CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214094Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 214094
Assessment #1

Drug Product Name	Berotralstat capsules
Dosage Form	Capsules
Strength	110 and 150 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Biocryst Pharmaceuticals, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	03-DEC-2019	All
Amendment	26-DEC-2019	Drug product
Amendment	24-FEB-2020	Drug product, biopharmaceutics
Amendment	03-MAR-2020	Drug product (labeling)
Amendment	07-APR-2020	Drug product/manufacturing
Amendment	15-APR-2020	Drug product/manufacturing
Amendment	08-MAY-2020	Drug product, biopharmaceutics
Amendment	20-MAY-2020	Biopharmaceutics
Amendment	04-JUN-2020	Drug product/manufacturing
Amendment	08-JUL-2020	Manufacturing
Amendment	09-JUL-2020	Drug product (labeling)
Amendment	17-JUL-2020	Drug product (labeling)

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Larry Perez	Donna Christner
Drug Product	Jane Chang	Moo Jhong Rhee
Manufacturing	Ted Chang	Chengjiu Hu
Microbiology	Ted Chang	Chengjiu Hu
Biopharmaceutics	Kamrun Nahar	Haritha Mandula
Regulatory Business Process Manager	Florence Aisida	

Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
Environmental	Jane Chang	

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U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)		N/A	N/A	Sufficient information provided in the NDA
	III			N/A	N/A	Sufficient information provided in the NDA

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

Document	Application Number	Description
IND	135058	Berotralstat capsule for hereditary angioedema (HAE)
IND	142879	Berotralstat (b) (4) for HAE

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	N/A			

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

N/A – Other than some minor labeling changes to be negotiated with the applicant, the CMC team recommends **approval** of the application.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product is indicated for the prevention of attacks of hereditary angioedema (HAE) in patients 12 years and older. The drug is a NME and the drug product has been granted Orphan Drug and Fast Track Designations. HAE is considered to be a serious, potentially life-threatening disease. The API is said to be classified as BCS class 1 in its salt form, and it is prepared from a (b) (4) from three starting materials. The dosage form is a hard gelatin capsule for oral administration and the encapsulated formulation contains the berotralstat drug substance as a dihydrochloride salt as well as common compendial-grade excipients. (b) (4) there are two distinct drug product manufacturing sites (b) (4) Also, at the filing meeting, the clinical team expressed concerned that the proposed 150 mg once-daily dose may have a lower benefit/risk ratio as compared to the lower strength 110 mg dose. Therefore, the CMC team requested the applicant to amend the application with the pertinent data for the lower strength. Both strengths have been evaluated from a quality perspective.

Proposed Indication(s) including Intended Patient Population	Prophylaxis to prevent attacks of HAE in patients 12 years and older
Duration of Treatment	Chronic
Maximum Daily Dose	150 mg (proposed)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance berotralstat (formulated as the berotralstat dihydrochloride salt) is a synthetic small molecule and new molecular entity (NME) that has been developed by BioCryst Pharmaceuticals, Inc. in the form of ORLADEYO™ (berotralstat) Capsules, an orally administered plasma kallikrein inhibitor for the indication prophylaxis treatment to prevent attacks of hereditary angioedema in patients 12 years and older. The chiral drug substance berotralstat dihydrochloride has the (*R*)-configuration with a molecular weight of 635.49 g/mol and a

molecular formula of $C_{30}H_{26}F_4N_6O \cdot 2HCl$. The drug substance has one stereocenter and does not show epimerization under long-term storage. The drug substance is supplied as an off-white powder and is manufactured [redacted] (b) (4) that has been adequately documented. The starting materials for the commercial manufacturing process have been designated in accordance with ICH Q11 guidance. The release specification for berotralstat dihydrochloride is in accordance with ICH Q6A guidance and the limits for impurities have been adequately set in accordance with ICH Q3A, ICH Q3C and ICH M7 guidances. The drug substance is packaged and stored [redacted] (b) (4) A retest period of [redacted] (b) (4) months for the drug substance when stored at [redacted] (b) (4) % RH in the commercial package is acceptable.

Drug Product: Adequate

CMC information for two strengths (110 and 150 mg) of berotralstat capsules are provided in the NDA. Since the clinical team has not reached a final decision on which strength(s) are approvable, this review has evaluated both drug product strengths.

The 150 mg strength is a size 1 hard gelatin capsule, light blue opaque cap with a black imprint “BCX” and white opaque body with a black imprint “150. The 110 mg strength is a size 2 capsule, light blue opaque capsule with a white imprint “BCX” on cap and a white imprint “110” on body. Both strengths of berotralstat capsules contain white or almost white or off-white powder [redacted] (b) (4). Each strength is packaged in a 7-count blister card (primary packaging) inserted into a child-resistant shellpak (secondary packaging). Four shellpaks are packaged into a carton (tertiary packaging). The excipients include capsule shell, colloidal silicon dioxide, crospovidone, magnesium stearate, and pregelatinized starch. The maximum daily dose (MDD) is 150 mg if the 150 mg strength is approved or 110 mg if only 110 mg strength is approved.

The proposed drug product specification is appropriate and includes testing and acceptance criteria for description, identification (HPLC and UV), assay, degradation products, content uniformity, dissolution, [redacted] (b) (4) and microbial limits, as recommended by ICH Q6A. Impurities specification acceptance criteria followed the recommendations of ICH Q3B. The associated analytical methods were found to be suitable for their intended use. There are no plans for specific tests for elemental impurities in the drug product, and this is supported by the risk assessment and data from 12 registration lots.

Stability data of the drug product packaged in the proposed commercial container closure system provided include:

- 150 mg strength: 18 months long-term and 6 months accelerated data for three registration lots manufactured by [redacted] (b) (4) at the proposed commercial scale and 9 months long-term and 6 months accelerated data for three registration lots manufactured by [redacted] (b) (4) at the proposed commercial scale.

- 110 mg strength: 18 months long-term and 6 months accelerated data for three registration lots manufactured by [redacted] (b) (4) at the proposed commercial scale and 12 months long-term and 6 months accelerated data for three registration lots manufactured by [redacted] (b) (4) at the proposed commercial scale.

- Long term and accelerated stability data do show a trend of [redacted] (b) (4) and remains well below the acceptance criterion limit. In summary, the stability data support the proposed [redacted] (b) (4) expiration dating period for both strengths when stored at controlled room temperature.

The applicant's request for a categorical exclusion from the requirements to submit an environmental assessment per 21 CFR 25.31(b) is acceptable.

Labeling: Inadequate

Minor labeling changes are needed and these changes involve the proprietary name, established name, the location of strength, salt equivalence statement, and lack of manufacturer, packer, or distributor for the blister card label are identified (see deficiency comments below and chapter IV below for details).

Manufacturing: Adequate

The drug product is manufactured [redacted] (b) (4)

(b) (4)

All the facilities have been Approved Based on Previous History—and with concurrence with ORA recommendations.

Biopharmaceutics: Adequate

The Applicant seeks approval of this NDA via the 505(b)(1) regulatory pathway and the drug product is formulated as an immediate release capsule dosage form. The two strengths of the drug product (110 and 150 mg) (b) (4) a biowaiver was not required. Berotralstat Dihydrochloride demonstrated high solubility across the physiological pH range from pH 1.2 to pH 6.8, dissolution data demonstrated rapid release of the drug from the formulation with low variability. Discriminating ability studies for the dissolution method demonstrated that dissolution method does not have significant impact on dissolution due to differences in critical quality attributes (differences in drug substances PSD), formulation variables (b) (4) in composition) and process parameters (b) (4)

Therefore, based on the drug solubility, drug dissolution rate of the pivotal clinical and registration batches for both strengths of Berotralstat capsules, low variability of drug release with the proposed dissolution method, the Applicant's proposed dissolution method and acceptance criterion are considered adequate.

Microbiology (if applicable): N/A

C. Risk Assessment

DP attribute/ CQA	Factors that may impact the CQA	O[1]	S[1, 2]	D[1]	FMECA RPN #	Comments & considerations for initial RA	Final RA	Comments/Lifecycle considerations
Assay/ content uniformity	• degradation of API • incorrect amt. formulated (b) (4)	2	3	5	30	• No appreciable degradation of drug substance noted for drug product (no degradants greater than (b) (4)% reporting threshold) • No drug substance process impurities are degradants • Based on API physicochemical properties, it is not expected that the drug product manufacturing process will lead to API degradation • Compliance with cGMPs should mitigate any errors in formulation (b) (4)	1 x 3 x 5 = 15	(b) (4)
Dissolution [3]	• polymorph conversion • PSD change during processing to prepare drug product • Variation of API PSD from manufacturing process (specification does not include a test for PSD) • Sampling details for dissolution are not delineated in application	1	3	5	15	• API is claimed to be BCS class 1 (b) (4)		
Degradants /impurities	• API degradation in drug product/CCS protection from environment (bulk packaging or blisters)	2	3	3	18	• Stability data provided for dosage form packaged in both bulk and primary CCSs; no individual impurities exceed the		

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[2] Severity of effect can only be estimated; input from clinical or pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact.
[3] Preliminary assessment: detailed evaluation by biopharmaceutics team may be necessary

	• process-related impurities in API • API interaction with excipients • API degradation (alone or in drug product) • API racemization (b) (4) • elemental impurities in drug product (b) (4)					reporting threshold with long term storage up to 12 months in the primary CCS • Batch analyses data for API (3 from each site) show levels of individual impurities are all below the identification threshold of Q3A • Excipient compatibility studies performed (8 weeks at 40 C/75%RH) with only a slight increase in total impurities with three excipients • API stability studies do not show significant trending in terms of degradation • API racemization has not been observed during manufacture of the API or during storage of the drug product (b) (4) • A risk assessment from each drug product manufacturer is provided re: elemental impurities (see P.5.6) (b) (4)		
API physical stability (solid state)	• polymorph conversion	1	3	5	15	(b) (4)		
Description	• capsule color or imprint variation	2	3	2	12	• examination of appearance to assure the correct colors of the bodies and caps as well as the imprints • No changes in capsule appearance were noted during the stability studies		
(b) (4)								

[redacted] (b) (4)

Microbio-logical Quality[4]	• Increase in drug product (b) (4)	3	3	3	27	• The drug product acceptance criteria are consistent with the recommendations of USP <1111> • All excipients are common and of compendial grade (b) (4)	2 x 3 x 3 = 18	• Stability data for the drug product indicate that microbial limits testing acceptance criteria were met.

[4] Preliminary assessment: detailed evaluation by microbiology team may be necessary

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

A. Full Prescribing Information

(b) (4)

Section 11: Description

2. Per 201.10(g)(1), the established name shall accompany the proprietary name, i.e., ORLADEYO (berotralstat) capsules.

3. Revise the amount of berotralstat dihydrochloride per capsule from (b) (4) to 169.4 mg.

4. We recommend listing the inactive ingredients in alphabetical order.

B. Regarding the Container/Carton Labels

5. Revise the proprietary name, established name, and strength as below for the blister card, shellpak, and carton labels.

Orladeyo
(berotralstat) capsules 150 mg

Please note strength should not be in the middle of the proprietary name and established name. Capsules (i.e., the plural form) should be used. Proprietary name should be capitalized.

6. Add the name of the manufacturer, packer, or distributor to the blister card label.

7. Revise the salt equivalence statement from "equivalent to [redacted] (b) (4) "equivalent to 169.4 mg Berotralstat dihydrochloride" for the shellpak and carton labels.

8. Revise the statement from [redacted] (b) (4) to "Recommended Dosage: See Prescribing Information" for the shellpak and carton labels.

5. Manufacturing Deficiencies

N/A

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

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

N/A

Application Technical Lead Name and Date:
Craig M. Bertha, CMC Lead for DPACC/DRTM *July 24, 2020*

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0000 (SDN-1)	12/03/2019
eCTD-0012 (SDN-13)	03/03/2020

1.0 PRESCRIBING INFORMATION

The information provided in eCTD-0012 is summarized below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

1) PRODUCT TITLE

ORLADEYO™ (berotralstat) capsules, for oral use.
Initial U.S. Approval: 20YY

2) DOSAGE FORMS AND STRENGTHS

Capsules: 150 mg

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Drug name [201.57(a)(2)]		
Proprietary name and established name	ORLADEYO™ (berotralstat) capsules	**Acceptable**
Dosage form, route of administration	capsules, oral	**Acceptable** However, the "." After "for oral use" should be deleted.
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval	20YY	**Acceptable** The drug substance is an NME. The year this drug is approved will be listed.
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	Capsules: 150 mg	**Acceptable**
Whether the drug product is scored	N/A	

Conclusion: Satisfactory

Per DMEPA assessor, Sarah K. Vee, dated 2/5/2020, the proposed proprietary name Orladeyo is acceptable. A minor edit is made to the Product Title to delete the period after "for oral use". That is,

ORLADEYO™ (berotralstat) capsules, for oral use.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 3: DOSAGE FORMS AND STRENGTHS

Each ORLADEYO capsule contains 150 mg berotralstat (equivalent to (b) (4) mg of berotralstat dihydrochloride) and has a white opaque body imprinted with "150" and a light blue opaque cap imprinted with "BCX".

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Available dosage forms	capsule	**Acceptable**
Strengths: in metric system	150 mg	**Acceptable**
Active moiety expression of strength (if applicable)	Strength is based on free base content (150 mg). An equivalence statement (b) (4) mg of berotralstat dihydrochloride) is provided.	**Unacceptable** Salt equivalent statement should not be included in this section.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	white opaque body imprinted with "150" and a light blue opaque cap imprinted with "BCX"	**Unacceptable** Add the color of imprint (black)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A

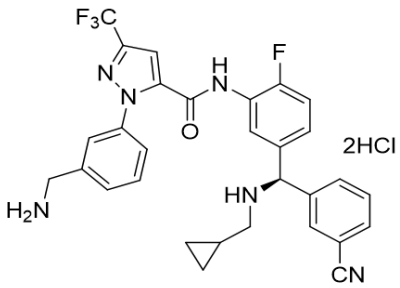
Conclusion: **Unsatisfactory**

The recommended revisions are shown below:

Each ORLADEYO capsule contains 150 mg berotralstat (b) (4) ~~)~~ and has a white opaque body (b) (4) with a black imprint "150" and a light blue opaque cap (b) (4) with a black imprint "BCX".

1.2.2 Section 11: DESCRIPTION

ORLADEYO capsules (b) (4)
Berotralstat is presented as the dihydrochloride salt with the chemical name (b) (4) . The chemical structure is:



Berotralstat dihydrochloride is a white to off-white powder that is soluble in water at pH ≤ 4. The molecular formula is $C_{30}H_{26}F_4N_6O$ • 2HCl and the molecular weight is 635.49 (dihydrochloride).

ORLADEYO is supplied as a 150 mg hard gelatin capsule for oral administration, (b) (4) . Each capsule contains the active ingredient berotralstat dihydrochloride (b) (4) and the inactive ingredients pregelatinized starch, crospovidone, colloidal silicon dioxide and magnesium stearate.

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	ORLADEYO berotralstat	**Unacceptable** Per 201.10(g)(1), the established name shall accompany the proprietary name.
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Capsules, oral	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	berotralstat dihydrochloride (b) (4) mg equivalent to 150 mg free base	**Unacceptable** The weight of the dihydrochloride salt should be 169.4 mg, (b) (4)
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any)]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	pregelatinized starch, crospovidone, colloidal silicon dioxide and magnesium stearate	**Acceptable** Established names of inactive ingredients are provided. A minor editorial change to list them in alphabetical order (recommended, but not required).
Statement of being sterile [if applicable, 21 CFR 201.57(c)(12)(i)(D)]	N/A	N/A

Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	inhibitor of plasma kallikrein	**Acceptable** Minor editorial change to "plasma kallikrein inhibitor". Per Established Pharmacologic Class (EPC) terms in eLIST, there is no established pharmacological/ therapeutic class for berotralstat. This is likely due to the NME status of berotralstat.
Chemical name, structural formula [21 CFR 201.57(c)(12)(i)(F)]	(*R*)-1-(3-(Aminomethyl)phenyl)-*N*-(5-((3-cyanophenyl)((cyclopropylmethyl)amino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide dihydrochloride	**Unacceptable** See below for minor editorial change. Chemical structure is also provided.
If radioactive, statement of important nuclear characteristics [21 CFR 201.57(c)(12)(i)(G)]	N/A	N/A
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	Berotralstat dihydrochloride is soluble in water at pH ≤ 4.	**Acceptable**
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

Conclusion: **Unsatisfactory**

As of the date of this assessment, berotralstat hydrochloride has not been published in USAN Online. Per AMA website, berotralstat hydrochloride was approved in 2019 as the USAN. Therefore, the established name of the drug substance is berotralstat hydrochloride. The strength of 150 mg is consistent with the established name of the drug product, which uses the name of the active moiety per USP <1121>.

The recommended revisions are shown below:

> ORLADEYO (berotralstat) capsules (b) (4) is a (b) (4)-plasma kallikrein inhibitor. Berotralstat is presented as the dihydrochloride salt with the chemical name (b) (4)-1-~~(~~[3-(~~A~~aminomethyl)phenyl~~)~~]-*N*-(5-{(*R*)-(3-cyanophenyl)~~(~~[(cyclopropylmethyl)amino~~)~~]methyl~~)~~}-2-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide dihydrochloride. The chemical structure is:
>
> Berotralstat dihydrochloride is a white to off-white powder that is soluble in water at pH ≤ 4. The molecular formula is $C_{30}H_{26}F_4N_6O$ • 2HCl and the molecular weight is 635.49

(dihydrochloride).

ORLADEYO is supplied as a 150 mg hard gelatin capsule for oral administration, (b) (4) [redacted] (b) (4)-colloidal silicon dioxide, crospovidone, (b) (4) magnesium stearate, and pregelatinized starch.

1.2.3 Section 16: HOW SUPPLIED/STORAGE AND HANDLING

Each ORLADEYO capsule contains 150 mg of berotralstat and has a white opaque body with black imprint “150” and a light blue opaque cap with black imprint “BCX”.

A 28-day supply of ORLADEYO is provided in a carton (b) (4) [redacted] containing four child-resistant shellpaks, each containing a 7-capsule blister card. Each carton contains a tamper evident seal.

Store at 20ºC to 25ºC (68ºF to 77ºF). Excursions permitted between 15ºC and 30ºC (59ºF to 86ºF) *[see USP Controlled Room Temperature]*.

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Dosage form	capsule	**Acceptable**
Strength of dosage form in metric system	150 mg	**Acceptable**
Available units (e.g., bottles of 100 tablets)	A carton contains four blister cards. Each blister card contains 7 capsules	**Acceptable**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	a white opaque body with black imprint "150" and a light blue opaque cap with black imprint "BCX"	**Acceptable** Minor editorial changes by adding "a" before "black".
Special handling (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.)	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	20ºC to 25ºC (68ºF to 77ºF). Excursions permitted between 15ºC and 30ºC (59ºF to 86ºF) *[see USP Controlled Room Temperature]*	**Acceptable**
Include information about child-resistant packaging (if manufacturer choose to include)	child-resistant shellpaks	**Acceptable** In 3.2.P.7, the applicant states that the shellpak meets the Consumer Product Safety Commission's (CPSC) standards under 16 CFR 1700.

Conclusion: Satisfactory

Minor editorial changes are shown below:

Each ORLADEYO capsule contains 150 mg of berotralstat and has a white opaque body with a black imprint "150" and a light blue opaque cap with a black imprint "BCX".

1.2.4 Section 17: PATIENT COUNSELING INFORMATION

Manufactured for:
BioCryst Pharmaceuticals, Inc.
Durham, NC 27703

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Manufacturer/distributor name [21 CFR 201.1(h)(5)]	Manufactured for: BioCryst Pharmaceuticals, Inc. Durham, NC 27703	**Acceptable**

Conclusion: Satisfactory

The information in Section 17 meets the regulatory expectation.

2.0 CARTON AND CONTAINER LABELS

The information provided in eCTD-0000 is summarized below.

2.1 CONTAINER LABEL

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	orladeyo (berotralstat) 150 mg capsule	**Unacceptable** Proprietary name should be capitalized. Plural form of capsule should be used. Strength should not be in the middle of proprietary name and established name. Strength should be placed after the established name.
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	Not provided	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)][&]	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.
Names of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Not provided	**Acceptable** Names of inactive ingredients is not required for oral drugs.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Provided	**Acceptable**
Storage conditions	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.
Bar code [21CFR 201.25(c)(2)]	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.

Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Not provided	**Unacceptable**
And others, if space is available	Not provided	**Acceptable**

Conclusion: **Unsatisfactory**

Blister card, shellpak, and carton are the primary, secondary, and tertiary packaging for this drug product. However, because the shellpak's serves the function of child-resistant, the secondary packaging is intended to be always used together with the primary packaging for the product except when patients remove the capsule for administration. Even though there seems to be space for additional labeling information, only the labeling information required for small container labels, i.e., proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug per 21 CFR 201.10(i)(1), will be asked for the blister card label.

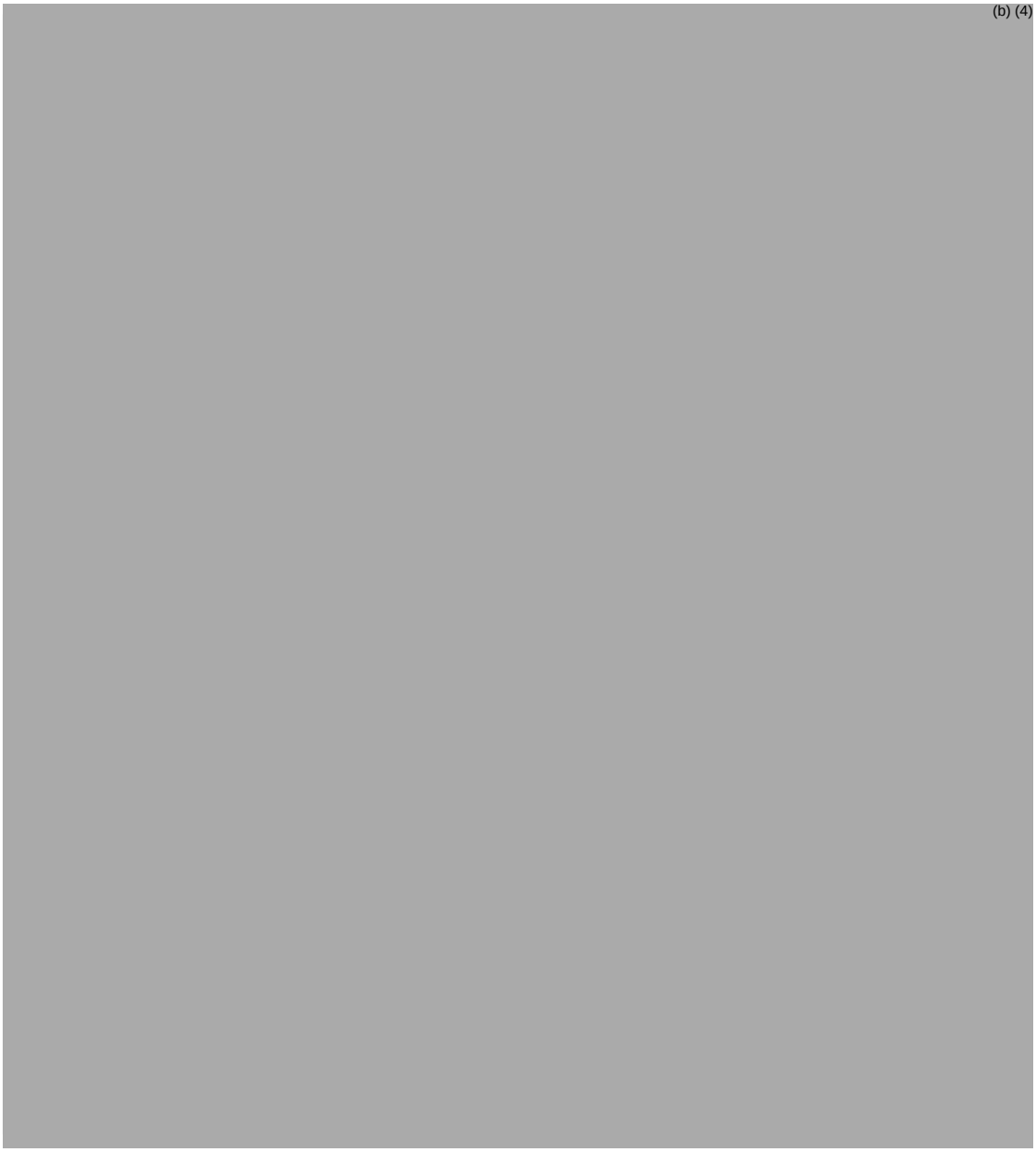
The recommended revisions are shown below:

1. Revise the proprietary name, established name, and strength as below:

   Orladeyo
   (berotralstat) capsules 150 mg

2. Add the name of the manufacturer, packer, or distributor to the blister card label.

2.2 SHELLPAK LABEL



Item	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	orladeyo (berotralstat) 150 mg capsule	**Unacceptable** Proprietary name should be capitalized. Plural form of capsule should be used. Strength should not be in the middle of proprietary name and established name. Strength should be placed after established name.
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	For ORAL USE ONLY	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Each capsule contains: Berotralstat 150 mg (equivalent to (b) (4) mg Berotralstat dihydrochloride).	**Unacceptable** The equivalence statement should be "equivalent to 169.4 mg Berotralstat dihydrochloride"
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]&	Seven (7) 150 mg capsules	**Acceptable**
Names of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Not provided	**Acceptable** Names of inactive ingredients is not required for oral drugs.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC number is allocated	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Provided	**Acceptable**
Storage conditions	Store capsules at room temperature, 20°C to 25°C (68°F to 77°F)	**Acceptable**
Bar code [21CFR 201.25(c)(2)]	Provided	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Dosage: One capsule once per day. (b) (4)	**Unacceptable** Recommend changing " (b) (4) to "Recommended Dosage: See Prescribing Information".

Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Manufactured For: BioCryst Pharmaceuticals, Inc. Durham, NC 27703	**Acceptable**
And others, if space is available	To Open: Step 1: Press and hold button gently Step 2: Pull out medication card	**Acceptable**

Conclusion: **Unsatisfactory**

In an email communication dated 8/9/2019 with DMEPA assessor for labeling of another NDA, the assessor stated that based on DMEPA management's involvement with the Labeling Workgroup, it was recently determined that the usual dosage statement be changed from (b) (4) to "Recommended Dosage: See Prescribing Information".

The recommended revisions are shown below:

1. Revise the proprietary name, established name, and strength as below:

   Orladeyo
   (berotralstat) capsules 150 mg

2. Revise the salt equivalence statement from "equivalent to (b) (4) mg Berotralstat dihydrochloride" to "equivalent to 169.4 mg Berotralstat dihydrochloride".
3. Revise the statement from (b) (4) to "Recommended Dosage: See Prescribing Information".

2.3 CARTON LABEL

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	orladeyo (berotralstat) 150 mg capsule	**Unacceptable** Proprietary name should be capitalized. Plural form of capsule should be used. Strength should not be in the middle of proprietary name and established name. Strength should be placed after established name.
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	For ORAL USE ONLY	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Each capsule contains: Berotralstat 150 mg (equivalent to (b) (4) mg Berotralstat dihydrochloride).	**Unacceptable** The equivalence statement should be "equivalent to 169.4 mg Berotralstat dihydrochloride"
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	Carton contains 4 shellpaks of 7 capsules each (28 day supply)	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Not provided	**Acceptable** Names of inactive ingredients is not required for oral drugs.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided on the main panel, upper right corner	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Provided on the main panel, upper left corner	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Provided on the side panel	**Acceptable**
Storage conditions	Store capsules at room temperature, 20°C to 25°C (68°F to 77°F)	**Acceptable**
Bar code [21 CFR 201.25(c)(2)]****	Provided	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Dosage: One capsule once per day. (b) (4)	**Unacceptable** Recommend changing (b) (4) to "Recommended Dosage: See Prescribing Information".

"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Provided	**Acceptable**
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Manufactured For: BioCryst Pharmaceuticals, Inc. Durham, NC 27703	**Acceptable**
And others, if space is available	N/A	N/A

Conclusion: Unsatisfactory

The recommended revisions for shellpak as described on page 12 are also applicable to the carton label.

3.0 LIST OF DEFICIENCIES:

A. Regarding PI

Full Prescribing Information

Section 3: Dosage Forms and Strengths

(b) (4)

Section 11: Description

2. Per 201.10(g)(1), the established name shall accompany the proprietary name, i.e., ORLADEYO (berotralstat) capsules.
3. Revise the amount of berotralstat dihydrochloride per capsule from (b) (4) mg to 169.4 mg.
4. Recommend listing the inactive ingredients in alphabetical order.

B. Regarding the Container/Carton Labels

5. Revise the proprietary name, established name, and strength as below for the blister card, shellpak, and carton labels.

   Orladeyo
   (berotralstat) capsules 150 mg

   Please note strength should not be in the middle of the proprietary name and established name. Capsules (i.e., the plural form) should be used. Proprietary name should be capitalized.

6. Add the name of the manufacturer, packer, or distributor to the blister card label.
7. Revise the salt equivalence statement from "equivalent to (b) (4) mg Berotralstat dihydrochloride" to "equivalent to 169.4 mg Berotralstat dihydrochloride" for the shellpak and carton labels.

8. Revise the statement from [redacted] (b) (4) to "Recommended Dosage: See Prescribing Information" for the shellpak and carton labels.

OVERALL ASSESSMENT:

Issues on the proprietary name, established name, the location of strength, salt equivalence statement, and lack of manufacturer, packer, or distributor for the blister card label are identified.

Recommendation:

From the ONDP perspective, this application is ***not*** ready for approval in its present form per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Jane Chang, Ph.D.
Senior reviewer
DNDP II/ONDP
05/22/2020

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

Moo-Jhong Rhee, Ph.D.
Chief, Branch 4
DNDP II/ONDP
05/22/2020

Jane Chang

Digitally signed by Jane Chang
Date: 5/22/2020 12:28:47PM
GUID: 5034f819000053b21e2574590781f330

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 5/22/2020 12:46:16PM
GUID: 502d0913000029f9798ca689a802fa55

BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 214094-ORIG-1

Drug Product Name / Strength: Berotralstat capsule, 110 mg and 150 mg

Route of Administration: Oral

Applicant Name: BioCryst Pharmaceuticals, Inc.

FDA Received date: 11/27/2019

Review Summary: ADEQUATE

The proposed drug product, Berotralstat capsule, 110 mg and 150 mg is indicated as a prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older. The Applicant seeks approval of this NDA via the 505(b)(1) regulatory pathway. The product formulation is an immediate release capsule dosage form.

List Submissions being reviewed: Dissolution method and acceptance criterion among formulations.

1. 0000 (1) 12/03/2019 ORIG-1/ Multiple Categories/Subcategories (NDA#214094)
2. 0011 (12) 02/24/2020 ORIG-1/ Multiple Categories/Subcategories (NDA#214094)
3. 0015(16) 04/15/2020 ORIG-1/Quality/Response to information request (NDA# 214094)
4. 0021(21) 05/20/2020 ORIG-1/Quality/Response to information request (NDA# 214094)

Highlight Key Outstanding Issues from Last Cycle: None

Solubility: At the beginning of the NDA submission, the Applicant claimed Berotralstat is a BCS class 1 compound. The Applicant measured the solubility of the compound across the physiological pH range. The solubility was reported to be from approximately 0.6 to approximately 1 mg/mL at pH 6.8. The pKa of Berotralstat is close to 6.8, experimental variation can be observed when determining solubility at or close to this pH. The applicant claimed that considering the BCS class for solubility and the proposed highest strength of the capsules is 150 mg which requires only 90 mL of aqueous media across the pH range of 1.2 to 6.8 at 37°C.

Table 1: List of aqueous solved required to dissolve Berotralstat Dihydrochloride

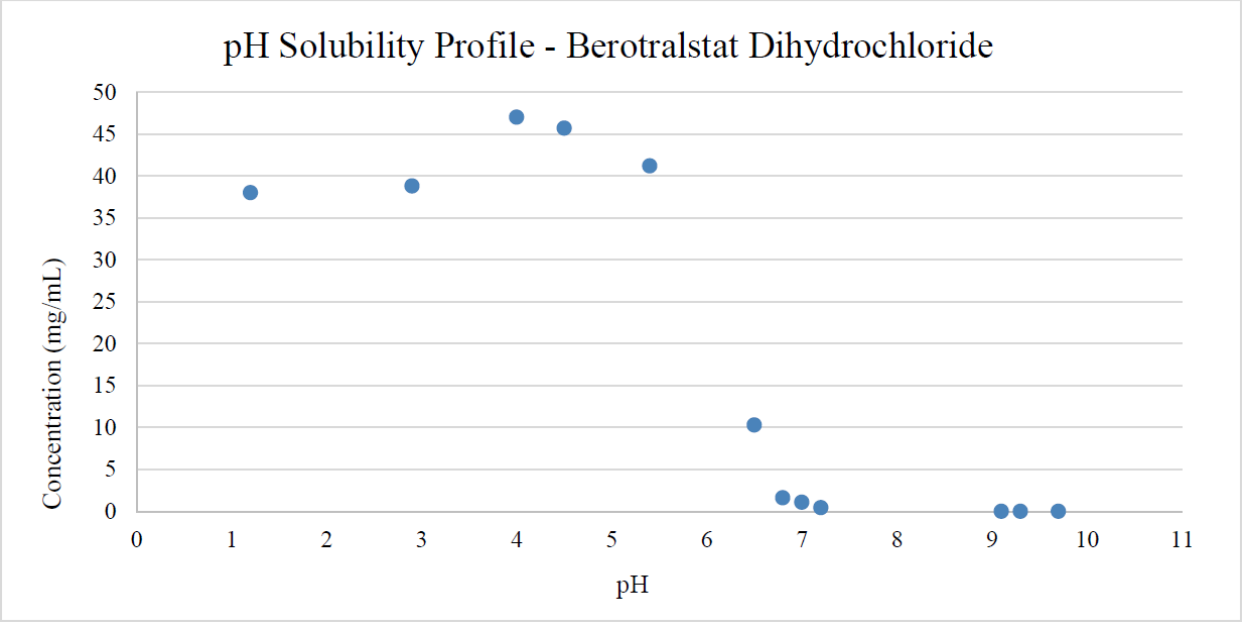
Aqueous Solubility	
pH 1.2	≈ 38.0 mg/mL at ambient temperature (soluble)
pH 4.0	≈ 47.0 mg/mL at ambient temperature (soluble)
pH 7.0	≈ 1.09 mg/mL at ambient temperature (slightly soluble)

Calculation: The label has mentioned that the recommended dose of Berotralstat capsule is 150 mg capsules once daily. Therefore, maximum amount of aqueous solvent required to dissolve 150 mg (highest strength) of Berotralstat Dihydrochloride-

At pH 1.2: (1x150/38)= 3.95 mL
At pH 4.0: (1x150/47)= 3.19 mL
At pH 7.0 (1x150/1.09)= 137.61 mL

Therefore, based on the solubility data in aqueous solvent, Berotralstat is considered as highly soluble compound. The pH solubility profile is presented in figure 1 below-

Figure 1: pH solubility of Berotralstat Dihydrochloride



The applicant also investigated permeability of the Berotralstat Dihydrochloride by in vitro permeation studies using digoxin as a highly permeable reference standard across an epithelial cell (Caco-2) monolayer. The result demonstrated that Berotralstat is highly permeable based on a higher apparent permeability coefficient compared to digoxin, Papp value of Berotralstat Dihydrochloride is at $1.70x10^{-6}$ cm/s whereas digoxin Papp is reported at $1.04x10^{-6}$ cm/s.

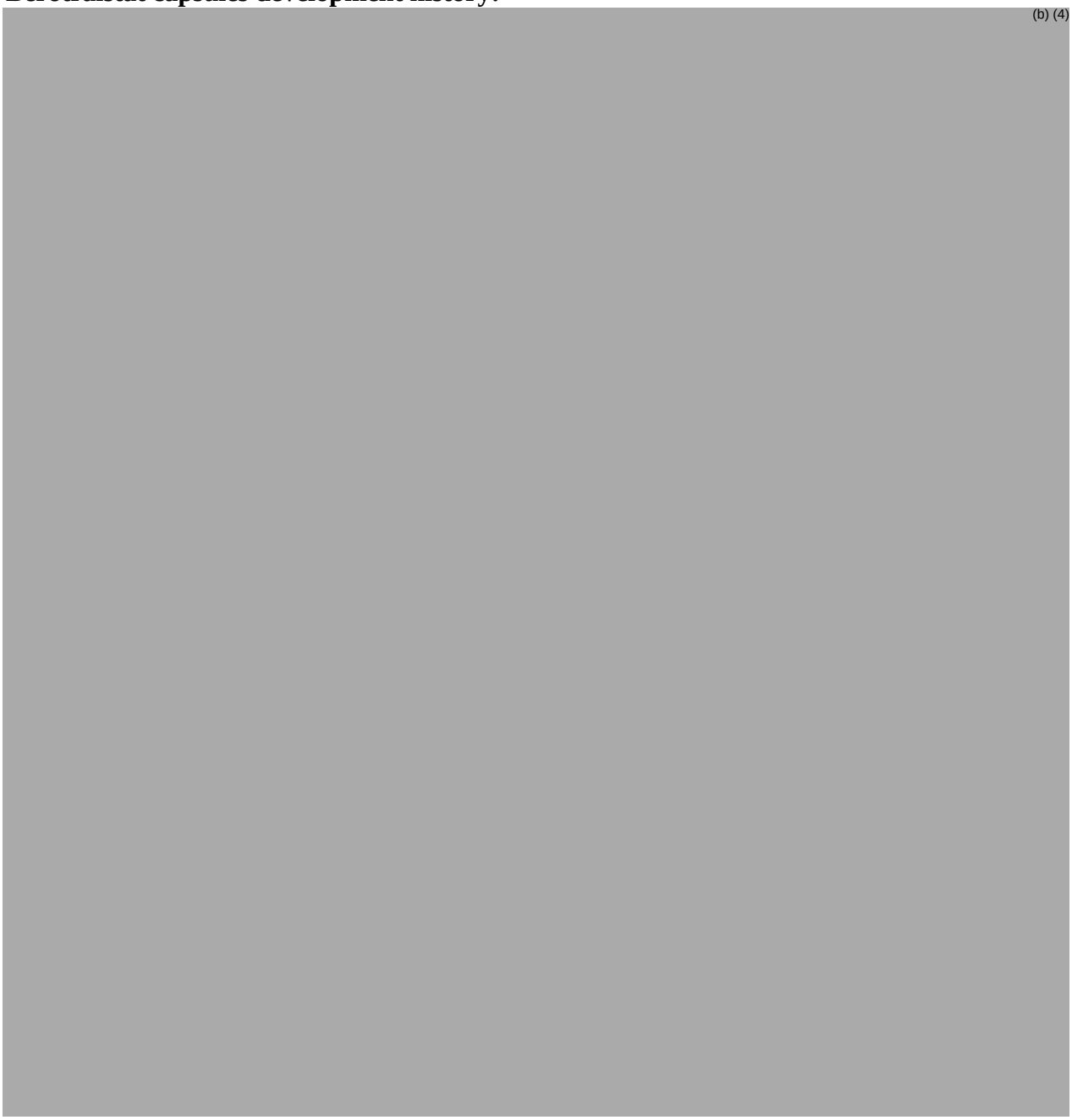
Table 2: summary of Caco-2 study results

Article	Direction	P_{app} ($\times 10^{-6}$ cm/s)			Adsorption Potential Classification
		R1	R2	Average	
Berotralstat dihydrochloride	A to B	2.09	1.31	1.70	High
Digoxin	A to B	0.96	1.12	1.04	High

Based on the solubility and permeability data, the Applicant claimed that Berotralstat Dihydrochloride drug substance is a BCS class 1 compound. Therefore, the Agency asked the Applicant to submit a complete report of BCS classification of the Berotralstat compound. In response, the Applicant withdrawn the request for BCS class 1 classification at this time. Refer to the Appendix 2 for detail information of the information request (IR) and applicant's response.

Berotralstat capsules development history:

(b) (4)



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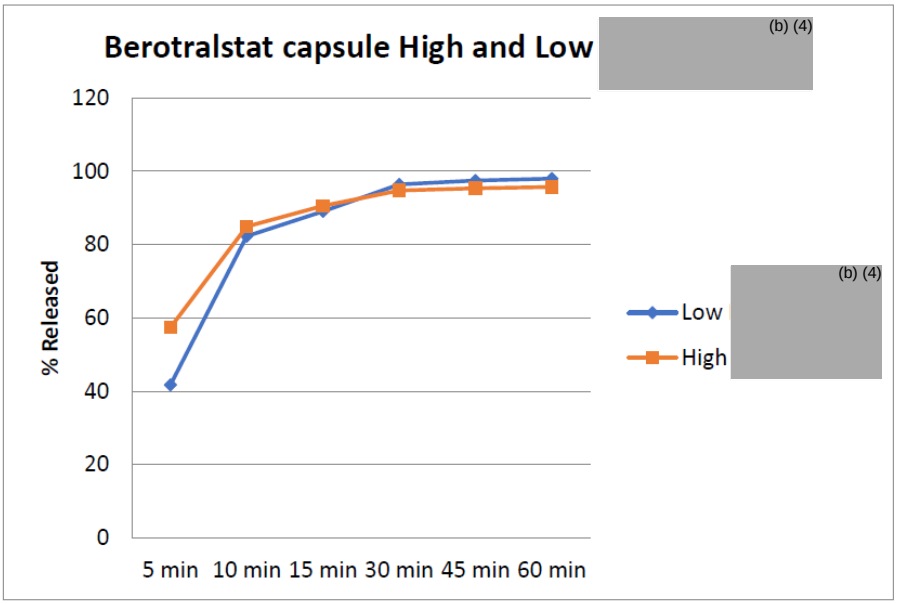
Discriminating ability of the dissolution method:

The Applicant assessed discriminating ability of the dissolution method by varying the formulation variables, process parameters (b) (4) and critical material attributes (e.g. particle size and moisture).

(b) (4)

Figure 7: Dissolution profiles for high and low (b) (4) content Berotralstat capsules (n=6)



To determine the discriminatory ability of the dissolution method, the Applicant considered the following process parameters: (b) (4). The Applicant developed Berotralstat capsules 110 mg and 150 mg using (b) (4). Therefore, Berotralstat 110 mg capsules were chosen for DOE (b) (4)

(b) (4).

Dissolution data demonstrated that none of the process parameters have any impact on dissolution.

Batch #C19944:25A is the batch with ideal condition. Two other batches, i.e. C19944:25B and C19944:25C were developed by varying process parameters.

Table 12: DOE run conditions for comparative dissolution

(b) (4)

Figure 8: Dissolution profiles process development batches Berotralstat capsules.

(b) (4)

Dissolution data presented above indicated that dissolution of the drug product was not affected much due to the changes in process parameters.

The Applicant developed three batches of Berotralstat capsules 50 mg with small- and large- API particle size and API (b) (4). Comparative dissolution study indicated no significant impact on dissolution due to changes in critical material attributes.

Figure 9: Comparative dissolution of API particle size and moisture

Dissolution acceptance criteria:
The Applicant provided dissolution data of the Berotralstat capsules used in pivotal clinical studies and registration batches.

Table 13: Berotralstat capsules dissolution data to be presented

Lot No.	Capsule Strength (mg)	Use
L0608493	55	Pivotal Study BCX7353-302; Bioequivalence Study BCX7353-113
L0608494	75	Pivotal Study BCX7353-302; Bioequivalence Study BCX7353-113
L0609524	110	Registration Batch
L0609526	110	Pivotal Study BCX7353-302; Bioequivalence Study BCX7353-113; Registration Batch
L0609527	110	Pivotal Study BCX7353-302; Registration Batch
L0609528	150	Registration Batch
L0609529	150	Pivotal Study BCX7353-302; Bioequivalence Study BCX7353-113; Registration Batch
L0609530	150	Pivotal Study BCX7353-302; Registration Batch
3171419R	110	Registration Batch
3171420R	110	Registration Batch
3171421R	110	Registration Batch
3171422R	150	Pivotal Study BCX7353-302; Registration Batch
3171423R	150	Pivotal Study BCX7353-302; Registration Batch
3171424R	150	Pivotal Study BCX7353-302; Registration Batch

Table 14: Dissolution data of Berotralstat capsules 110 mg, batch# L0609524

	BCX7353 110 mg Capsule - Lot L0609524						
	5	10	15	20	30	45	60
Vessel	minutes	minutes	minutes	minutes	minutes	minutes	minutes
1	(b) (4)						
2							
3							

4	(b) (4)						
5							
6							
7							
8							
9							
10							
11							
12							
Mean	(b) (4)						
Low							
High							
SD	8.5	4.9	4.9	4.3	3.1	1.8	1.5
%RSD	15	6	5	5	3	2	1

Table 15: Dissolution data of Berotralstat capsules 110 mg, batch# L0609526

	BCX7353 110 mg Capsule - Lot L0609526						
	5	10	15	20	30	45	60
Vessel	minutes	minutes	minutes	minutes	minutes	minutes	minutes
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	(b) (4)						
Low							
High							
SD	8.5	4.2	4.1	3.2	2.1	1.4	1.2
%RSD	14	5	5	3	2	1	1

Table 16: Dissolution data of Berotralstat capsules 110 mg, batch# L0609527

	BCX7353 110 mg Capsule - Lot L0609527						
	5	10	15	20	30	45	60
Vessel	minutes	minutes	minutes	minutes	minutes	minutes	minutes
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	(b) (4)						
Low							
High							
SD	6.1	3.7	3.1	2.4	1.3	1.0	0.9
%RSD	12	4	3	3	1	1	1

Table 17: Dissolution data of Berotralstat capsules 150 mg, batch# L0609528

	BCX7353 150 mg Capsule - Lot L0609528						
	5	10	15	20	30	45	60
Vessel	minutes	minutes	minutes	minutes	minutes	minutes	minutes
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	(b) (4)						
Low							
High							
SD	8.0	3.5	2.3	2.0	1.4	1.2	1.0
%RSD	16	4	3	2	1	1	1

Table 18: Dissolution data of Berotralstat capsules 150 mg, batch# L0609529

	BCX7353 150 mg Capsule - Lot L0609529						
	5	10	15	20	30	45	60
Vessel	minutes	minutes	minutes	minutes	minutes	minutes	minutes
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	(b) (4)						
Low							
High							
SD	5.9	4.9	4.1	3.3	2.5	2.0	1.7
%RSD	12	6	4	3	3	2	2

Table 19: Dissolution data of Berotralstat capsules 150 mg, batch# L0609530

	BCX7353 150 mg Capsule - Lot L0609530						
	5	10	15	20	30	45	60
Vessel	minutes	minutes	minutes	minutes	minutes	minutes	minutes
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	(b) (4)						
Low							
High							
SD	9.7	6.0	4.0	2.8	1.9	1.4	1.2
%RSD	21	7	4	3	2	1	1

Dissolution data showed rapid dissolution of the drug from the Berotralstat 150 mg capsule, i.e. more tha (b) (4)% drug was released from the formulation at (b) (4) The Applicant set the dissolution acceptance criterion as Q (b) (4)% at 30 minutes as per the FDA guidance for industry on Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Contain High Solubility Drug Substances, August 2018.

Conclusion: Berotralstat Dihydrochloride demonstrated high solubility across the physiological pH range from pH 1.2 to pH 6.8, dissolution data demonstrated rapid release of the drug from the formulation with low variability. Discriminating ability studies of dissolution method demonstrated that dissolution method does not have significant impact on dissolution due to differences in- critical quality attributes (differences in drug substances PSD), formulation variables (b) (4) and process parameters (b) (4)

Therefore, based on the drug solubility, drug dissolution rate of the pivotal clinical and registration batches for both strengths of Berotralstat capsules, low variability of drug release in the proposed dissolution method, the Applicant's proposed dissolution method and acceptance criterion is considered adequate.

Dissolution test parameters for quality control test:
The Approved dissolution method and acceptance criterion of Berotralstat capsules, 110 mg and 150 mg-

Apparatus	Media and temperature	Media volume (mL)	Speed (rpm)	Acceptance Criterion
USP Apparatus II (with 4-turn sinkers)	0.1N HCl, 37.0°C±0.5°C	500 mL	50	Q = (b) (4)% in 30 minutes

Signature Block

Primary Biopharmaceutics Reviewer Name:

Kamrun Nahar, PhD.

Secondary Biopharmaceutics Reviewer Name:

Haritha Mandula, Ph.D.

Appendix 1

Berotralstat Capsules clinical batch list and dissolution data link:

a. **\\cdsesub1\evsprod\nda214094\0000\m3\32-body-data\32p-drug-prod\berotralstat-capsule-common\32p2-pharm-dev\pharmaceutical-development-2.pdf (page 13)**
b. **\\cdsesub1\evsprod\nda214094\0021\m1\us\111-information-amendment\response-to-rfi-cmc-dissolution.pdf**

Appendix 2

Information request 1:

IR to be sent:

1. We could not locate the individual dissolution test data of the formulations used in the clinical studies. Provide the location of that data. If not already submitted, submit complete dissolution multi-point profile data (n=12).
2. You did not mention the type of dissolution vessel you've used to conduct the dissolution studies. Confirm the type of dissolution vessel type.
3. Provide us the solubility data of the drug substance over the physiologic pH range along with the detailed description of the dissolution method being proposed for the evaluation

of the product, along with the developmental parameters supporting the selection of the proposed dissolution method as the optimal test for the proposed drug product (e.g., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, media pH, sink conditions, use of sinker and enzyme, if applicable, etc.). If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. Clearly specify the testing conditions associated with each method development study.

4. You did not provide the discriminating ability of the dissolution method. Provide the data supporting the discriminating ability of the selected dissolution method. In general, ensure that the testing conducted to demonstrate the discriminating ability of the selected dissolution method compares the dissolution profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes, critical formulation variables, and critical process parameters (e.g., ± 10-20% change to the specified values or ranges for these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f2 values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product.
5. A list of the critical material attributes (CMAs) and critical process parameters (CPPs) affecting dissolution.
6. You've claimed that Berotralstate is a BCS class I compound. However, you did not submit the complete report of BCS classification of the Berotralstate compound. Therefore, we are advising you to submit the complete information addressing the following questions should be provided to support a BCS Class I classification request for a drug product.

1.1 Determination of the Drug Substance Solubility Class

1.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance?

1.1.2. What is the nature of the drug substance (acid, base, amphoteric, or neutral)? What is the dissociation constant(s), PKa(s) of the drug substance?

1.1.3. What is the solubility profile of the drug substance under physiological pH conditions (i.e., pH range 1-7.5 at 37^{o}C in aqueous media)?

1.1.4. Were five pH conditions used to define the solubility pH profile? How many replicate determinations of solubility of the drug substance at each pH condition were

performed? Note that at least three replicates are recommended. Refer to current BCS guidance for additional information on number of pH values to be evaluated.

1.1.5. What type of buffer solutions were used to define the solubility profile? What are the compositions of the buffer solutions? How they were prepared?

1.1.6. Was the buffer solution's pH verified after the addition of the drug substance to the buffer?

1.1.7. What type of method was selected to evaluate the equilibrium solubility of the drug substance? What are the specific experimental testing conditions?

1.1.8. What analytical method was used to determine the concentration of the drug substance in the selected buffers (or pH conditions)? What data support the validation of the assay?

1.1.9. What are the solubility pH profile results (individual, mean, standard deviation, coefficient of variation, and graphics)?

1.1.10. Is the highest dose strength of the proposed drug-product soluble in 250 ml of aqueous media over the pH range of 1 to 7.5?

1.1.11. Is the overall solubility information supportive of a BCS high soluble Class 1 classification for the drug substance?

1. 2. Determination of Drug Substance Permeability Class (refer to current BCS guidance for further details). Include this information with all details delineated below in the IND amendment.

1.2.1. What approach was used to determine the permeability class of the drug substance (*i.e., in vivo mass balance or absolute BA or intestinal permeability*)? If more than one method was used to demonstrate permeability classification, what is the other(s) approach?

1.2.2. For human pharmacokinetic approaches - Which approach was selected (*i.e., mass balance and/or absolute BA*)? What is the information describing the study design, methods, results, etc.?

1.2.3. For the intestinal permeability approaches – Which method was selected (*i.e., 1) in vivo intestinal perfusion studies in humans; 2) in vivo or in situ intestinal perfusion studies using suitable animal models; 3) in vitro permeation studies using excised human or animal intestinal tissues; or 4) in vitro permeation studies across a monolayer of cultured epithelial cells*) and what is the rationale for its selection? In this regard, we noted that the PAMPA system was used to support your claim. However, we highly

recommend that data on Caco-2 cells which includes the expression of appropriate transporters are also submitted to confirm your findings.

1.2.4. Is the drug substance being testing a passively transported drug? What is the information supporting this assumption?

1.2.5. Was the linear relationship between the dose and measures of bioavailability (*humans*) demonstrated?

1.2.6. Was there a lack of dependency of the measured in vitro permeability of the test article on initial drug concentration or transport direction (*no difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction*) using a suitable in vitro cell culture method. What is the supportive information?

1.2.7. For the in vivo-human perfusion studies, in vivo or in situ-animal intestinal perfusion studies or in vitro cell culture methods, how many model drugs were used? What model drugs were selected, and did they represent a range of absorption values? What are the permeability values for each model drug (mean, SD, CV) and what is the permeability class of each model drug?

1.2.8. What information supports the suitability of the selected method (i.e., description of the study, criteria for the selected approach, analytical method, method used to estimate the extent of absorption, (where appropriate, efflux potential), results (individual, mean,

Applicant's response:

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Reviewer's assessment:

a. The Applicant provided dissolution data of some batches of both 75 mg, 100 mg, 110 mg and 150 mg Berotralstat capsules. Which was not sufficient. Therefore, the Applicant was again asked to submit pivotal clinical and registration batches data for both strengths 110 mg and 150 mg. Refer to the IR#2 for detail information.
b. In response, the Applicant provided dissolution method development report. Which was adequate.
c. The Applicant claimed that Berotralstat Dihydrochloride is a BCS class I compound. However, they did not submit the complete report of BCS classification of the Berotralstate compound. Therefore, they were asked to submit the complete information addressing certain questions to support a BCS Class I classification request for a drug product. In response, the Applicant has withdrawn their request for BCS class 1 classification at this time. Their response is adequate.

IR#2:

We acknowledge that you provided dissolution data of the Berotralstat capsules. However, you did not provide sufficient dissolution data of the pivotal clinical /registration batches. Provide

additional dissolution data in the QC dissolution method, multi-point dissolution data (n=12) from the pivotal clinical/PK drug product-batches and primary registration batches of both strengths to determine the dissolution acceptance criterion of the proposed drug products.

The Applicant's response:
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Reviewer's assessment:
In response, the Applicant provided a list of Berotralstat capsules used in pivotal clinical studies and used as registration batches. As per the request from the Agency, the Applicant has generated dissolution data (n=12) from the retained samples. The dissolution data can be found in Applicant's response for the IR#1 and IR#2 (the link is provided above as the Applicant's response). The Applicant provided sufficient dissolution data of Berotralstat capsules used in pivotal clinical studies and used as registration batches to set the dissolution acceptance criteria. From the dissolution data is was observed that, Dissolutio_ data showed rapid dissolution of the drug from the Berotralstat 150 mg capsule, i.e. more than (b) (4)% drug was released from the formulation (b) (4). The Applicant also mentioned that they are proposing dissolution acceptance criterion as Q= (b) (4)% at 30 minutes as per the FDA guidance for industry on Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Contain High Solubility Drug Substances, August 2018. Berotralstat Dihydrochloride demonstrated high solubility across the physiological pH range from pH 1.2 to pH 6.8, dissolution data demonstrated rapid release of the drug from the formulation with low variability. Therefore, the Applicant's proposed dissolution acceptance criterion is adequate.

Kamrun Nahar

Digitally signed by Kamrun Nahar
Date: 7/08/2020 04:22:15PM
GUID: 57b38236009c032e2a84627cd295a5cd

Haritha Mandula

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Craig Bertha

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/s/

CRAIG M BERTHA
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