

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213969Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

<input checked="" type="checkbox"/> Approval
<input type="checkbox"/> Approval with Post-Marketing Commitment
<input type="checkbox"/> Complete Response

NDA 213969 Assessment 1

Drug Product Name	Zokinvy (lonafarnib) capsules
Dosage Form	Capsule
Strength	50 mg and 75 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Eiger Biopharmaceuticals Inc.; Palo Alto, CA
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Jan 31, 2020	OPQ
Amendment	Apr 17, 2020	OPMA
Amendment	May 14, 2020	ONDP
Amendment	Jun 12, 2020	OPMA
Amendment	Jul 31, 2020	OPMA
Amendment	Sep 11, 2020	OPMA

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sharon Kelly	Donna Christner
Drug Product	Caroline Strasinger	Moo-Jhong Rhee
Manufacturing / Facilities/Microbiology	Jingbo Xiao	Yubing Tang
Biopharmaceutics	Kamrun Nahar	Tapash Ghosh
Environmental	Caroline Strasinger	Moo-Jhong Rhee
Regulatory Business Process Manager	Oumou Barry	
Application Technical Lead	Hitesh Shroff	

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Zokinvy (lonafarnib) capsules.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made a final overall “**Approval**” recommendation for the facilities involved in this application,

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling issues have been satisfactorily resolved from the CMC perspective.

Therefore, from the OPQ perspective, this NDA is recommended for “**Approval**”.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

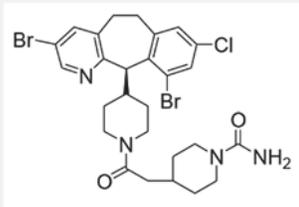
Zokinvy (lonafarnib) capsules are supplied as 50 mg and 75 mg immediate-release capsules in high-density polyethylene (HDPE) bottles. Each capsule contains either 50 mg or 75 mg of lonafarnib as the active pharmaceutical ingredient. The drug product is manufactured by a typical capsule manufacturing process. A shelf-life of 48 months at 20°C– 25°C is granted.

<p>Proposed Indication(s) including Intended Patient Population</p>	<p>Zokinvy, a farnesyltransferase inhibitor, is indicated in adult and pediatric patients 12 months of age and older with a body surface area of 0.39 m² and above:</p> <ul style="list-style-type: none"> • To reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS) • For the treatment of processing-deficient Progeroid Laminopathies with either: <ul style="list-style-type: none"> ○ Heterozygous LMNA mutation with progeroid-like protein accumulation ○ Homozygous or compound heterozygous ZMPSTE24 mutations <p><u>Limitations of Use</u> Zokinvy is not indicated for use in patients with non-HGPS Progeroid Syndromes or with Progeroid Laminopathies known to be processing- proficient. Based upon its mechanism of action, Zokinvy would not be expected to be effective in these populations.</p>
<p>Duration of Treatment</p>	<p>As needed</p>
<p>Maximum Daily Dose</p>	<ul style="list-style-type: none"> • Recommended starting dosage is 115 mg/m² twice daily with morning and evening meals • After 4 months, increase dosage to 150 mg/m² twice daily
<p>Alternative Methods of Administration</p>	<p>Patients unable to swallow capsules can mix the contents of Zokinvy with Ora Blend SF[®], Ora-Plus[®], orange juice, or applesauce.</p>

B. Quality Assessment Overview

Drug Substances: Adequate

The drug substance in Zokinvy capsules is lonafarnib. It is a white to off-white powder. It is non-hygroscopic, practically insoluble in water and known to have only one polymorph. Lonafarnib is a chiral molecule containing one chiral center. The chemical name for lonafarnib is 4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[1,2]cyclohepta[2,4-b]pyridin-11-yl]piperidin-1-yl]-2-oxoethyl]piperidine-1-carboxamide.



Molecular formula: $C_{27}H_{31}Br_2ClN_4O_2$
Molecular mass: 638.8 g/mol

Lonafarnib is manufactured by [REDACTED]

(b) (4)

[REDACTED] The applicant has also provided sufficient information for both Agency approved starting materials. The detailed information regarding the raw materials, intermediates and drug substance manufacturing process is deemed adequate.

Its chemical structure was unambiguously confirmed by many modern analytical methods such as proton (1H) and carbon (^{13}C) NMR spectroscopy; Infrared (IR) spectroscopy, mass spectroscopy and X-ray crystallography.

The identity, purity and quality of the drug substance, lonafarnib, is assured by its specification for appearance, identity by IR and HPLC; assay by HPLC, impurities by HPLC, chiral impurities by chiral HPLC, elemental impurities by ICP-MS per USP <233>, residual solvents by GC and microbial limits testing per USP <61> and <62>. The potential genotoxic impurities were also controlled and assessed by LC-MS. The non-compendial analytical methods were validated per ICH Q2R1. Satisfactory batch analyses of multiple batches up to $^{(b) (4)}$ kg each of the drug substance used in nonclinical, clinical, and stability studies confirmed that the drug substance manufacturing process is robust.

Based on long-term and accelerated stability testing of multiple batches of lonafarnib, a retest period of $^{(b) (4)}$ months is granted when stored $^{(b) (4)}$

The drug substance reviewer, Dr. Sharon Kelly, concluded that the applicant has

submitted adequate CMC information regarding the raw materials, starting materials, intermediates, manufacturing process as well as the specification for identity, purity and quality of the drug substance, Lonafarnib. (see the **Drug Substance** review).

Drug Product: Adequate

Zokinvy is a farnesyltransferase inhibitor. It is supplied as 50 mg and 75 mg hard gelatin capsules for oral administration. The 50 mg Size 4 hard capsules are opaque yellow with “LNF” and “50” printed in black. The 75 mg Size 3 hard capsules are opaque light orange with “LNF” and “75” printed in black. Each capsule contains either 50 mg or 75 mg of lonafarnib as the active ingredient and the following inactive ingredients: croscarmellose sodium, magnesium stearate, poloxamer 188, povidone, and silicon dioxide. The capsule shells contain gelatin, titanium dioxide, and yellow iron oxide; the 75 mg capsule also contains red iron oxide.

The overall control strategy for the drug product’s identity, strength, purity and quality is deemed adequate based on raw material controls, drug product specification. The drug product specification includes the acceptance limits and following tests: visual appearance, identity by UV and HPLC, strength by HPLC assay, purity assessment of related substances by HPLC, microbial limit testing per USP <61> and USP <62>; quality dissolution per USP <711>, Uniformity of dosage units per USP <905> and crystallinity by XRPD. The in-house developed non-compendial analytical methods were validated per ICH Q2(R1).

During the drug product development there was one drug product formulation change [REDACTED] (b) (4). However, no bridging was deemed necessary because both formulations were used in clinical studies. The dissolution method showed discriminating ability to differentiate change in formulations and process variability. The dissolution method and method development; dissolution data and dissolution acceptance criteria were reviewed and deemed adequate from the biopharmaceutics perspective. (see **Biopharmaceutics Review**)

The drug product can be mixed with soft-food and diluents prior to administration for patients who are unable to swallow whole capsules. In order to demonstrate that there is no significant degradation in overall quality of the drug product in soft-food, juice and diluents the applicant conducted a compatibility study with the contents of the capsule mixed with Ora-Plus, Ora-Blend, orange juice and applesauce.

The date of drug product manufacture has been defined as the date [REDACTED] (b) (4). Based on the long-term and accelerated stability data of the [REDACTED] (b) (4) and drug product assuring the identity, strength, purity and quality, a 48-month of expiration dating period when stored at 20-25°C (68-77°F) in high-density

polyethylene (HDPE) bottles capped with white (b) (4) child-resistant cap lined with induction seal liner containing 1g silica gel desiccant canister is granted. (See the **Drug Product** review by Dr. Caroline Strasinger)

Manufacturing: Adequate

The drug product is manufactured and tested by (b) (4)
The crystallinity testing for release and stability is performed (b) (4)
(b) (4) The drug product manufacturing process includes (b) (4)

Microbiology: Adequate

Zokinvy is a non-sterile drug product. The drug product specification includes microbial enumeration test for total aerobic microbial count and total combined yeast/molds count per USP <61> and test for specified micro-organisms Escherichia Coli per USP <62>. The acceptance criteria will adhere to USP <1111> for non-sterile products. Microbial limits testing will be performed at release and stability.

The microbiology related information in the drug product manufacturing process, analytical methods, stability data of the commercial scale registration batches, post-approval stability protocol and specification were reviewed by Dr. Jingbo

Xiao and deemed acceptable. (See the **Manufacturing Integrated Assessment** review).

Labeling: Adequate

The proposed labels and labeling after revision are deemed adequate from the CMC perspective. (see the **Labeling** review).

Facilities Adequate

The Office of Process and Facilities (OPF) reviewer, Dr. Jingbo Xiao has made an “Adequate” recommendation for the drug substance and drug product manufacturing and testing facilities. (see the **Manufacturing Integrated Assessment** review).

Environmental Assessment Adequate

The applicant has submitted a claim of categorical exclusion including a statement of no extraordinary circumstances. The categorical exclusion cited at 21 CFR 25.31(b or c) is appropriate for the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is acceptable. (see the **Drug Product** Review).

Post-marketing Commitments (PMC): None

Lifecycle Management Considerations:



C. LIST OF DEFICIENCIES: None

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
September 28, 2020

**Hitesh N.
Shroff -S**

Digitally signed by Hitesh N. Shroff -S
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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)	Type III		(b) (4)	Active	N/A	LOA: Jul 10, 2019
	Type III		Active	N/A	LOA: Jul 22, 2019	
	Type III		Active	N/A	LOA: Nov 13, 2019	
	Type III		Active	N/A	LOA: Nov 12, 2019	
	Type III		Active	N/A	LOA: Nov 12, 2019	
	Type III		Active	N/A	LOA: Nov 12, 2019	
	Type III		Active	N/A	LOA: Aug 30, 2019	
	Type III		Active	N/A	LOA: Sep 19, 2019	

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

Document	Application Number	Description
IND	139923	Rely on all information and clinical trials conducted under this IND.
IND	(b) (4)	Rely on all information and clinical trials conducted under this IND.
IND		Refer to all information in this IND.
IND		Refer to all information in this IND.
IND		Refer to all information in this IND.
IND		Refer to all information in this IND.

2. CONSULTS

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

CHAPTER I: DRUG SUBSTANCE

Drug Substance Name	Lonafarnib
NDA Number	213969
Assessment Cycle Number	1
DMF Number	N.A.
DMF Status	N.A.
Applicant Name	Eiger Biopharmaceuticals, Inc.
DMF Holder	N.A.

Assessment Recommendation: Adequate

Assessment Summary:

(b) (4)

Based on the available stability data, the applicant proposes a re-test period of (b) (4) months for Lonafarnib Drug Substance when stored at (b) (4) Granted.

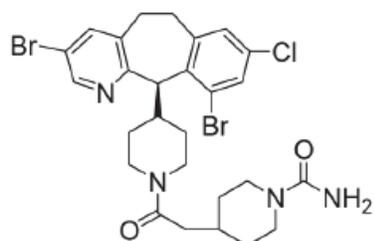
List Submissions being assessed:

Document(s) Assessed	Date Received
Original	March 20, 2020
Amendment SDN 08	May 14, 2020

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues: None

S.1 GENERAL INFORMATION



Active is the (R)-enantiomer

Molecular Formula C₂₇H₃₁Br₂ClN₄O₂ **Relative Molecular Mass** 638.8

Chemical Name

IUPAC Name: 4-[2-[4-[(11*R*)-3,10-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[1,2]cyclohepta[2,4-*b*]pyridin-11-yl]piperidin-1-yl]-2-oxoethyl]piperidine-1-carboxamide

INN/USAN Lonafarnib

Company or Laboratory Code: MK-6336, SCH-66336, BP1515-YYC

CAS: 193275-84-2

General Properties

Physical/Chemical Properties	Description
Description	White to off-white, powder
Thermal Analysis by Differential Scanning Calorimetry	217 °C (melting onset)
Dissociation Constant	pKa = 2.8
Partition Coefficient (n-octanol/water)	Log Ko/w = 4.7
Hygroscopicity	not hygroscopic; 0.1 % moisture absorption after exposure for 1 month at 40 °C/75 % relative humidity.
Solubility Organic Solvent	
Dimethyl Sulfoxide	50 mg/mL
Isopropanol	2 mg/mL
Ethanol	6 mg/mL
Aqueous Solution	
Deionized Water	practically insoluble (< 0.1 mg/mL)
1 M Citric Acid	0.4 mg/mL
0.1 M Citric Acid	practically insoluble (< 0.1 mg/mL)
Polymorphism	Only a single crystalline polymorphic form is known.

Assessment: Adequate

The general properties of the DS are sufficiently understood to enable assessment of their impact on the manufacture of the drug product.

S.2 MANUFACTURE

Commercial Synthetic Scheme and Process Flow Diagram





Donna
Christner

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Sharon
Kelly

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CHAPTER II: DRUG PRODUCT

[IQA NDA Assessment Guide Reference](#)

Product Information	
NDA Number	213969
Assessment Cycle Number	1
Drug Product (DP) Name / Strength	TRADENAME (lonafarnib) capsules, 50 and 75 mg
Route of Administration	Oral
Drug Product Manufacturer	Applicant: Eiger Biopharmaceuticals Manufacturer: Patheon
RLD Information (Brand Name of Product, Applicant)	N/A This is a 505 (b)(1) submission
RLD/RS Number	N/A
Proposed Indication	Treatment of Hutchinson-Gilford Progeria Syndrome and Progeroid Laminopathies

Assessment Recommendation: Adequate

Assessment Summary:

The drug product is an immediate-release hard gelatin capsule for oral administration. The 50 mg strength is a size 4, opaque, yellow, hard gelatin capsule with a black imprint. The 75 mg strength is a size 3, opaque, light orange, hard gelatin capsule with a black imprint. 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 applicant has conducted a compatibility study with the contents of the capsule mixed with Ora-Plus, Ora-Blend, orange juice and applesauce for patients unable to swallow whole capsules.

For treatment of Hutchinson-Gilford Progeria Syndrome the MDD is 300 mg and for treatment of Progeroid Laminopathies the MDD is (b) (4) mg per day.

The only specified impurity is Compound (b) (4) and has been limited to NMT (b) (4)%. A control for (b) (4) of NMT (b) (4)% is also included in the specification to (b) (4). The finished drug product is packaged in a white 30 count HDPE bottle with (b) (4) closure and 1 g desiccant canister.

The date of manufacture has been defined as the date (b) (4)

Based on the available

stability data, a shelf-life of 48 months for Lonafarnib Capsules, 50 mg and 75 mg is supported when stored at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F).

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle # 1	Comments
Assay/ Related Substances	Medium	(b) (4)	Low	(b) (4)
(b) (4)	Medium		Medium	
Dissolution	Low		Low	
Content Uniformity	Low		Low	
Crystallinity	Low		Low	Specification includes test for absence of crystal.
Microbiology	Low		Low	Microbial controls included in specification
(b) (4)	Medium		Low	Specification adequate: (b) (4)

Document(s) Assessed	Date Received
0002 Module 3 Submission	31-JAN-2020
0003 Stability Summary/Data	20-MAR-2020
0008 Updated Specification	14-MAY-2020

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): None

P.1 DESCRIPTION AND COMPOSITION

The drug product is an immediate-release hard gelatin capsule for oral administration, available in 50 mg and 75 mg strength.

The 50 mg strength is a size 4, opaque, yellow, hard gelatin capsule with a black LNF imprint on the cap and "50" imprint on the body of the capsule. The 75 mg strength is a size 3, opaque, light orange, hard gelatin capsule with a black "LNF" imprint on the cap and "75" imprint on the body.

Component/Composition Table

Component	Function	Quantity		
		% w/w	50 mg Unit (mg/capsule)	75 mg Unit (mg/capsule)
Lonafarnib				
Povidone				
Poloxamer 188				
Croscarmellose sodium				
Silicon dioxide				
Magnesium stearate				

Capsule	
Capsule Fill Weight	
Hard gelatin capsule size 4	Capsule shell
Hard gelatin capsule size 3	Capsule shell

(b) (4)

Assessment: ADEQUATE

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) who certifies (certificates provided) they are free from BSE. The applicant has provided an LOA to reference DMF (b) (4) for all additional capsule information. DMF (b) (4) was most recently reviewed and deemed adequate for use in April 2020.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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P.7 CONTAINER CLOSURE

The container closure system for the 50 mg and 75 mg Lonafarnib Capsules consists of a white 50 mL HDPE bottle with canister desiccant (silica gel) and white (b) (4) cap. Components of the container closure are commonly used for oral dosage forms, schematics, certificates of compliance of the plastic components, and specifications for all components have been provided. Historically, only the amount and type of desiccant has changed (0.5 g silica sachet to 1.0g silica canister).

(b) (4)

Assessment: ADEQUATE

The container closure description and control of materials is adequate. The registration batches have been packaged in the proposed commercial packaging (including desiccant) and stability data (discussed below) supports its use to ensure quality of the product through shelf life.

P.8 STABILITY

Submitted in eCTD [#0001] dated [16/12/2019]

Review of the formal stability data for the finished drug product and the spray dried intermediate is captured below.

Drug Product

Six registration batches (3 for each strength) manufactured at the proposed commercial manufacturing site and in the proposed commercial packaging have been placed on stability. Additional historical stability and forced degradation data have also been provided to support a shelf-life of 48 months. In summary:

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In summary, stability data on nine batches for up to 60 months (50 mg) and 36 months (75 mg) have been provided. In all studies and under all storage conditions, the product met the specification throughout shelf-life. No significant changes in appearance, assay and dissolution were noted. (b) (4)

(b) (4) increased gradually over time and was more pronounced under accelerated conditions but remained within specification. Notable, to extend the life of clinical trial material, the applicant retested a lot ((b) (4) 00061878) 8 years after its original manufacturing date. The stability results (b) (4) showed that there were no significant change in appearance, assay, compound (b) (4) or dissolution. Assay was out of trend but still within specification.

(b) (4)

Proposed Storage Conditions and Shelf Life

The applicant intends to define the date of manufacture for Lonafarnib Capsules, 50 mg and 75 mg as the date [REDACTED] (b) (4)

[REDACTED] An expiry period of 48 months is proposed when stored under USP Controlled room temperature conditions [20°C to 25°C (68°F to 77°F)].

Assessment: ADEQUATE

The date of manufacture has been defined as the date [REDACTED] (b) (4)

[REDACTED] (b) (4)

(b) (4)

The stability of the product is supported by three registration batches of each strength manufactured at the commercial manufacturer, using the commercial process and the commercial formulation through 18 months, with only the exception of the color and printing on the hard gelatin capsule. One registration batch of each strength with the commercial color capsule and printing have been provided. The color and printing on the capsule have been shown not to impact the finished product. All registration batches were packaged in the proposed commercial packaging with desiccant. In total, the data for 9 batches have been provided to support the proposed shelf-life (and up to (b) (4) months of storage at long term conditions). All batches remained within the acceptance criteria of the specification. (b) (4)

(b) (4)

Post-Approval Stability Protocol and Commitment

The applicant commits to continue stability studies on the primary registration batches, to place the first three commercial batches (i.e. the validation batches) on stability, and to assess the stability of one commercial batch per year (if manufactured that year). (b) (4)

Assessment: ADEQUATE

R REGIONAL INFORMATION

Environmental

It is estimated that the highest quantity of the active moiety, lonafarnib, to be produced for direct use in the next five years will **not exceed** (b) (4) **kg/year**. The Progeria Research Foundation's (PRF) Progeria Registry, based this quantity upon estimates of disease prevalence, the maximum daily dose and market forecasts for the indications being sought.

Assessment: ADEQUATE

CDER EA Team communicated the following on 3-FEB-2020:

Based on the very low production level of lonafarnib, environmental impacts are not anticipated and a full EA Team review is not required. We consider this NDA to have di minimus environmental risk.

The applicant has submitted an adequate claim of categorical exclusion, including a statement of "no extraordinary circumstances."

The Applicant's claim for Categorical Exclusion under 25.31 (b) is acceptable.

Methods Validation or Verification Package

Assessment: N/A

Comparability Protocols

Assessment: N/A

Post-Approval Commitments

Assessment: N/A



DRUG PRODUCT LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date:

Caroline Strasinger, Ph.D.

OPQ/ONDP/DNDP2/Branch 4

06/08/2020

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

I agree with Dr. Caroline's assessment on the overall control strategy for the production of the proposed drug product in terms of raw materials, specification, container closure system, and stability data to ensure the identity, strength, purity and quality of the drug product during the shelf-life, and therefore, I agree with her recommendation of Approval of this application from the drug product perspective with 48-month of expiration dating period.

Moo-Jhong Rhee, Ph.D.

Chief, Branch IV

DNDP II/ONDP/OPQ

June 8, 2020



Caroline
Strasinger

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Moo Jhong
Rhee

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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

The below information and labeling deficiencies were agreed to by the Applicant on 10-AUG-2020. The deficiencies are presented below only for completeness of review. The Label and Labeling is now ADEQUATE from the ONDP perspective.

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)	(lonafarnib) 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: 50 mg and 75 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)	<p>For patients unable to swallow capsules, the contents of TRADENAME can be mixed with Ora Blend SF® or Ora-Plus®. For patients unable to access or tolerate Ora Blend SF® or Ora-Plus®, the contents of TRADENAME capsules can be mixed with orange juice or applesauce....mix with a small amount of liquid (Ora Blend SF®, Ora-Plus®, orange juice) (b) (4)</p> <p>mix thoroughly with a spoon and consume entire serving. The mixture must be prepared fresh for each dose and be taken within approximately 10 minutes of mixing.</p>	ADEQUATE

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3 DOSAGE FORMS AND STRENGTHS

(b) (4) Capsules:

- 50 mg.: ~~Size 4 hard capsule~~, opaque yellow with "LNF" and "50" printed in black
- 75 mg.: ~~Size 3 hard capsule~~, opaque light orange with "LNF" and "75" printed in black

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Capsules	INADEQUATE: Revise for formatting This was satisfactorily resolved on 8/10/20
Strength(s) in metric system	50 mg, 75 mg	INADEQUATE: Revise for formatting
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	Size 4/5 hard capsule, opaque yellow/light orange with LNF and 50/75 printed in black	INADEQUATE: Remove Size 4/5 hard capsule This was satisfactorily resolved on 8/10/20
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

11 DESCRIPTION

TRADENAME (lonafarnib) is a farnesyltransferase inhibitor.

The chemical name for lonafarnib is 4-[2-[4-[(1R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[1,2]cyclohepta [2,4-b]pyridin-11-yl]piperidin-1-yl]-2-oxoethyl]piperidine-1-carboxamide. Its molecular formula is $C_{27}H_{31}Br_2ClN_4O_2$, molecular mass is 638.8 g/mol, and its chemical structure is depicted below.



TRADENAME (lonafarnib) capsules for oral administration contain 50 mg or 75 mg of lonafarnib as the active ingredient and the following inactive ingredients: povidone, poloxamer 188, croscarmellose sodium, silicon dioxide, and magnesium stearate. The capsule shells of both strengths contain gelatin, titanium dioxide, and yellow iron oxide; the 75 mg capsule also

contains red iron oxide. The imprinting ink contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, ammonia solution, potassium hydroxide, and black iron oxide.

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRADENAME (lonafarnib) capsules	ADEQUATE
Dosage form(s) and route(s) of administration	Capsules for oral administration	ADEQUATE
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 This was satisfactorily resolved on 8/10/20
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	farnesyltransferase inhibitor	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)	N/A	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)

16 HOW SUPPLIED/STORAGE AND HANDLING

TRADENAME is supplied as:

— 50 mg capsules:

Size 4 hard capsule, opaque yellow with "LNF" and "50" printed in black.

Bottles of 30 capsules each (NDC 73079-050-30)

75 mg capsules:

Size 3 hard capsule, opaque light orange with "LNF" and "75" printed in black.

Bottles of 30 capsules each (NDC 73079-075-30)

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], age: Do not store above 25°C (77°F)

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	50 mg; 75 mg	ADEQUATE
Available units (e.g., bottles of 100 tablets)	Bottles of 30 capsules	ADEQUATE
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Size 4/3, hard capsule, opaque yellow/light orange with "LNF" and "50"/ "75" printed in black	ADEQUATE
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.)	N/A.	N/A
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Storage: Do not store above 25°C (77°F).	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 8/10/20
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	N/A	N/A

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: Eiger BioPharmaceuticals, Inc., 2155 Park Boulevard Palo Alto, CA 94306	ADEQUATE

ASSESSMENT OF THE PI: ADEQUATE

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

Section 3

- Revise section for clarity as indicated above
- Remove Size 4 Hard Capsule or Size 5 Hard Capsule

Section 11

- List inactive ingredients in alphabetical order

Section 16

- Revise storage conditions to read:
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].

On AUGUST 10, 2020 the Applicant agreed to all OPQ related deficiencies. The Labeling of NDA 213969 is ADEQUATE.

2.0 CARTON AND CONTAINER LABELING

Reviewer Note: For review purposes the revised 50 mg labels (provided on 8/11/2020) and the originally submitted 75 mg labels.

3.1 Container Label



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	TRADENAME (Lonafarnib) capsules	ADEQUATE
Dosage strength	50 mg/ 75 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	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	Present	ADEQUATE
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-30°C (59°F-86°F) [see USP Controlled Room Temperature]. Do not refrigerate.	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: Eiger BioPharmaceuticals, Inc., Palo Alto, CA 94306	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 listed Active Ingredient: lonafarnib	INADEQUATE: On the carton list the inactive ingredients in alphabetical order Change active to read: Each capsule contains: Lonafarnib....50 mg Or Lonafarnib....75 mg

Assessment of Carton and Container Labeling: *INADEQUATE*

For the Carton change the side panel to read:

Each capsule contains:

Lonafarnib.....50 mg

Inactive Ingredients:

(List inactive ingredients in alphabetical order)

Or

Each capsule contains:

Lonafarnib.....75 mg

On AUGUST 11, 2020 the Applicant agreed to all OPQ related deficiencies. The Label of NDA 213969 is ADEQUATE.

Overall Assessment and Recommendation:

On August 10, 2020 the Applicant agreed to all OPQ related deficiencies. The Label and Labeling of NDA 213969 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):

I agree with Dr. Strasinger's assessment of the labeling and labels and concur with her recommendation that this application is ready for APPROVAL.

Moo-Jhong Rhee, Ph.D.

Chief, Branch 4

DNDP II/ONDP



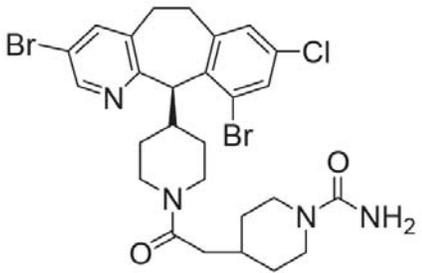
Caroline
Strasinger

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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	NDA 213969	
Drug Product Name	Lonafarnib	
	Chemical Structure	
	Molecular Formula	C ₂₇ H ₃₁ Br ₂ ClN ₄ O ₂
	Relative Molecular Mass	638.8
	<i>Submission Classification:</i> Type 1 - New Molecular Entity <i>Regulatory Pathway:</i> 505(b)(1) <i>Review Priority:</i> Priority <i>PDUFA Goal Date:</i> 11/20/2020	
Strengths	50 mg and 75 mg	
Dosage Form	Capsule	
Administration Route	Oral	
Indication	Treatment of Hutchinson-Gilford Progeria Syndrome and Progeroid Laminopathies	
Applicant Name	Eiger BioPharmaceuticals, Inc.	

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary: Review #1	(b) (4)
Redacted content	

Facility: Following a review of the application and inspectional documents, there are no significant facility risks that prevent approval of this application from a cGMP facility assessment perspective. All manufacturing and testing facilities listed in NDA 213969 are currently found to be acceptable based on firms' previous inspection history and the cGMP compliant status. Therefore, CDER/OPMA is recommending Approval for the Overall Manufacturing Inspection Recommendation (OMIR) for NDA 213969.

Overall, NDA 213969 is recommended for approval from manufacturing assessment perspective per Review #1.

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List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Pre-Submission-1, Seq. 0001 (1)	12/16/2019
Pre-Submission-1 (CMC rolling), Seq. 0002 (2)	01/31/2020
Origianl-1, Seq. 0003 (3)	03/20/2020
CMC Amendment (Response to Filing IR), Seq. 0004 (4)	04/17/2020
CMC Amendment (Response to BP IR), Seq. 0008 (8)	05/14/2020
CMC Amendment (Response to BP IR), Seq. 0009 (9)	05/28/2020
CMC Amendment (Response to Manufacturing IR), Seq. 0012 (12)	06/26/2020
CMC Amendment (Response to Manufacturing IR), Seq. 0016 (16)	07/31/2020
CMC Amendment (Response to Manufacturing IR), Seq. 0018 (18)	08/14/2020
CMC Amendment (Response to Manufacturing IR), Seq. 0022 (22)	09/11/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A, 1st Review Cycle

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

1. Post-Approval Commitments and Lifecycle Management Considerations

Postmarketing commitments (PMC)?	No
Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
	(b) (4)	Drug product: Manufacturing (b) (4); Release and stability testing (excluding crystallinity testing); Labeling, Packaging and Storage 356h Status: Pending CHG	Approve - Based on Previous History
		Crystallinity testing (release and stability) for drug product 356h Status: Pending LCP	Approve - Based on Previous History
		Manufacturing and packaging (b) (4) 356h Status: Pending (b) (4)	Approve - Based on Previous History
		Release and stability testing (excluding microbiological testing) (b) (4) 356h Status: Pending (b) (4)	Approve - Based on Previous History
		Drug substance: Manufacture; Release and stability testing (excluding microbiological testing); Packaging and Storage 356h Status: Pending CSN	Approve - Based on Previous History
		Microbiological testing (release and stability) for drug substance and (b) (4) 356h Status: Pending LMN	Approve - Based on Previous History
		Storage of intermediate (b) (4) 356h Status: Pending (b) (4)	Approve - Based on Previous History

During the filing review, there were no facilities identified on FDA Form 356h in the original (initial) submission dated 03/20/2020 (see below manufacturing IR#1).

#IR1	<p>No facilities were identified on FDA Form 356h in your original (initial) submission dated 03/20/2020. Please be advised that all identified facilities should be listed on FDA Form 356h or associated continuation sheet with complete identifying information for each submission. Please refer to Form FDA 356h Questions/Answers #1 in Guidance for Industry - <i>Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers, October 2019.</i></p>
<p>Summary of Applicant’s Response (dated 4/17/2020) and Assessment: Adequate Form FDA 356h dated 04/17/2020 was updated with all identified facilities listed as shown in above table. – Acceptable --</p>	

II. Drug Product Manufacturing

1. *Batch Formula*

(b) (4)





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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 213969-ORIG-1

Drug Product Name / Strength: lonafarnib capsules, 50 mg and 75 mg

Route of Administration: Oral

Applicant Name: Eiger BioPharmaceuticals, Inc.

FDA Received date: 12/16/2019

Review Summary: ADEQUATE

The proposed drug product, lonafarnib capsules, 50 mg and 75 mg is indicated for the treatment of Hutchinson-Gilford Progeria Syndrome and Progeroid Laminopathies. The Applicant seeks approval of this NDA via the 505(b)(1) regulatory pathway. The product formulation is an immediate release capsule formulation. This biopharmaceutics review commented on the dissolution method and acceptance criterion.

Overall, the proposed dissolution method and acceptance criterion as described below is acceptable and the NDA 213969 is **adequate** for approval from Biopharmaceutics perspective.

The approved dissolution method and acceptance criterion-

Apparatus	Dissolution medium	Dissolution medium volume (mL)	RPM	Dissolution medium temperature (°C)	Dissolution acceptance criterion
USP apparatus I (basket)	0.2% sodium lauryl sulfate (SLS) in water	900	75	37.0	Q= ^(b) ₍₄₎ % in 30 minutes

List of the documents reviewed:

- 1.0001(1)12/16/2019 ORIG-1/Multiple categories/subcategories
2. 0008(8) 5/14/2020 ORIG-1/Quality/Response to information request
3. 0009(9) 5/28/2020 TRIAGE-1/Electronic submission/Gateway

Biowaiver request: None.

The strength 50 mg and 75 mg are compositionally proportional (refer to the CMC review for detail information). The applicant conducted clinical studies using both 50 mg and 75 mg strengths. Therefore, biowaiver is not required.

Solubility: The Applicant mentioned that Lonafarnib drug substance is insoluble in water (<0.01 mg/mL); the manufacturing process for the drug product involves (b) (4)

Table 1: Solubility data of Lonafarnib

Media and pH	Solubility (µg/mL)
0.01N HCl, pH 2.0	55.9
Acetate buffer, pH 4.5	2.0
Phosphate buffer, pH 6.8	4.2
Water	6.7

Source: Appendix I: (b) (4) Method Development and Evaluation Report for Dissolution of Lonafarnib Capsules

Clinical and registration batches of the Lonafarnib capsules, 50 mg and 75 mg:

During the developmental phase of the Lonafarnib capsules, 50 mg and 75 mg, the applicant made only one formulaiton change (formulation adjustment). (b) (4)

The applicant considered it identical and nearly identical drug product compositon. Both identical and nearly identical formulations were used in clinical studies and therefore, no bridging was deemed necessary by the Drug Product (DP) and/or any other discipline. The formulaiton lists are included in the table below-

Table 2: Summary of clinical batches for lonafarnib capsules, 50 mg and 75 mg

Batch Number	Manufacturing Date	Manufacturing Site	Batch Size (No. Capsules)	Use of Batch	Batch Comparison
50mg					
79369-008-E	15 Oct 2002	(b) (4)	(b) (4)	Clinical, Development	Identical Composition
(b) (4) 00061878	02 Aug 2011			Clinical, Development	
Lot 16-0109	10 Aug 2016			Clinical, Development	
Lot 16-0139	15 Aug 2016			Clinical, Development	
CBMGB	26 Jul 2018			Clinical, Registration	Nearly Identical Composition ¹
CBWVC	05 Nov 2018			Clinical, Registration	
CDMMM	23 Oct 2019			Clinical, Registration	
75mg					
78578-145-E	27 Jun 2002	(b) (4)	(b) (4)	Clinical, Development	Identical Composition
Lot 16-0140	16 Sep 2016			Clinical, Development	
ZWZY	11 Apr 2018			Clinical, Registration	Nearly Identical Composition ²
CBWVD	05 Nov 2018			Clinical, Registration	
CDMMN	23 Oct 2019			Clinical, Registration	

The applicant provided dissolution data of the clinical and registration batches for both strengths of Lonafarnib capsules 50 mg and 75 mg before and after modification in the dissolution data section of the review (refer to the Appendix 1 for dissolution data link). Dissolution data demonstrated (b) (4) that all the formulations are meeting dissolution acceptance criterion of “Q=(b) (4)% in 30 minutes”.

All clinical batches and the first two registration batches were manufactured at (b) (4) that used same color opaque white capsule shells but different sizes shell for different strengths, i.e. size#4 and size#3 are used for Lonafarnib capsules, 50 mg and 75 mg, respectively. For the third registration batch#CDMMM for 50 mg and batch#CDMMN for 75 mg and all other product intended for commercial use, the color of the capsule shells were changed to yellow opaque for Lonafarnib capsules, 50 mg and light orange opaque

for Lonafarnib capsules, 75 mg. Both strengths of the capsules have imprint in their shell. To determine the impact of the shell color and imprint, the applicant was asked to provide comparative dissolution data of Lonafarnib capsules, 50 mg and 75 mg with different color in capsule shells (refer to the Appendix 2 for detail information). In response, the applicant provided individual unit dissolution data of these formulation. Dissolution profile and f2 value is given below-

Figure 1: Dissolution profiles of Lonafarnib capsules, 50 mg in white and yellow imprinted capsules

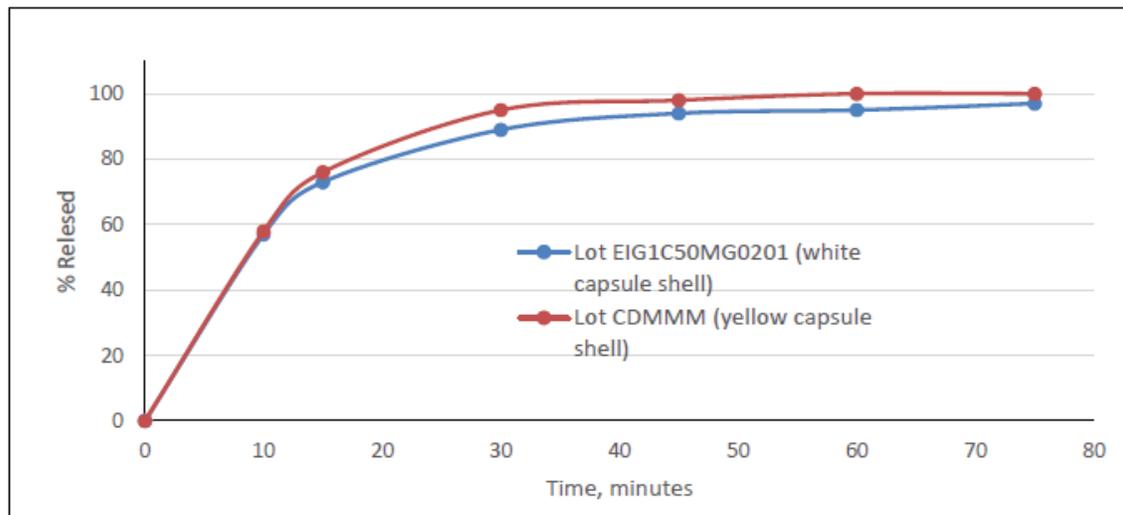


Figure 2: Dissolution profiles of Lonafarnib capsules, 75 mg in white and light orange imprinted capsules

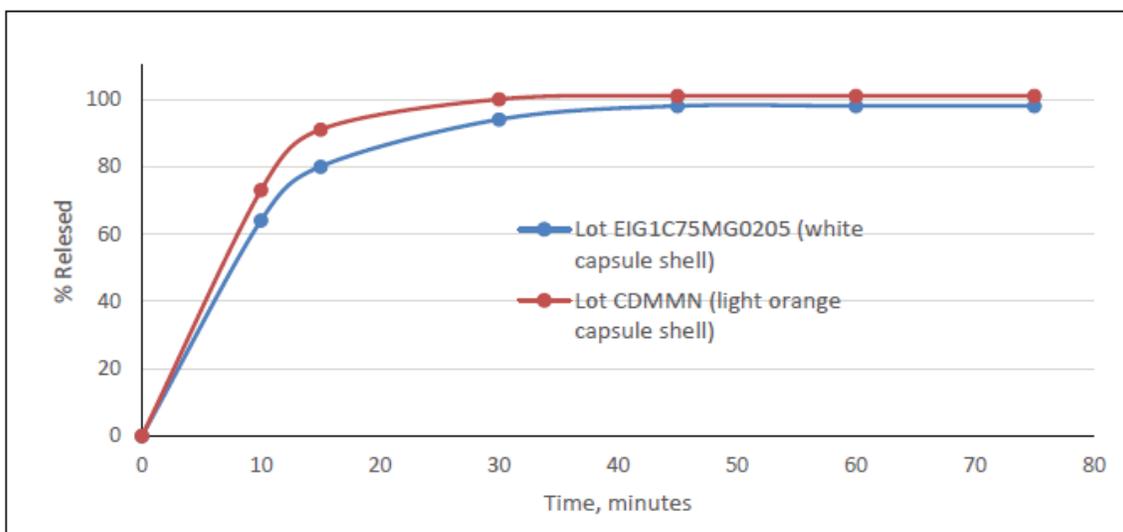


Table 3: Lonafarnib capsules, 50 mg and 75 mg: calculated f1 and f2 results for white and colored imprinted capsules shells

	Difference Factor ¹ f ₁	Similarity Factor ¹ f ₂
Lonafarnib Capsules, 50mg	4	70
Lonafarnib Capsules, 75mg	9	55

¹ f₁ values between 0 to 15, and f₂ values between 50-100 indicate the dissolution profiles of reference and test products are similar

From the dissolution profiles and f2 value calculation of Lonafarnib capsules 50 mg and 75 mg, it was observed that Lonafarnib capsules, 50 mg in white capsules and imprinted yellow capsules; and Lonafarnib capsules, 75 mg in white capsules and imprinted light orange capsules have similar release rate, i.e. more than ^{(b) (4)} % drug is released at 30 minutes and similarity factor for both strengths are above 50 in ^{(b) (4)} stating that color differences and imprint on the capsules shells did not have impact on the dissolution of the formulations.

Based on the provided comparative dissolution data, ^{(b) (4)} and capsule shell color and imprints have been adequately bridged.

In vitro dissolution method development:

The Applicant developed an in vitro dissolution method for quality control (QC) purpose. The development of the dissolution method was based on the testing of the equipment, apparatus settings, dissolution media (i.e. pH, volume and surfactant), and evaluation of the discriminating capability of the method.

^{(b) (4)}

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(b) (4)

Discriminatng ability of the dissolution media of various formulations in selected dissolution media with selected dissolution parameters:

The applicant evaluated discriminating ability of the dissolution method with selected apparatus type and rotating speed (i.e. 50 rpm and 75 rpm using basket) using targeted and intentionally manufactured deviant formulations. The applicant formulated four deviant formulations (b) (4)

Below is the list of formulations used to demonstrate discriminating ability of the dissolution method-

Table 5: List of target and deviant batches of Lonafarnib capsules, 75 mg

Product Batch	Batch#	Deviant batch info
Target batch	CBYZF	(b) (4)
Target batch	EIG1C75mg0205	
Deviant batch-1	EIG1C75mg0201	
Deviant batch-2	EIG1C75mg0202	
Deviant batch-3	EIG1C75mg0203	

		(b) (4)
Deviant batch-4	EIG1C75mg0204	

Figure 6: Dissolution profiles of deviant batches of Lonafarnib capsules, 75 mg at (b) (4) rpm baskets

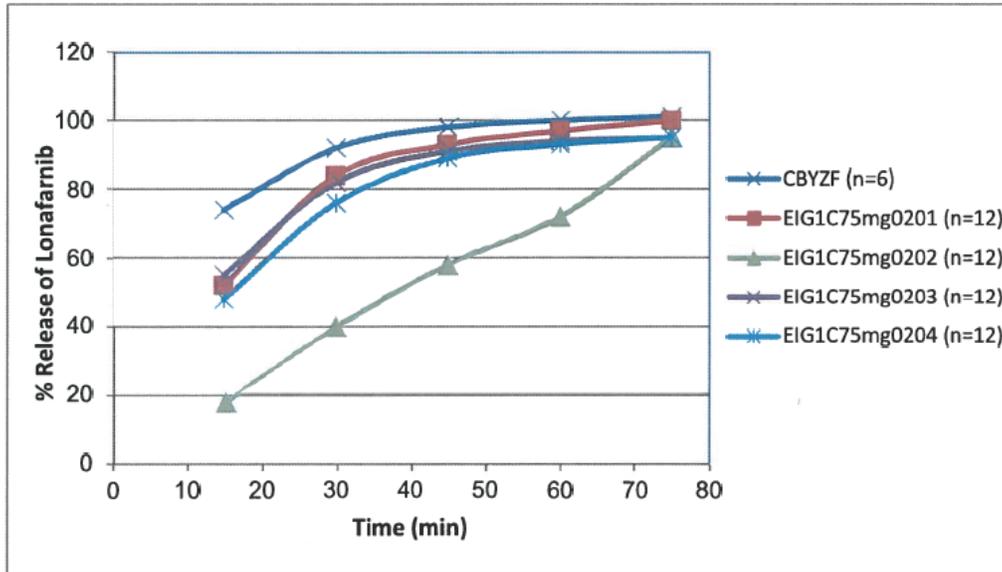


Figure 7: Dissolution profiles of deviant batches of Lonafarnib capsules, 75 mg, at 75 rpm baskets

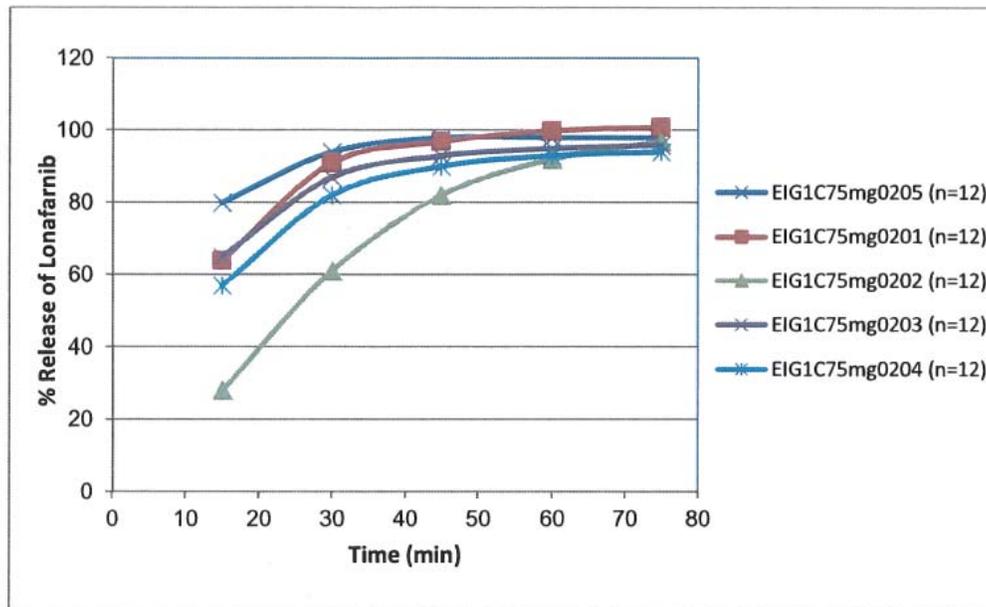


Table 6: Dissolution profile comparison tests

rpm	Time point (min)	Target batch (R _t)	Deviant batch (T _i)			
			EIG1C75m g0201	EIG1C75m g0202	EIG1C75m g0203	EIG1C75m g0204
(b) (4)						
75 (Target batch# EIG1C75 mg0205)	15	80	64	28	65	57
	30	94	91	61	87	82
	45	98	97	82	93	90
	60	98	100	92	95	93
	Infinity	98	101	97	95	94
	Similarity factor f2		56	27	55	45

Similarity factors (f₂) analysis demonstrated that dissolution at (b) (4) rpm can differentiate the differences between the target and aberrant formulations, i.e. variability in formulations and process. However, dissolution test at 75 rpm, could discriminate between the formulation EIG1C75mg202 (b) (4) and the formulation (b) (4) resulted in lower f₂ value when compared to the target formulation. In case of formulation EIG1C75mg0202, (b) (4) which leads to slower dissolution rate. In case of formulation EIG1C75mg0204, when (b) (4) particle size is expected which further delayed dissolution rate. For two other formulations EIG1C75mg0201 and EIG1C75mg0203, f₂ values are 56 and 55, respectively. Although dissolution at (b) (4) rpm could discriminate all the variability mentioned above, the applicant preferred 75 rpm basket rpm over (b) (4) rpm basket as 75 rpm basket resulted in faster dissolution rate and at 75 rpm a plateau of drug dissolved can be reached at 45 minutes with no obvious increase in the release from 45, 60 minutes and infinity.

Reviewer’s assessment:

Dissolution method demonstrated complete release of the drug from the proposed formulations, i.e. Lonafarnib capsules, 50 mg and 75 mg at 30 minutes with less variability. Discriminating ability of the developed dissolution method demonstrated that the dissolution method has discriminating ability to differentiate formulation (b) (4) and process variables (b) (4)

Dissolution acceptance criterion:

The applicant provided dissolution data of the clinical and registration batches. Please refer to the Appendix 1 for the individual dissolution release data for Lonafarnib capsules, 50 mg and 75 mg used in phase 3 clinical studies location.

Please refer to the Appendix 2 for detail information of the IR and applicant’s response.

Dissolution Profiles and Acceptance Criteria

The Applicant has provided the dissolution data of Lonafarnib capsules using apparatus I, 0.2% SLS in D.I. water, 75 rpm, 900 mL at different time points (i.e. 15, 30, 45 and 60). Dissolution study was conducted using the clinical batches. From the dissolution it is observed that more than (b) (4) % drug was released at 30 minutes and there is not much variability is observed in the data. Therefore, the proposed dissolution acceptance criteria of Q= (b) (4) % in 30 minutes is acceptable.

The table below is showing the batches used in clinical studies-

Highlight Key Outstanding Issues from Last Cycle: None.

Reviewer’s Assessment: Overall, the proposed dissolution method and acceptance criterion as described below is acceptable and the NDA 213969 is **adequate** for approval.

The approved dissolution method and acceptance criterion-

Apparatus	Dissolution medium	Dissolution medium volume (mL)	RPM	Dissolution medium temperature (°C)	Dissolution acceptance criterion
USP apparatus I (basket)	0.2% sodium lauryl sulfate (SLS) in water	900	75	37.0	Q= (b) (4) in 30 minutes

Signature Block

Primary Biopharmaceutics Reviewer Name:

Kamrun Nahar, PhD.

Secondary Biopharmaceutics Reviewer Name:

Tapash Ghosh, Ph.D.

Appendix 1

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Appendix 2

Information request 1:

Biopharmaceutics IR comments for the NDA 213969-

1. Reference is made to your NDA 213969. We could not locate the complete profile at different time point of the individual dissolution test data of the formulations used in the clinical studies (both commercial and nearly identical to commercial formulations). Please provide the location of that data. If not already submitted, please submit the data.
2. Provide us the tabulated dissolution data of the comparative dissolution tests of Lonafarnib capsules, 50 mg and 75 mg with differences in capsule shells (Module 3.2.P.2., Drug Product, Figure 1 and 2)
3. Provide us the list of the Lonafarnib capsules, 50 mg and 75 mg batches number of the identical commercial and nearly identical to commercial batches and in which clinical studies they were used including clinical study phase number.
4. Provide us the bridging information between the formulation in the drug product development stage up to commercial formulation.
5. Dissolution method:
 - a. Provide us the solubility data of the drug substance over the physiologic pH range.
 - b. A list of the critical material attributes (CMAs) and critical process parameters (CPPs) affecting dissolution.
 - c. You did not provide the discriminating ability of the dissolution method. Please 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., f_2 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.

Applicant's response: <\\cdsesub1\evsprod\nda213969\0008\m1\us\111-info-amend\qual-info-amend-2020423.pdf>

Reviewer's assessment:

The applicant provided dissolution method development report and discriminating ability of the developed method. The dissolution data of the clinical batches that the applicant provided did not have individual unit data. Therefore, the applicant was asked to provide individual unit data in the IR2.

Information request 2:

1. We acknowledge that you have submitted the dissolution data of the clinical batches of Lonafarnib capsules for both strengths, 50 mg and 75 mg. However, you did not provide the individual vessel data of each batch. Therefore, provide dissolution data in the QC dissolution method, multi-point dissolution data (n=12), % average data and %CV 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. An example of an excel sheet is given below-

Example - Reporting of individual vessel dissolution data

Cell A1 – Identifying Batch/Lot Label, and dissolution method/media used

	A	B	C	D	E	F	G	H	I	J
1	Test lot 12345 (QC method/QC media)									
2		1	2	4	6	8	10	12		
3	1	3	15	62	98	99	99	98		
4	2	3	15	64	94	92	95	95		
5	3	3	9	37	80	96	97	97		
6	4	4	13	44	79	97	98	99		
7	5	3	12	39	71	96	98	98		
8	6	3	14	60	98	97	99	99		
9	7	4	13	44	82	93	98	98		
10	8	5	22	89	97	98	97	97		
11	9	4	16	64	96	98	96	96		
12	10	4	14	57	98	96	99	99		
13	11	4	16	63	96	96	97	97		
14	12	6	22	87	96	93	96	96		
15										
16										
17										
18										
19										
20										
21										
22										

Cell A2 – blank

Individual Unit Number (starting from cell A3 numerical values signifying the test unit)

Use one sheet for each unique batch/lot. Label accordingly in Cell A1

Sampling Times (starting from cell B2 numerical values indicating collection times (minutes or hours))

Dissolution Data (starting from cell B3 numerical values indicating percent drug release)

Sheet1 Sheet2 Sheet3

Follow the instructions provided in “Specifications for File Format Types Using eCTD Specifications” – updated March 2, 2017 (link below).

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf>

2. In your response to the Biopharmaceutics IR dated April 23, 2020, you have provided a table summarizing the clinical batches for Lonafarnib capsules, 50 mg and 75 mg. From the Table 1 clearly identify which batch are identical and nearly identical to the clinical batches.
3. Dissolution acceptance criterion:
In general, for immediate release products, the selection of the acceptance criterion time point should be where Q=80% dissolution occurs or the plateau of drug

dissolved is reached for a routine quality control test for batch-to-batch consistency, considering the setting of the dissolution acceptance criterion is based on USP Level 2 testing (n=12) and therefore sometimes Level 2 testing and occasional Level 3 testing may be needed. Therefore, your proposed dissolution acceptance criterion of “Q= $(b) (4)$ % LC in $(b) (4)$ minutes” is not acceptable.

We recommend the following dissolution acceptance criterion:

Q $(b) (4)$ % LC in 30 minutes.

We request that you acknowledge your acceptance of the recommended acceptance criterion and update your drug product release and stability specifications accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised dissolution specification in your stability program through your proposed expiry period.

Applicant's response: <\\cdsesub1\evsprod\nda213969\0008\m1\us\111-info-amend\qual-info-amend-2020423.pdf>

Reviewer's assessment:

The applicant provided individual unit data of the clinical and registration batches and accepted dissolution acceptance criterion. Therefore, the response is adequate



Kamrun
Nahar

Digitally signed by Kamrun Nahar

Date: 6/23/2020 05:30:51PM

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Tapash
Ghosh

Digitally signed by Tapash Ghosh

Date: 6/23/2020 07:20:54PM

GUID: 508da7230002a2433ddcef616ca190df

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/

HITESH N SHROFF

09/28/2020 01:15:34 PM

This NDA is recommended for "Approval" from the OPQ drug product perspective.