compendial, however the components of the band itself are all compendial.

The Maximum Daily Dose (MDD) for treatment of Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis is 60 mg.

The only specified impurity (b) (4) has been limited to NMT (b) (4) %.

The container closure system (b) (4) used for registration stability studies was identical to the to-be-marketed version with only the exception of (b) (4) which is not to be included for marketing. Bottle count for the drug product includes 180 and 30 count capsules in 250 mL and 75 mL HDPE bottles respectively.

A bulk storage shelf life of (b) (4) months (b) (4) is supported. Based on the stability data submitted to date, the **expiry dating period for (avacopan) capsules shall be 36 months** when stored at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F).

Labeling: Adequate

This application is deemed ready for APPROVAL from the OPQ/ONDP label/labeling perspective.

Manufacturing: Adequate

(b) (4) (FEI # (b) (4)) is the manufacturing facility for the drug product. (b) (4)

Based on process experience at the facility the site was considered acceptable. The DS manufacturing facility is (b) (4) (FEI (b) (4)) and the DS intermediate manufacturing facilities are (b) (4) (b) (4) (FEI (b) (4)) and (b) (4) (FEI (b) (4)). These three facilities have acceptable profile (b) (4) and compliance coverage based on review of inspectional history. Testing facilities were approved based on inspectional coverage and compliance history and based on information in FACTS, CMS and OSAR databases. OMIR is "approve".

The manufacturing process entails (b) (4)

Registration batches (as well as PPQ/stability batches included in 3.2.R) were made at commercial scale at the same site utilizing the same equipment (i.e. same design and operating principles) as the commercial process (no scale-up). The applicant provided development studies to

support the proposed parameter ranges for the commercial scale equipment, and a detailed explanation of the control strategy; minor issues have been resolved during the review.

Biopharmaceutics: Adequate

The Biopharmaceutics review is focused on the evaluation of dissolution method and acceptance criterion. The to-be-marketed drug product is the same as that used in phase 2 and 3 clinical studies as well as the stability studies, so no formulation bridging was necessary. Dissolution of the drug is observed (b) (4) and sink conditions were observed for pH (b) (4) The dissolution method was found to be sufficiently discriminating (b) (4) Dissolution profiles of the phase 3 clinical and registration stability lots were comparable, reaching 100% dissolution within 30 minutes. The dissolution acceptance criteria of Q = (b) (4) % in 30 minutes is deemed adequate from a quality control perspective.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

DP CQA	Factors that may impact the CQA	O[1]	S[1, 2]	D[1]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Comments/Lifecycle considerations
Identification	• formulation of incorrect API	2	3	1	6	(b) (4)		
Assay	• impurities in API • degradation of API during manufacture or during drug product shelf life • incorrect amt. formulated	2	3	2	12			
Uniformity of dosage units	• Non-homogeneity of formulation • encapsulation variability	3	3	2	18			
Dissolution[3]	• Crystallization of API during shelf life	1	3	2	12		6	Dissolution method found to be sufficiently discriminatory to both formulation changes (b) (4) (b) (4)
Degradation Products	• degradation of API during manufacture or during drug product shelf life	2	3	2	12			

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability

[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" will be used throughout)

[3] Preliminary assessment: detailed evaluation by biopharmaceutics team may be necessary

	• API interaction with excipients					(b) (4)		
Appearance	• Incoming capsule shell defects • Capsule damage during manufacture • Gelatin band variability	2	3	3	18			
(b) (4)	• Excipient (b) (4) • API (b) (4)	3	3	2	18			
Microbial Limits Test	• Failure of (b) (4) package (b) (4) to support microbial growth	2	3	3	18			

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

N/A

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

N/A

4. Labeling Deficiencies

N/A

5. Manufacturing Deficiencies

N/A

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies (Specify discipline, such as Environmental)

Application Technical Lead Name and Date:

Craig M. Bertha, CMC Lead for DPACC/DRTM
22-MAR-2021

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	IV		(b) (4)	Adequate	08-APR-2020	
	III			N/A		Sufficient information in NDA
	III			N/A		Sufficient information in NDA
	III			N/A		Sufficient information in NDA

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

Document	Application Number	Description
IND	120784	Avacopan investigational application

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other				

51 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRADENAME	ADEQUATE Location established, name pending approval
Established name(s)	(avacopan) capsules	ADEQUATE
Route(s) of administration	For oral use	ADEQUATE
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Capsules: 10 mg	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	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
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)	(b) (4) [redacted]	INADEQUATE. The strength of the product is 10 mg. (b) (4) [redacted] This was **satisfactorily** resolved on 3/19/20

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3 DOSAGE FORMS AND STRENGTHS

Capsules: 10 mg, opaque, yellow and light orange with CCX168 printed in black

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Capsules	ADEQUATE
Strength(s) in metric system	10 mg	ADEQUATE
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not applicable	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Not provided	INADEQUATE: Add "opaque yellow and light orange with CCX168 printed in black This was **satisfactorily** resolved on 3/19/20
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4)	INADEQUATE Add (avacopan) capsules This was **satisfactorily** resolved on 3/19/20
Dosage form(s) and route(s) of administration	(b) (4)	INADEQUATE add for oral administration This was **satisfactorily** resolved on 3/19/20
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	All ingredients listed	INADEQUATE List in alphabetical order and remove (b) (4) This was **satisfactorily** resolved on 3/19/20
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	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	C5aR antagonist	ADEQUATE
Chemical name, structural formula, molecular weight	present	ADEQUATE
If radioactive, statement of important nuclear characteristics.	N/A	N/A

Other important chemical or physical properties (such as pKa or pH)	solubility	N/A

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	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	N/A

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Capsules	ADEQUATE
Strength(s) in metric system	Not provided	INADEQUATE Add 10 mg This was **satisfactorily** resolved on 3/19/20
Available units (e.g., bottles of 100 tablets)	Bottles of 180 capsules or 30 capsules	ADEQUATE (formatting changes)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Not provided	INADEQUATE Add: size 0, hard, opaque yellow and light orange capsule with "CCX168" printed in black. This was **satisfactorily** resolved on 3/19/20
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	N/A

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

Item	Information Provided in the NDA	Assessor's Comments
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.)	Do not use if seal is broken or missing	ADEQUATE
If the product contains a desiccant, ensure the size and shape differ from the dosage	N/A	N/A

form and desiccant has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	(b) (4) Presented as °F (°C)	INADEQUATE change to: Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature]. This was **satisfactorily** resolved on 3/19/20
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	N/A
Include information about child-resistant packaging	Child resistant induction seal closure	ADEQUATE

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: ChemoCentryx, Inc. By: Thermo Fisher Scientific, 2110 East Galbraith Road Cincinnati, OH 45237	ADEQUATE

ASSESSMENT OF THE PI: *ADEQUATE* (The below deficiencies were satisfactorily resolved on 3/19/20)

The following Items should be addressed for the PI. Refer to screen shots above for specifics of text and format.

Section 3

- Include capsule description

Section 11

- Include established name
- Include route of administration
- List inactive ingredients in alphabetical order and remove (b) (4)

Section 16

- Include strength
- Include capsule description

- Revise storage conditions to read:

Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30ºC (59°F-86ºF) [see USP Controlled Room Temperature].

2.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling


(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	TAVNEOS (avacopan) capsules	ADEQUATE
Dosage strength	10 mg	ADEQUATE
Route of administration	Not present	ADEQUATE (product for oral use therefore this statement is not required to be present)
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	30 capsules; 180 capsules	ADEQUATE
"Rx only" displayed on the principal display	Present on Carton	ADEQUATE
NDC number	Present on Container and Carton	ADEQUATE
Lot number and expiration date	NOT present	INADEQUATE Include lot number and expiration date on label **(Communicated Via DMEPA on 2/17/2021)**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30ºC (59°F-86ºF) [see USP Controlled Room Temperature].	ADEQUATE
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Present	ADEQUATE

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Manufactured for: ChemoCentryx, Inc. By: Thermo Fisher Scientific, Cincinnati, OH 45237	ADEQUATE
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	N/A	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	N/A
And others, if space is available	Inactive ingredients not listed Active Ingredient: avacopan 10 mg	ADEQUATE

Assessment of Carton and Container Labeling: ***INADEQUATE (these deficiencies were communicated on 2/17/2021 via DMEPA)***

- **Include lot number**
- **Include expiration date (DMEPA has provided language for this)**

Overall Assessment and Recommendation:

On March 12, 2020, the above deficiencies were communicated to the Applicant. The Applicant agreed to all OPQ related deficiencies on March 19, 2020. The Label and Labeling of NDA 214487 is ADEQUATE.

This application is deemed ready for APPROVAL from the OPQ/ONDP label/labeling perspective.

Primary Labeling Assessor Name and Date:

Caroline Strasinger, PhD
OPQ, ONDP, DNDP II, B4

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

Wendy Wilson, Ph.D.
Chief, Branch 4
DNDP II/ONDP

Caroline Strasinger

Digitally signed by Caroline Strasinger
Date: 3/22/2021 08:46:04AM
GUID: 5051dfdd000013b995075b4d54108ed8

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 3/22/2021 09:10:23AM
GUID: 50816dbc000085595ca3284bbca465a8

51 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

Product Background:

NDA: NDA 214487-ORIG-1

Drug Product Name / Strength: Avacopan capsules (liquid filled hard gelatin)/10 mg

Indication: Treatment of patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated Vasculitis.

Route of Administration: Oral

Applicant Name: ChemoCentryx, Inc.

Review Recommendation: **ADEQUATE**

Review Summary:
Avacopan is a new molecular entity that is indicated for the treatment of patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated Vasculitis synthesized by a convergent synthesis. ANCA-associated vasculitis is an orphan autoimmune disease and if left untreated patients typically die in a couple of years. There is standard of care therapy for moderate to severe ANCA-associated vasculitis that consists of a combination of high-dose glucocorticoids and either cyclophosphamide or rituximab. The avacopan is said to be different in that it supposedly prevents complement 5a from binding to its receptor, which would stop the production of the components that cause the autoimmune disease.

The 10 mg capsules are for immediate release and are formulated as (b) (4) (b) (4) hard gelatin capsules sealed with a gelatin band. The total daily dose is 60 mg (taken BID).

Biopharmaceutics review is focused on the evaluation and acceptability of bridging of formulations, dissolution method, and dissolution acceptance criterion.

In Vitro Dissolution Method and Acceptance Criterion: ADEQUATE
The following dissolution method and acceptance criterion for the release of avacopan from the capsules are deemed acceptable:

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
Apparatus 2 with sinker	50	0.1N HCl/37°C ± 0.5°C	900	Q= (b) (4) % in 30 minutes

Formulation development and bridging: ADEQUATE from Biopharm perspective
The to-be-marketed (TBM) formulation is same as the formulation for Phase 2, Phase 3 clinical studies and registration stability batches. Hence, no bridging is required.

Biowaiver Request: Not Applicable
Only one strength is developed.

List of Submissions being reviewed:

Application 214487 - Sequence 0001 Original
Application 214487 - Sequence 0019 Response to IR

Highlight Key Outstanding Issues from Last Cycle: The Applicant was requested to provide individual dissolution data and to revise acceptance criterion.

Concise Description Outstanding Issues Remaining: None.

From Biopharmaceutics perspective, NDA 214487 for Avacopan capsules (10 mg) is recommended for APPROVAL.

BCS Designation

Reviewer's Assessment:

BCS Designation:

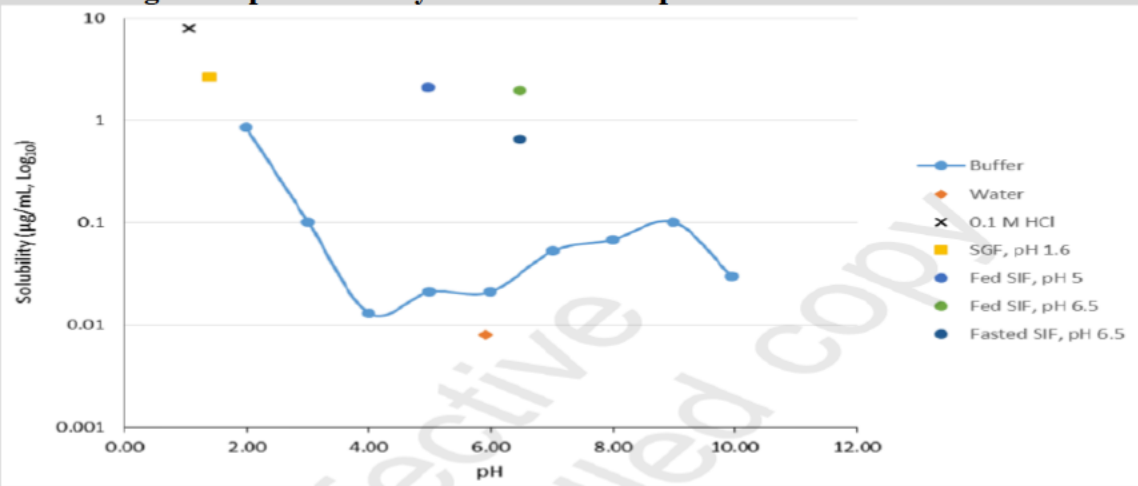
The Applicant noted that Avocapon is a Biopharmaceutics Classification System (BCS) Class 2 compound based on low solubility and high permeability. For this reason, avacopan 10 mg hard capsule is formulated (b) (4) The details are provided in the document\\cdsesub1\evsprod\nda214487\0001\m3\32-body-data\32p-drug-prod\avacopan\32p2-pharm-dev\pharmaceutical-development-drugprod-phys.pdf

Solubility:
Avacopan drug substance is practically insoluble (≤10 µg/mL) in buffered aqueous systems pH 2 - pH 10 and in physiologically-relevant media (SGF, FaSSIF, and FeSSIF). The pH solubility profile performed across a range of pH is shown in the table below.

Table 1: pH Solubility Profile of Avacopan Batch 05CCX03-10-95

Solvent	Actual pH	µg/mL
0.1 M HCl	1.05	8.050
pH 2 Buffer	1.99	0.863
pH 3 Buffer	3.01	0.101
pH 4 Buffer	4.01	0.013
pH 5 Buffer	5.00	0.021
pH 6 Buffer	6.00	0.021
pH 7 Buffer	7.03	0.053
pH 8 Buffer	8.00	0.068
pH 9 Buffer	9.00	0.101
pH 10 Buffer	9.95	0.030
Water	5.92	0.008
SGF, pH 1.6	1.39	2.645
FeSSIF, pH 5	4.98	2.092
FeSSIF, pH 6.5	6.47	1.961
FaSSIF, pH 6.5	6.47	0.656

Figure 1: pH Solubility Profile of Avacopan Batch 05CCX03-10-95



Permeability:
The Applicant noted that avacopan is highly permeable across the Caco-2 monolayer membrane (Papp (A-B) = 36.4 × 10^{-6} cm/s; Papp (B-A) = 39.3 × 10^{-6} cm/s) and does not appear to be a substrate for active efflux. A good oral bioavailability of the drug product has been observed, which confirms the permeability.

Dissolution: See below.

1. Composition of proposed drug product:
The quantitative composition of each component of the proposed drug product is listed in Table 2. \\cdsesub1\evsprod\nda214487\0001\m3\32-body-data\32p-drug-prod\avacopan\32p1-desc-comp\description-and-composition.pdf

Table 2: Composition of the proposed drug product

Component	Function	Quality Standard	10 mg Capsule	
			(mg)	% w/w
Avacopan	Drug Substance	In-House	10.0	(b) (4)
Polyoxyl-40 hydrogenated castor oil (b) (4)				(b) (4)
Polyethylene glycol 4000 (PEG-4000) (b) (4)				
(b) (4)				
Hard gelatin capsule, light orange opaque/ yellow opaque, Size 0				
Gelatin sealing band				
Total				(b) (4)
				(b) (4)

Manufacturing Process

The manufacturing process summary is provided in the link \\cdsesub1\evsprod\nda214487\0001\m2\23-qos\drug-product.pdf. The avacopan 10 mg hard capsule is formulated (b) (4) The drug product is manufactured by (b) (4)

When the drug product disintegrates, the excipients dissolve in GI fluids (b) (4) (b) (4)

2. In vitro dissolution method and acceptance criterion:

The following dissolution method and acceptance criterion were proposed for dissolution testing of avacopan for QC purposes.

Table 3: Dissolution method parameters

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
Apparatus 2 with sinker	50	0.1N HCl/37°C ± 0.5°C	900	Q= (b) (4)% in 30 minutes

Sinker: Spiral 316 Stainless Steel; 25.4 mm x 14.6 mm

Dissolution method development

(b) (4)

2 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

Discriminating ability

The discriminating capability of the dissolution method was demonstrated by evaluating the dissolution performance of avacopan capsules with the following two formulations and process variants by design

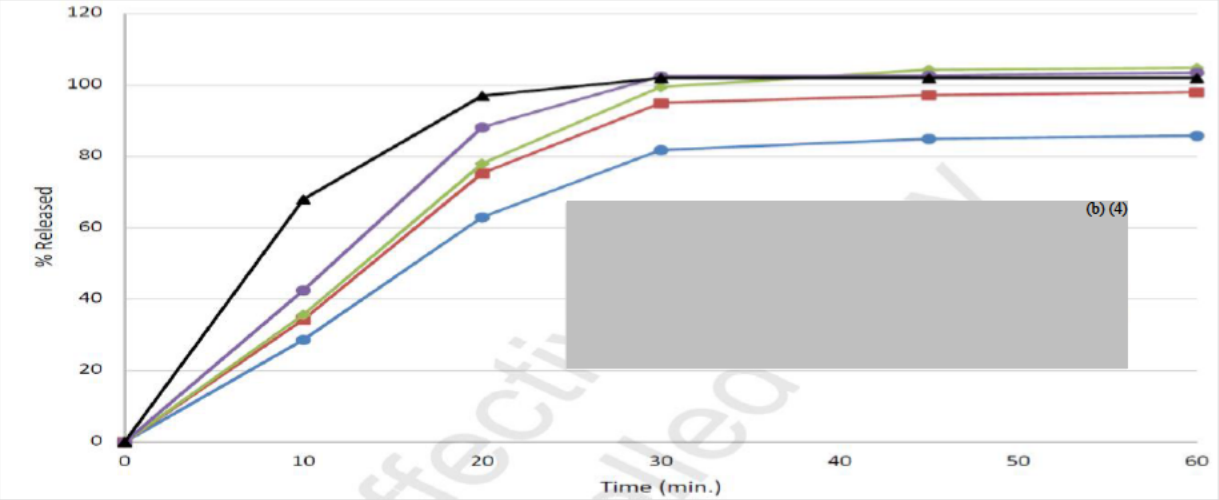
(b) (4)

The formulations are presented in the table below.

Table 4: Dissolution Method Discriminating Capability- Avacopan Capsule Formulations

Material	(b) (4)
Avacopan	
(b) (4)	

Figure 8: Dissolution Discriminating Capability - Avacopan 10 mg Capsule



(b) (4)

The discriminating capability of the dissolution method was further explored by evaluating the dissolution performance of avacopan capsules with the following two formulation and process variations:

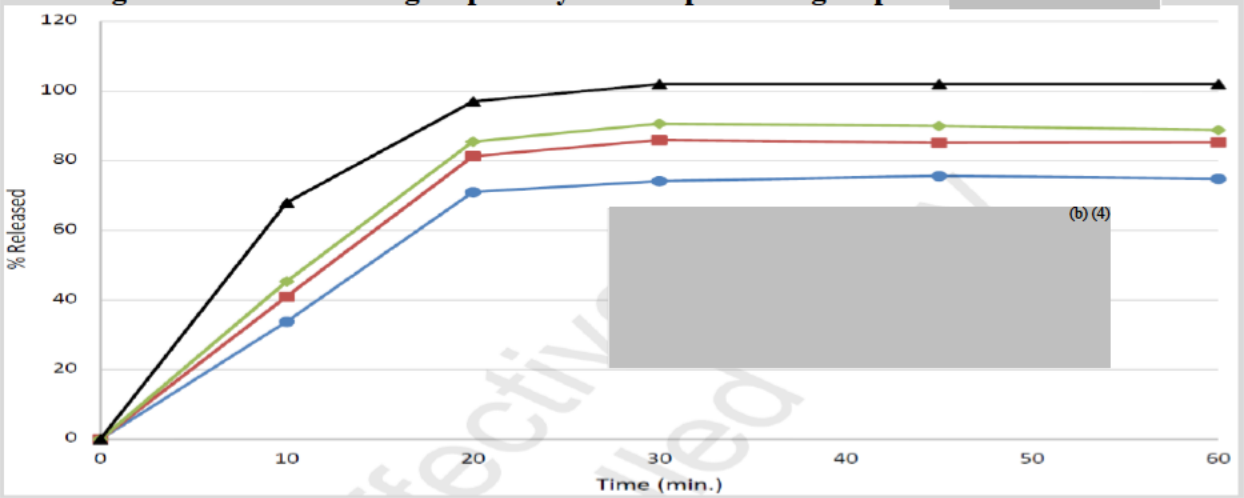
(b) (4)

The experimental formulations are presented in the table below.

Table 5: Dissolution Method Discriminating Capability - Avacopan Capsule Formulations

Material	(b) (4)
Avacopan	
(b) (4)	

Figure 9: Discriminating Capability - Avacopan 10 mg Capsule (b) (4)



(b) (4)

The results show that the dissolution method is sensitive to (b) (4) (b) (4) and capable of discriminating formulation changes.

Method Validation

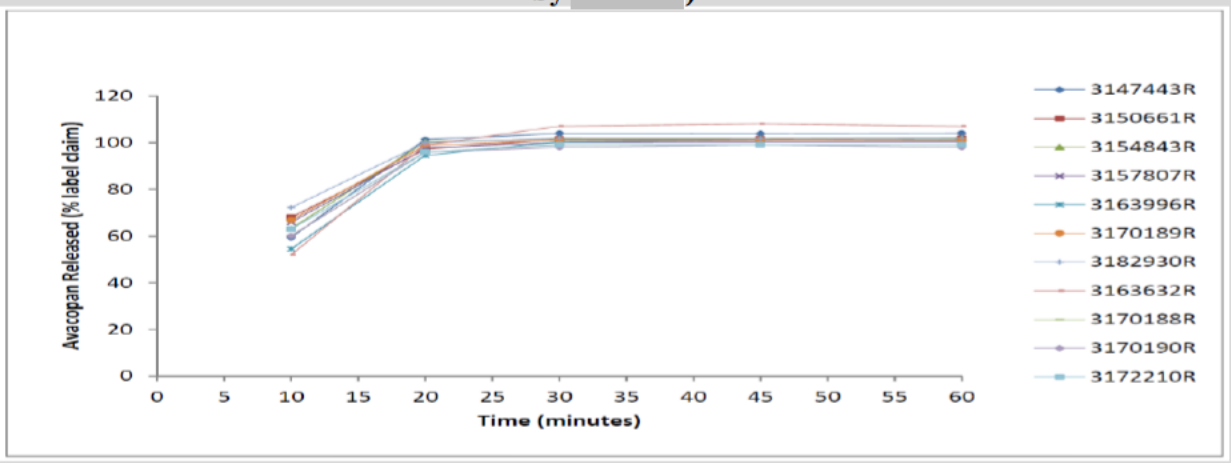
The analytical method for the dissolution was fully validated by performing the specificity, linearity, precision, accuracy, range, filter test, and solution stability. The details are provided in the link below:
\\CDSESUB1\evsprod\nda214487\0001\m3\32-body-data\32p-drug-prod\avacopan\32p5-contr-drug-prod\32p53-val-analyt-proc\validation-analytical-procedures.pdf
This information will be reviewed by Drug Product reviewer.

Dissolution data

The *in vitro* dissolution profile of avacopan capsule 10 mg in 0.1 N HCl (pH (b) (4)) is summarized in \\cdsesub1\evsprod\nda214487\0001\m2\27-clin-sum\summary-biopharm.pdf.

The Phase 3 clinical and registration lots of avacopan 10 mg capsules were rapidly dissolved reaching full dissolution (~100%) within 30 minutes as shown in the figure below.

Figure 10: Dissolution Profiles of Phase 3 Clinical and Registration Lots (Manufactured by (b) (4))



The Applicant was requested to provide the complete dissolution profile data for above batches (see IR1.1 in Appendix) as these could not be located in the original submission. The Applicant has provided these data and can be found in the link below (page 8):
\\CDSESUB1\evsprod\nda214487\0019\m1\us\111-info-amend\qual-info-amend.pdf

In vitro dissolution acceptance criterion

The Applicant's proposed dissolution acceptance criterion for Avacopan capsules *is* (b) (4)*% (Q =* (b) (4)*%) at 30 minutes*. The Applicant was requested to revise the acceptance criterion to *Q =* (b) (4)*% in 30 minutes* based on the data provided (see IR1.2 in Appendix). The Applicant has accepted the Agency recommended acceptance criterion *Q =* (b) (4)*% in 30 minutes*.

Reviewer's Assessment

- The Applicant has developed and validated a dissolution method using Apparatus II (paddles) and 900 mL of 0.1 N HCl at a rotation speed 50 rpm. The Applicant has provided method development report. The dissolution method is acceptable.
- The Applicant's proposed dissolution acceptance criterion is (b) (4)*% (Q =* (b) (4)*%) at 30 minutes*. The Applicant has accepted the Agency recommended acceptance criterion *Q =* (b) (4)*% in 30 minutes*.

Formulation development and bridging

The to-be-marketed (TBM) formulation is same as the formulation for Phase 2, Phase 3 clinical studies and registration stability batches. Hence, no bridging is required.

Bridging of manufacturing sites:

The manufacturing process for avacopan 10 mg hard capsule was established during prototype formulation development activities (b) (4) (b) (4) The manufacturing process was transferred from (b) (4) (b) (4) for Phase 1 and 2 clinical manufacture, and then to (b) (4)

(b) (4) for Phase 3 clinical manufacture, registrations lot manufacture, and commercialization. Bridging of manufacturing sites is not needed as Phase 3, registration, and commercial batches are all manufactured at (b) (4)

Primary Biopharmaceutics Reviewer Name: Kalpana Paudel, Ph.D.

***Secondary Reviewer Name*:** Haritha Mandula, Ph.D.

Appendix 1

List of deficiencies communicated during the review cycle

1. Provide the complete dissolution profile data [individual, mean, range, % CV at each time point] in QC medium for all batches that are included in Figure 13 of Justification of Specification document in a tabulated form. Also provide the details on manufacturing date, site, size and the dissolution test date.

2. In general, for immediate release products, the selection of the acceptance criterion time point should be where Q= (b) (4)% dissolution occurs. Therefore, the proposed dissolution acceptance criterion of *Q =* (b) (4)*% at 30 minutes* is permissive for your drug product. The following data-driven dissolution acceptance criterion is recommended:

   Q = (b) (4)*% of the labeled amount of avacopan is dissolved in 30 minutes*

   Implement the recommended acceptance criterion for your drug product at release and on stability and update the specifications of your drug product with the revised acceptance criterion for the dissolution test, accordingly.

   In addition, please be advised, that all proposed exhibit batches are expected to meet the revised dissolution acceptance criterion in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

Kalpana Paudel

Digitally signed by Kalpana Paudel
Date: 2/23/2021 04:07:08PM
GUID: 562e1e15002f200f35c6ccac959cdb34

Haritha Mandula

Digitally signed by Haritha Mandula
Date: 2/23/2021 05:57:06PM
GUID: 508da6fb000282df41459408f32a1ce0

DOCUMENT HISTORY

Document History	
Author: Integrated Quality Assessment Team, and Don Henry.	
Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team. Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.	This process (CDER OPQ Integrated Quality Assessment Template) will be assessed at the following intervals and changes to the work aid will be captured as needed: This process will be assessed approximately 150 days from date issued (February 1, 2019).
Version	**Summary of Changes** **Date Issued**
04	Content update 01/17/2017
05	10/15/2017 GDUFA II Drop-down option added
06	1/3/2019 1. The Previous template and assessment guide contained information relevant to both ANDA and NDA. The document is now separated into two documents for each application type. 2. Replaced distinct Process and Facilities chapters with the new integrated Manufacturing chapter. 3. Made content updates to NDA Labeling chapter. 4. Added Maximum Daily Dose (MDD) field.

Craig Bertha

Digitally signed by Craig Bertha
Date: 3/22/2021 12:29:52PM
GUID: 50841a65000098a9383c817879a6a84d

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CRAIG M BERTHA
03/22/2021 12:48:54 PM