

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208462Orig1s000

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Amit Mitra, CMC Reviewer
Office of New Drug Product (CDER/OPQ/ONDP/DNDPI/NDPBII)
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FROM: FDA
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Through: David Keire, Lab Chief, Branch 1
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SUBJECT: Methods Validation Report Summary

Application Number: 208462

Name of Product: Ninlaro (ixazomib) capsules, 2.3 mg, 3.0 mg, 4.0 mg

Applicant: Millennium Pharmaceuticals, Inc..

Applicant's Contact Person: Melissa Anderson, RAC, Directory Regulatory Affairs

Address: 40 Landsdowne Street, Cambridge, MA USA 02139

Telephone: 617-444-2209

Date Methods Validation Consult Request Form Received by DPA: 8/14/2014

Date Methods Validation Package Received by DPA: 8/14/2014

Date Samples Received by DPA: 9/10/2015

Date Analytical Completed by DPA: 10/30/2015

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments: See attached summary for analyst comments and results.



Date: October 30, 2015
To: Amit Mitra, CMC Reviewer, ONDP
Through: David Keire Ph. D, Acting Lab Chief, Branch I, Division of Pharmaceutical Analysis
From: Diem (Cindy) Ngo, Michael E. Hadwiger, Ph.D.
Subject: Evaluation of NDA 208462 quality control and regulatory purposes.

Link to analyst's worksheets: <http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880c09090>

Background:

Millennium Pharmaceuticals, maker of Ninlaro (ixazomib) drug product (2.0, 3.0 and 4.0 mg capsules) – submitted a validation package which utilized HPLC-UV and XRPD analytical methods to characterize either the drug. DPA was requested to evaluate these methods for quality control and regulatory purposes. The methods evaluated were:

- 1) 3.2. S.4.2 Analytical Procedures for Assay and Impurities by reversed-phase HPLC, *MLN9708-29278 Ver. 1.0, page 1-8*:
- 2) 3.2. S.4.2 Analytical Procedures for (b) (4) Impurity by Chiral HPLC, *MLN9708-(b) (4) Ver. 1.0, page 1-6*:
- 3) 3.2. S.4.2 Analytical Procedures for Identification and Ixazomib Content by HPLC *MLN9708-29279 Ver. 1.0, page 1-8*.
- 4) 3.2. S.4.2 Analytical Procedure for Ixazomib Citrate (b) (4)
- 5) 3.2. P.5.2 Analytical Procedures- Identification, Assay, and Related Substances by HPLC, *MLN9708-(b) (4) Ver. 1.0, page 1-9*.
- 6) 3.2. P.5.2 Analytical Procedures- Dissolution with HPLC, *MLN9708-29290 Ver. 1, page 1-7*.

Conclusion:

- Based on these results, all listed methods used for 2.3 mg or 4.0 mg Ixazomib capsules were acceptable for quality control and regulatory purposes.

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/s/

MICHAEL E HADWIGER
11/12/2015
MV Final Report for NDA 208462

DAVID A KEIRE
11/12/2015



Recommendation: Approval, pending an approval facility recommendation.

NDA 208462 Review #1

Drug Name/Dosage Form	NINLARO (ixazomib) capsules
Strength	2.3 mg, 3.0 mg, 4.0 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Millennium Pharmaceuticals, Inc.
US agent, if applicable	None

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0000 (1)	7/10/2015	All Disciplines
0005 (6)	8/7/2015	Drug Product
0008 (9)	8/21/2015	Biopharmaceutics
0010 (11)	9/1/2015	Drug Product
0011 (12)	9/9/2015	Drug Product
0012 (13)	9/9/2015	Drug Product
0013 (14)	9/15/2015	OTR - Sample request for method validation
0018 (19)	10/1/2015	Drug Substance, Process, and Micro
0022 (23)	10/9/2015	Drug Substance
0023 (24)	10/9/2015	Drug Product
0025 (27)	10/15/2015	Drug Product
0026 (28)	10/15/2015	Application Technical Lead
0027 (29)	10/23/2015	Process
0028 (30)	10/23/2015	Drug Product
0029 (31)	10/26/2015	Application Technical Lead

QUALITY REVIEW TEAM

DISCIPLINE	REVIEWER	BRANCH/DIVISION	REVIEW RECOMMENDATION
Drug Substance	Katherine Windsor	Branch I/DNDAP1/ONDP	Approval
Drug Product	Amit Mitra	Branch II/DNDP1/ONDP	Approval
Process	Diane Goll	Branch II/DPA1/OPF	Approval
Microbiology	Diane Goll	Branch II/DPA1/OPF	Approval
Facility	Steve Hertz	Branch 1/DIA/OPF	Pending
Biopharmaceutics	Gerlie Gieser Okpo Eradiri	Branch 1/DB/ONDP	Approval
Regulatory Business Process Manager	Rabiya Laiq	Branch1/DRBPMI/OPRO	NA
Application Technical Lead	Janice Brown	Branch II/DNDP1/ONDP	Approval, pending an approval recommendation from the facility reviewer
Laboratory (OTR)	None assigned	None	NA
ORA Lead	None assigned	None assigned	NA
Environmental Assessment (EA)	Amit Mitra	Branch II/DNDP1/ONDP	Categorical exclusion accepted

Table of Contents

Table of Contents	3
Quality Review Data Sheet	4
Executive Summary	5
Primary Quality Review	12
ASSESSMENT OF THE DRUG SUBSTANCE	12
2.3.S DRUG SUBSTANCE	12
ASSESSMENT OF THE DRUG PRODUCT	35
2.3.P DRUG PRODUCT EXECUTIVE SUMMARY	35
R.2 Comparability Protocols	63
ASSESSMENT OF THE PROCESS	64
ASSESSMENT OF THE FACILITIES	108
2.3.S DRUG SUBSTANCE	108
2.3.P DRUG PRODUCT	109
ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION	112
ASSESSMENT OF MICROBIOLOGY	123
2.3.P.7 Container/Closure System	123
A APPENDICES	123
ASSESSMENT OF ENVIRONMENTAL ANALYSIS	125
I. Review of Common Technical Document-Quality (Ctd-Q) Module 1	126
Labeling & Package Insert	126
II. List of Deficiencies To Be Communicated	135
III. Attachments	135

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type IV		(b) (4)	4	None	Adequate information provided in the NDA
	Type IV			4		Adequate information provided in the NDA
	Type III			Adequate	Jennifer H Nguyen 10/21/2015	None

A. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		(b) (4)
IND	104482	MLN9708 Capsules

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

I. Recommendations

NDA 208462 is recommended for approval from a product quality perspective, pending an approval facility recommendation.

Include the following statement in the action letter:

A 36 month shelf life is granted for Ixazomib capsules stored at room temperature not to exceed 30°C (86° F).

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: Not Applicable
2. Action letter language, related to critical issues such as expiration date:
Refer to section I above.
3. Benefit/Risk Considerations

The risks associated with product quality have been described and adequately controlled to assure the quality of the drug product and consistent clinical performance. Based on the data provided, the quality of the ixazomib drug product is considered acceptable. Pending an approval recommendation from the Office of Process and Facilities, there are no unresolved quality issues which might have a negative impact on the risk benefit of this product.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no product quality post marketing commitments or agreements.

II. Summary of Quality Assessments

A. Drug Substance [ixazomib citrate] Quality Summary

Ixazomib is a reversible selective inhibitor of the $\beta 5$ site of the 20S proteasome

(b) (4)

1. Chemical Name or IUPAC Name/Structure

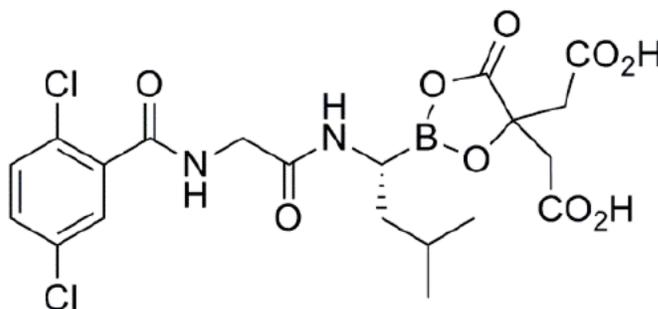
Ixazomib citrate contains one chiral center and has been unambiguously determined as the R-stereoisomer.

(b) (4)

(b) (4)

Ixazomib is highly soluble across a physiological pH range (1.2 to (b) (4) The

chemical name of ixazomib citrate is 1,3,2-dioxaborolane-4,4-diacetic acid, 2-[(1*R*)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]-5-oxo- and has the following structure:



Molecular Formula: C₂₀H₂₃BCl₂N₂O₉

Molecular Weight: 517.12 g/mol

2. Properties/CQAs Relevant to Drug Product Quality

(b) (4)

3. List of starting materials

(b) (4)

4. Suppliers of starting materials (site)

The suppliers of the starting materials was not provided in the NDA submission.

5. Summary of Synthesis

(b) (4)

6. Process

a. Sterilization processes of the sterile bulk, as applicable

Not applicable. The drug substance is not sterile.

b. Critical equipment

There is no critical equipment used in the manufacture of the drug substance. There are

(b) (4)

7. Container Closure

Ixazomib citrate is packaged in a 68-ounce high-density polyethylene (HDPE).

(b) (4)

8. Retest Period & Storage Conditions

The retest period for ixazomib citrate is (b) (4) months when stored at $5\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$.

B. Drug Product [ixazomib capsules] Quality Summary

1. Strength

4 mg, 3 mg, and 2.3 mg hard gelatin capsules

2. Description/Commercial Image

NINLARO (ixazomib) capsules for oral use contain 4 mg, 3 mg, or 2.3 mg of ixazomib equivalent to 5.7 mg, 4.3 mg, or 3.3 mg of ixazomib citrate, respectively. Inactive ingredients include microcrystalline cellulose, magnesium stearate, and talc. Capsule shells contain gelatin and titanium dioxide. The 4 mg capsule shell contains red and yellow iron oxide, the 3 mg capsule shell contains black iron oxide, and the 2.3 mg capsule shell contains red iron oxide. The printing ink contains shellac, propylene glycol, potassium hydroxide, and black iron oxide.

3. Summary of Product Design

The applicant developed the Quality Target Product Profile (QTPP) of the quality characteristics for ixazomib capsules (see table 1).

Table 1: Quality Target Product Profile for Ixazomib Capsules

Product Attribute	Commercial Target
Drug Substance Category	Small molecule pro -drug
Route of Administration	Oral
Dosage Form	Capsule
Dose Strength	2.3 mg, 3.0 mg, 4.0 mg
Dose Frequency	One unit dose on days 1, 8 and 15 of 28-day cycle
Unit Description	At least 2 unique distinguishers (size, color, printing) between any two dose strengths
Compendia Requirements	Excipients must meet compendia requirements: USP/NF, Ph. Eur., and JP
Drug Release Profile	Immediate release
Drug Product Quality	Meets USP Chapter 2 quality attributes
Container Closure System	Blister pack
Shelf Life	3 years
Storage Condition	Room temperature at ICH climatic zones I, II, III, and IV
Degradants and Related Substances	Below safety ICH threshold or qualified within commercial specifications. Meets regulatory guidelines for genotoxic impurities from process or product
Bioburden	Meets compendia requirements: USP/NF, Ph. Eur., and JP

The quality attributes of ixazomib capsules based on the QTPP impact to drug efficacy and safety profile were described. The drug product quality attributes that are impacted by raw materials and/or the manufacturing process are managed by in-process controls, incoming material specifications, facility environmental controls and drug product specifications.

4. List of Excipients

The excipients in the ixazomib capsule formulation are microcrystalline cellulose, talc, and magnesium stearate. (b) (4)

(b) (4)

5. Process Selection (Unit Operations Summary)

The commercial batch size for the 2.3 mg and 3.0 mg ixazomib capsules is (b) (4) capsules, corresponding to a batch size of (b) (4) kg. The proposed commercial batch size for the 4.0-mg ixazomib capsules is (b) (4) capsules, corresponding to a batch of (b) (4) kg.

Ixazomib 2.3 mg, 3.0 mg, and 4.0 mg capsules are manufactured (b) (4)

(b) (4)

a. Critical equipment

No critical equipment was identified in the drug product review.

6. Container Closure

The primary container closure for ixazomib capsules is (b) (4) polyvinyl chloride-aluminum/aluminum (PVC-Al/Al) push through blister containing one capsule per blister. (b) (4)

(b) (4)

7. Expiration Date & Storage Conditions

A 36 month shelf life is granted for Ixazomib capsules stored at room temperature not to exceed 30°C (86° F). Stability studies were conducted at long-term conditions of 5 °C, 25 °C/60% RH and 30 °C/75% RH, and an accelerated storage condition, 40 °C/75% RH. All registration stability studies have been completed through six months at the accelerated storage condition, and will be continued through 48 months at the long-term storage conditions, with 24 months of real time data provided in the submission.

8. List of co-packaged components

There are no co-packaged components supplied with Ixazomib capsules.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	NINLARO
Non Proprietary Name of the Drug Product	Ixazomib capsules
Non Proprietary Name of the Drug Substance	Ixazomib
Proposed Indication(s) including Intended Patient Population	NINLARO is a proteasome inhibitor indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.
Duration of Treatment	Once a week on Days 1, 8, and 15 of a 28-day treatment cycle Continued until disease progression or unacceptable toxicity
Maximum Daily Dose	4 mg
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Classification: 3

- *Drug Substance*: high solubility/low permeability [solubility at 37°C, pH 1.2 is 0.61 mg/mL (as ixazomib), solubility increases as pH increases; absolute bioavailability is 57%]
- *Drug Product*: rapidly dissolving (on average, (b) (4)% within (b) (4) minutes) across the physiologic pH range.

2. Biowaivers/Biostudies

- *Biowaiver Requests* – Not Applicable
- *PK studies* - Refer to the assessment of the Clinical Pharmacology reviewer
- *IVIVC* - none

The Applicant's proposed dissolution method and acceptance criterion were evaluated and found acceptable. The NDA is recommended for approval from a Biopharmaceutics perspective.

USP Apparatus	Spindle Rotation	Medium/ Volume/Temperature	Acceptance Criterion
1, Basket (40 mesh)	100 rpm	500 mL 0.1 N HCl, pH 1.2 at 37 ± 0.5 °C	Q = ^(b) ₍₄₎ % at 20 min

E. Novel Approaches - None

F. Any Special Product Quality Labeling Recommendations: None

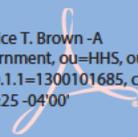
G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Janice Brown, M.S.
30-Oct-2015

Digitally signed by Janice T. Brown -A
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
 0.9.2342.19200300.100.1.1=1300101685, cn=Janice T. Brown -A
 Date: 2015.10.30 21:10:25 -04'00'



Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

For the drug substance:

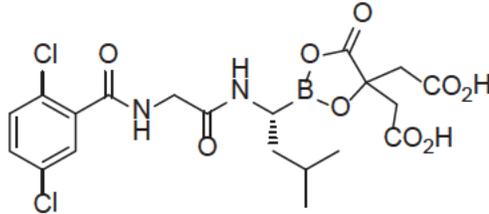
USAN: Ixazomib citrate

Chemical name: 1,3,2-Dioxaborolane-4,4-diacetic acid, 2-[(1*R*)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]-5-oxo-

Company or laboratory code(s): MLN9708^{(b) (4)}; MLN9708; ^{(b) (4)}

^{(b) (4)} MLN2238 citrate ester

CAS number: 1239908-20-3



Molecular Formula: C₂₀H₂₃BCl₂N₂O₉^{(b) (4)}

Molecular Weight 517.12

Description: ^{(b) (4)}

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Reviewer's Assessment: Adequate. Ixazomib citrate is a BCS Class III compound and a (b) (4)



2.3.S.2 Manufacture

S.2.2 Description of the Manufacturing Process and Controls

1. Is the commercial manufacturing process adequately described and controlled to ensure consistent manufacturing of acceptable drug substance batches?
2. Is there any proposal for online/at line/in line monitoring technologies for routine commercial production that allows for real-time process monitoring and control? If so, is it acceptable?



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Reviewer Dr. Gerlie Gieser confirmed that the proposed particle size acceptance criteria are reasonable, considering the influence of this attribute on both dissolution and chemical stability (email response, 23-SEP-2015).

The proposed specifications are consistent with those provided in the pre-NDA meeting package for IND 104482 (20-AUG-2014). Several of the individual specifications – (b) (4) impurity, unspecified impurities, elemental impurities – were commented on in the meeting minutes (18-SEP-2014), and the assessment in this review is consistent with our initial recommendations. The applicant also proposed the exclusion of the following tests/specifications: (b) (4)

(b) (4) We agreed that their justifications appeared reasonable at the time; however the applicant was asked to provide supporting data upon NDA submission. The data are provided in the submission (see Batch Analysis below) and support the exclusion of the respective tests.

10. Are all the analytical procedures appropriately described and validated for their intended use?

Analytical Procedures

The following analytical methods were validated for use in ixazomib citrate release testing: identification and ixazomib content (HPLC), assay and impurities (HPLC), (b) (4) impurity (HPLC), residual solvents (GC), particle size, (b) (4), and elemental impurities (b) (4)

Validation/Verification of Analytical Procedures

All of the HPLC and GC quantitation methods were validated with respect to specificity, accuracy, precision, linearity, solution stability, and robustness. LOD and LOQ were also established. Sufficient results were provided. The determined solution stabilities were as follows: For the HPLC method for ixazomib content (b) (4) also used for the second identification test), the ixazomib working standard and LOQ solutions and the DS ID solution were all stable for 16 days under refrigeration. The DS spiked sample solution was stable for 7 hours under refrigeration. For the HPLC method for assay and impurities (b) (4) the working standard solution is stable for 8 days, the LOQ solution is stable for 1 day, and the spiked sample solution is stable for 5 days, all at 5 °C. For the HPLC method for (b) (4) content determination (TMI-175), both the standard and sample solutions are stable for 7 days when stored at 5 °C. For the GC method for residual solvents (b) (4) (b) (4) both the working standard and sample solutions are stable for 6 days at room temperature. (b) (4) was identified as a parameter affecting the % recovery of (b) (4) based on robustness testing results.

(b) (4)

(b) (4)

The ICP-MS method for elemental impurities analysis (b) (4) was validated with respect to specificity, accuracy, precision, linearity, solution stability, and LOQ; this is acceptable. Levels of 18 metals were surveyed before paring down the list of metals for routine analysis (b) (4)

FDA methods verification was requested for the (b) (4) and the HPLC methods for ixazomib content, (b) (4) impurity, and assay and impurities; results are pending.

(b) (4)

Drug Substance Comment #1 of Mid-Cycle Communication (24-SEP-2015):

We acknowledge the provided discussion and data for the ixazomib citrate, ixazomib, and the ixazomib citrate (b) (4) reference standards. Clarify what other reference standards are used in testing the drug substance (i.e., standards for specified impurities (b) (4) and the corresponding qualification procedures.

Applicant Response #1 (01-OCT-2015):

The applicant qualified impurity reference standards for the three degradation products specified on the proposed specifications for ixazomib citrate (i.e., (b) (4) using the following tests (data not provided): appearance, ID (by NMR and MS), impurities (by HPLC), (b) (4) and residual solvents. These impurity reference standards were used for ICH method validation activities and to determine relative response factors.

FDA Evaluation of Response #1: *Acceptable.*

Reviewer's Assessment: Adequate. The ixazomib citrate (DS), ixazomib, DS (b) (4) and specified degradant (b) (4) reference standards were characterized using orthogonal analytical techniques, which supported the proposed structures (data not provided). In addition to structural elucidation, the identity and purity of each standard were determined to be adequate.

2.3.S.6 Container Closure System

13. Is the proposed container closure system(s) for commercial packaging of the drug substance adequate to protect the drug substance from the environment (oxygen, moisture, microorganism, etc.) during the storage?

The drug substance is packed in (b) (4). The applicant stated that the (b) (4).

Reviewer's Assessment: Adequate. The proposed container closure system appears to adequately (b) (4).

2.3.S.7 Stability

14. What is the proposed retest period for the drug substance? Do the drug substance stability data support the proposed retest period and storage conditions in the

- commercial container closure system? How does statistical evaluation of the stability data, if any and any observed trends support your proposed retest period?
15. Are the post-approval stability protocols and other stability commitments for the drug substance satisfactory?

The applicant provided 6 months of accelerated data (25 °C/60% RH) and 24 months of long-term data (5 °C) for three registration batches (102031, 102032, and 102033). Six months of accelerated and 36 months of long-term supportive stability data were provided for two clinical batches (100841 and 101296) of ixazomib citrate, along with 6 months each of long-term and accelerated data for a third clinical batch (101636), manufactured (b) (4)

processes cannot be compared. Also, it does not appear that long-term stability testing will continue for these three clinical lots. Three months of long-term and accelerated stability data were provided for three PPQ lots. Based on this data, the applicant initially requested a (b) (4) month retest date. According to ICH Q1E, the maximum retest period that could be g ed based on this amount of data would be (b) (4) months. The applicant was notified of this in an information request as follows.

Drug Substance Comment #2 of Mid-Cycle Communication (24-SEP-2015):

We acknowledge your proposal of a (b) (4)-month retest period for ixazomib citrate drug substance. However, the long-term data provided (24 months for three registration batches) only support a (b) (4)-month retest period. Adjust the retest period for the drug substance accordingly.

Applicant Response #2 (01-OCT-2015):

The (b) (4)-month retest period proposed for ixazomib citrate is based on the available stability data from clinical, registration stability and PPQ lot stability studies, including up to 36 months of long-term data. Considering the Agency's comment, the Applicant proposes a retest period of (b) (4) months for ixazomib citrate, supported by real-time data from the representative clinical lot studies in addition to the registration stability studies.

FDA Evaluation of Response #2: *No new stability data were provided. The available data (24 months for three registration batches) only support a (b) (4)-month retest period, given that ixazomib citrate is a refrigerated drug substance.*

Drug Substance Information Request (05-OCT-2015):

We acknowledge your proposal of a (b) (4) month retest period for ixazomib citrate drug substance. However, because this is a refrigerated drug substance, the long-term data provided (24 months for three registration batches) only support a (b) (4)-month retest period. Adjust the retest period accordingly.

Applicant Response #2 (01-OCT-2015):

The Applicant agrees with the Agency's recommendation and will adjust the retest period of ixazomib citrate drug substance to (b) (4) months. Additionally, please note that these two sections [3.2.S.7.1 and 2.3.S.7] now include 12-month stability data summary update for PPQ lots (for your information only).

FDA Evaluation of Response #2: *Acceptable. The applicant adjusted the retest period to (b) (4) months, in keeping with ICH Q1E.*

The stability specifications include routine testing of appearance, assay, impurities, ixazomib content, (b) (4) impurity, (b) (4) particle size, and microbial testing (TAMC, TYMC, absence of E. coli, and endotoxins); the acceptance criteria are consistent with the release specifications. No trending was observed, and there were no impurities present above the LOQ, except for the RRT (b) (4) impurity; this mixture (b) (4) (% area) and did not increase over time. All data remained well within specifications.

Long-term stability testing for the three registration batches and the three PPQ batches will continue up to 60 months. The applicant also committed to monitoring one annual batch according to an acceptable stability protocol. (“The resulting data from these studies [on future annual batches] will be submitted at the time intervals and in the format specified by the Agency.”)

Based on the applicant’s stress studies, ixazomib citrate is (b) (4)
(b) (4)

Reviewer’s Assessment: Adequate. The applicant has proposed a (b) (4)-month retest period for ixazomib citrate drug substance, based on 6 months of accelerated data and 24 months of long-term data for three registration batches. Supportive stability data are also provided for three clinical batches (b) (4)
(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer’s Assessment and Signature: I recommend approval based on the drug substance information presented in this application.
Katherine Windsor, Ph.D., 20-OCT-2015

Supervisor Comments and Concurrence: I concur.
Kasturi Srinivasachar, Ph.D.
Branch Chief (Acting) Division of ND API, ONDP
10/23/2015

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT EXECUTIVE SUMMARY

The ixazomib capsule is recommended for APPROVAL from the standpoint of the drug product reviewer. Based on the provided stability data, an expiration dating period of 36 months is tentatively granted for the drug product when stored at room temperature not exceeding 30°C (86° F).

Drug Product: The proposed commercial drug product is an immediate release capsule dosage form available in three different strengths. A) 2.3 mg ixazomib gelatin capsule: light pink, size 4, imprinted with the Takeda logo on the cap and 2.3 mg on the body in black ink; B) 3.0 mg gelatin capsule: light grey, size 4, imprinted with the Takeda (b) (4) logo on the cap and 3.0 mg on the body in black ink; C) 4 mg gelatin capsule: Light orange, size 3, imprinted with the Takeda (b) (4) logo on the cap and 4.0 mg on the body in black ink.

(b) (4)

The particle size of ixazomib citrate is controlled at D₅₀ and D₉₀. The ixazomib capsules are manufactured (b) (4)

Upon request the sponsor provided the control strategy for the functional properties of the excipients and those are satisfactory according to the current regulatory standard.

Ixazomib capsules are blister packed (b) (4)

(b) (4)

The specification of the drug product includes: 1) Appearance, 2) ID by UV and HPLC, 3) Content of by HPLC, 4) Uniformity of content by USP<905>, HPLC, 5) Related substances by HPLC. (b) (4) The sponsor has provided adequate justification to exclude Enantiomer, Ixazomib content, elemental impurities, and microbial limits (pending satisfactory microbiology review).

All drug product related CMC review issues have been resolved from the CMC reviewer's point of view except (b) (4)
(b) (4)

2.3.P.1 Description and Composition of the Drug Product

Ixazomib capsules are available in 2.3, 3.0, and 4 mg strengths. Ixazomib capsules, 2.3 mg, are size 4 capsules composed of light pink red capsules black printing of 2.3 mg on body and Takeda logo on the cap. The 3.0 mg capsules are size 4, light grey color with 3.0 mg and Takeda logo on the body and cap. The 4 mg capsules are of size 3 light orange capsules printed with black ink, 4.0 mg on body and Takeda logo on the cap.

Composition of the 2.3-mg Ixazomib Capsules

Components	mg per Capsule	% per Capsule	Function	Reference To Standards ^a
Ixazomib citrate (equivalent to ixazomib)	(b) (4) (2.3)	(b) (4)	Active ingredient	In-House
Microcrystalline cellulose ^b	(b) (4)	(b) (4)	(b) (4)	USP/NF, Ph.Eur., JP
Talc	(b) (4)	(b) (4)	(b) (4)	USP/NF, Ph.Eur., JP
Magnesium stearate	(b) (4)	(b) (4)	(b) (4)	USP/NF, Ph.Eur., JP
Total weight	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Imprinted hard gelatin capsule shell	(b) (4)	(b) (4)	(b) (4)	In-House ^c

JP = Japanese Pharmacopeia; NF = National Formulary; Ph.Eur. = European Pharmacopoeia; USP = United States Pharmacopeia.

a When referred to a Pharmacopeia, this means that the current edition of this Pharmacopeia is applied.

c All of the components of the capsule shell are compliant with USP/NF, Ph.Eur., and JP. See Module 3.2.P.4.1 for the non-compendial specifications.

Composition of the 3.0-mg Ixazomib Capsules

Components	mg per Capsule	% per Capsule	Function	Reference To Standards ^a
Ixazomib citrate (equivalent to ixazomib)	(b) (4) (3.0)	(b) (4)	Active	In-House
Microcrystalline cellulose ^b	(b) (4)	(b) (4)	(b) (4)	USP/NF, Ph.Eur., JP
Talc	(b) (4)	(b) (4)	(b) (4)	USP/NF, Ph.Eur., JP
Magnesium stearate	(b) (4)	(b) (4)	(b) (4)	USP/NF, Ph.Eur., JP
Total weight	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Imprinted hard gelatin capsule shell	-	(b) (4)	(b) (4)	In-House ^c

JP = Japanese Pharmacopeia; NF = National Formulary; Ph.Eur. = European Pharmacopoeia; USP = United States Pharmacopeia.

a When referred to a Pharmacopeia, this means that the current edition of this Pharmacopeia is applied.

c All of the components of the capsule shell are compliant with USP/NF, Ph.Eur., and JP. See Module 3.2.P.4.1 for the non-compendial specifications.

Composition of the 4.0-mg Ixazomib Capsules

Components	mg per Capsule	% per Capsule	Function	Reference To Standards ^a
Ixazomib citrate (equivalent to ixazomib)	5.7 (4.0)	(b) (4)	Active	In-House
Microcrystalline cellulose ^b		(b) (4)	Diluent	USP/NF, Ph.Eur., JP
Talc			Glidant	USP/NF, Ph.Eur., JP
Magnesium stearate			Lubricant	USP/NF, Ph.Eur., JP
Total weight				
Imprinted hard gelatin capsule shell			Capsule shell	In-House ^c

JP = Japanese Pharmacopoeia; NF = National Formulary; Ph.Eur. = European Pharmacopoeia; USP = United States Pharmacopoeia.

a When referred to a Pharmacopoeia, this means that the current edition of this Pharmacopoeia is applied.

(b) (4)

c All of the components of the capsule shell are compliant with USP/NF, Ph.Eur., and JP. See [Module 3.2.P.4.1](#) for the non-compendial specifications.

The proposed commercial packaging for ixazomib capsules is a PVC-Al/AL blister pack.

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Applicant's Response:

Reviewer's Assessment: All excipients for the drug product comply with their respective USP/NF monograph, which is acceptable.

2.3.P.2 Pharmaceutical Development

17. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

The reviewer summarizes the Quality Target Product Profile as follows:

- Ixazomib is a small molecule pro-drug
- Formulated for oral administration in a capsule dosage form at 2.3, 3.0 and 4.0 mg strengths. All dosage strengths can be distinguished by at least two distinguishers (size, color, printing).
- 4.0 mg is the recommended starting dose which can be reduced to 3 mg or 2.3 mg before discontinuation if necessary. The capsule strengths can cover the range of recommended doses. Dose frequency: one unit dose on days 1, 8 and 15 of a 28 day cycle.
- Drug substance particle size is controlled for optimum manufacturability, dissolution rate and stability.
- Drug-excipient compatibility

Container Closure System

Prior to final packaging operations, ixazomib capsules will be stored and shipped in a bulk packaging configuration. (b) (4)

(b) (4)

The container closure system proposed for the commercial product consists of polyvinyl chloride-aluminum blisters with aluminum lidding. A brief description of the blister pack is provided below:

Proposed Commercial Packaging Materials for Ixazomib Capsules

Strength	Configuration	Container/Closure
2.3 mg 3.0 mg 4.0 mg	Blister package	(b) (4)

PVC = polyvinyl chloride.

An open dish photostability study was conducted on the ixazomib capsules. There was no increase in degradation products; therefore, a photo-stability study was not conducted in the polyvinyl chloride/aluminum/aluminum (PVC-Al/Al) blister packs.

Capsules:

Components of the hard gelatin capsule shells: Size 4, (b) (4) used for the 2.3 mg strength

Component	mg/capsule	Conforms to
Gelatin	(b) (4)	Ph. Eur., USP/NF, JP
Titanium dioxide	(b) (4)	Ph. Eur., USP/NF, JP, 2008/128/EC, 21 CFR 73
Red iron oxide	(b) (4)	USP/NF, JPE, 2008/128/EC, 21 CFR 73

mg = milligrams

Components of the hard gelatin capsule shells: Size 4, light grey used for the 3.0 mg strength

Component	mg/capsule	Conforms to
Gelatin	(b) (4)	Ph. Eur., USP/NF, JP
Titanium dioxide	(b) (4)	Ph. Eur., USP/NF, JP, 2008/128/EC, 21 CFR 73
Black iron oxide	(b) (4)	JPE, 2008/128/EC, 21 CFR 73

mg = milligrams

Components of the hard gelatin capsule shells: Size 3, light orange used for the 4.0 mg strength

Component	mg/capsule	Conforms to
Gelatin	(b) (4)	Ph. Eur., USP/NF, JP
Titanium dioxide	(b) (4)	Ph. Eur., USP/NF, JP, 2008/128/EC, 21 CFR 73
Yellow iron oxide	(b) (4)	Ph. Eur., USP/NF, 2008/128/EC, JPE, 21 CFR 73
Red iron oxide	(b) (4)	USP/NF, 2008/128/EC, JPE, 21 CFR 73

mg = milligrams

The components of the imprinting ink and their quality standards are provided below:

(b) (4)

Component	Conforms to
(b) (4)	Ph. Eur. and USP/NF
(b) (4)	Ph. Eur. and USP/NF
(b) (4)	Ph. Eur. and USP/NF
(b) (4)	Ph. Eur. and USP/NF
(b) (4)	Ph. Eur. and USP/NF
(b) (4)	Ph. Eur. and USP/NF
(b) (4)	Ph. Eur. and USP/NF
(b) (4)	USP/NF

(b) (4)

The applicant accepts hard gelatin capsules based on their certificates of analyses. The certificate of analyses mainly contains dimensional, weight, disintegration, visual, microbial limits, (b) (4)

(b) (4)

Reviewer's Assessment:
The applicant discussed the impact of (b) (4), particle size and bulk density on the manufacturability and product performance with sufficient data.

Magnesium stearate is documented to meet the NF standard. However, the applicant failed to describe the control strategy for its functional property such as specific surface area.

(b) (4)

Talc: The applicant indicated that the excipient meets compendial specification. However, the compendial specification does not include functional properties like particle size, surface area, and densities.

Hard gelatin capsule shells: The certificate of analyses indicates that (b) (4)

(b) (4)

All the deficiencies above were combined as follows and sent to the sponsor via an IR letter:

(b) (4)

2.3.P.5 Control of Drug Product

19. Is the drug product specification adequate to assure the identity, strength, quality, purity, and potency, and bioavailability of the drug product so that future commercial production batches are comparable to the pivotal clinical batches for the clinical performance in terms of the safety and efficacy

20. Are all the analytical procedures appropriately described and validated for their intended use?

Applicant's Response:

Ixazomib Capsules (2.3 mg, 3.0 mg, and 4.0 mg) Specification

Test	Analytical Procedure	Acceptance Criteria
Appearance	Visual inspection	<u>2.3 mg</u> : Flesh/ Light pink hard capsule, Size #4 capsule <u>3.0 mg</u> : Light grey hard capsule, Size #4 capsule <u>4.0 mg</u> : Light orange hard capsule, Size #3 capsule Dose strength on body of the capsule,  on cap, printed in black ink
Identification ^a	UV	Consistent with reference standard
	HPLC	Relative retention time (b) (4) consistent with reference standard)
Assay	HPLC	(b) (4) % of label claim
Related Substances	HPLC	<u>Specified Degradation Products</u> (b) (4)
		<u>Unspecified Impurities</u> (b) (4)
(b) (4)	USP <921> Ph. Eur. 2.5.32 (b) (4)	<u>Total Impurities</u> (b) (4)
Uniformity of Dosage Units (Content Uniformity) ^a	HPLC	Conforms to USP <905> Conforms to Ph. Eur. 2.9.40
Dissolution	USP <711> Ph. Eur. 2.9.3 Apparatus I (baskets) at 100 rpm HPLC	Q = (b) (4) at 20 minutes

APPEARS THIS WAY ON ORIGINAL

^a These attributes are tested at release only.

The applicant provided the following test methods for 2.3, 3 and 4 mg capsules. These are: 1) Appearance (by visual inspection); 2) Identification, assay and related substance (by RP-HPLC); 3) Uniformity of dosage units (RP-HPLC, USP<905>); 4) (b) (4); 5) Dissolution (USP<711>, apparatus 1 at 100 rpm, HPLC).

1. Description: Examine visually 5 capsules against white and black backgrounds and record the appearance with respect to color of capsules and markings.

Reviewer's Assessment: Specifications are established for Appearance, ID, Assay, impurities/Degradation Products, Uniformity of Dosage Units, (b) (4) Dissolution. The sponsor also included justification for exclusion of ixazomib (b) (4) ixazomib base content, microbiological limits and elemental impurities in this section.

Appearance: The appearance specification correctly identifies the appropriate strength and fulfils the 21 CFR requirements for identifying marks.

Identification: Two identification methods are utilized by the applicant as recommended by ICH Q6A.

Assay: The assay of ixazomib capsules (as ixazomib) (b) (4) (b) (4) he proposed specification of (b) (4) % has been adopted based upon common pharmaceutical industry practice.

Uniformity of dosage units: The acceptance is set based on the current USP<905> requirement.

Related substances: The applicant identified several degradation products using a stability indicating assay method. The toxicologist was consulted for qualification limits of the specified and unspecified impurities. The toxicologist concluded that all the specified and unspecified impurities on the specification sheet are qualified.

(b) (4)

Dissolution: The appropriateness of the dissolution acceptance criteria was reviewed by the Biopharm reviewer. The dissolution acceptance criteria are satisfactory to the Biopharm reviewer.

The applicant also provided the following justification of exclusion of (b) (4) ixazomib content, elemental impurities, and microbiological limits:

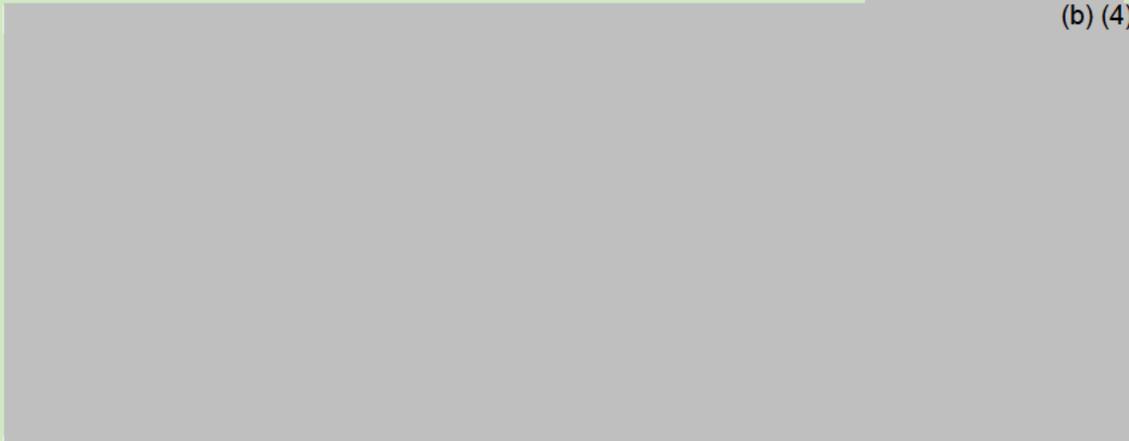
(b) (4)

Ixazomib content: The content of the active boronic acid (ixazomib) was monitored as a release test and on stability for development lots, clinical lots, and the primary registration stability studies. The ixazomib content results for release are consistently below the normal phase HPLC method limit of quantitation of (b) (4)% for batches made using the proposed commercial process. Additionally, the stability data supports the acceptance criteria.

Elemental impurities: The elemental impurities are currently being controlled for the drug substance. The sponsor proposed not to conduct the elemental impurities test for the drug product. The monitoring routine elemental impurities in the drug product are not currently a requirement; therefore, the reviewer has no objection to the applicant's proposal.

Microbial limits: Microbiology reviewer is reviewing the applicant's justification.

Reviewer's comment: The applicant has not included a resolution factor in the system suitability criteria. This is important since the specified impurity (b) (4)
(b) (4)



Since the drug substance is a new molecular entity, a method validation request was submitted to the FDA Methods Validation Laboratory.

21. Is the proposed control strategy for the drug product manufactured at commercial stage acceptable? Is there any residual risk upon implementation of the control strategy at the commercial scale (refer to question #33 of the process section)?

Applicant's Response: Batch analysis data for development and clinical lots of 0.2-



(b) (4)

The applicant conducted forced degradation studies of the drug product and identified the potential degradation products. The degradation products are reported to be also drug substance degradation products. The summary of all potential impurities in the drug product is provided below:

Impurity Name/Code	Source	Control Method

(b) (4)

Reviewer's Assessment: The batch release data is satisfactory to the reviewer.

2.3.P.6 Reference Standards or Materials

22. Are the proposed drug product reference standards acceptable?

(b) (4) the reviewer checked the section 3.2.S.3.2 for their characterization information. All the degradation product characterization information is provided in section 3.2.S.3.2. This section is being reviewed by the drug substance reviewer.

Applicant's Response:

Reviewer's Assessment: See Drug Substance Review for Reference standards information. The sponsor provided the following table of reference standards in the Drug Substance, Reference Standard Section in S5. Those are reviewed with the drug substance; therefore, not reviewed here.

2.3.P.7 Container Closure System

23. Is the proposed container closure system (describe it briefly with diagrams, if available) adequate to protect the product from the environment (oxygen, moisture) to ensure the strength, purity (extractables/leachables), and performance of the drug product through the proposed expiration dating period?



(b) (4)

2.3.P.8 Stability

24. What is the proposed shelf-life for the drug product? Do the product stability studies and data support the proposed shelf life and storage conditions in the commercial container/closure system? Does the statistical evaluation of the stability data and observed trends support the proposed shelf-life?
25. Are the post-approval stability protocols and other stability commitments for the drug product adequate?

Applicant's Response:

The registration batches were manufactured using (b) (4) The drug product batch size ranged from (b) (4) (b) (4) at the commercial manufacturing site. The capsules were blister packed (b) (4) (b) (4) The applicant placed three registration batches on stability. The applicant also provided stability data from one lot of each strength of clinical batches manufactured at the commercial manufacturing site at (b) (4) (b) (4) The applicant also included the bulk packaging stability data, heat and humidity stress studies, photo-stability data, freeze cycling data, heat cycling data from all three strengths. Very similar stability data are available for all three strengths. A summary of the stability studies are included below:

(b) (4)



The applicant is proposing a 36 months shelf life under long term storage conditions at 30° C/75% RH. Based on the stability data, a bulk hold time of 18 months at 5 °C was adopted. The photo-stability data indicate that ixazomib citrate is not light sensitive.

Post-approval Stability Protocol and Stability Commitment

Stability studies are ongoing for three registration batches of the three strengths. The registration stability lots were manufactured at the commercial site using a process that is representative of the commercial process, but not packaged at the commercial packaging site. The first three commercial scale production lots have been manufactured at the commercial site using commercial manufacturing process and packaged at the commercial site will be placed on stability according to the protocol provided below:



OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature: Recommend approval based on satisfactory drug product section review.
Amit K. Mitra, Ph.D/ 29-OCT-2015

Secondary Review Comments and Concurrence: I concur

Olen Stephens, Ph.D. OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII
29-Oct-15

ASSESSMENT OF THE PROCESS

Reviewer's Notes: *Breakthrough Application*

List Submission being reviewed: SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original Submission	07/10/2015
Sequence Number 0018 (<i>Response to IR letter dated 9/24/2015</i>)	10/01/2015
Sequence Number 0027 (<i>Response to IR letter dated 10/16/2015</i>)	10/23/2015
(<i>Response to IR letter dated 10/28/2015</i>)	10/30/2015
<i>Teleconference Response 10/30/2015 (Response to IR letter dated 10/30/2015)</i>	11/02/2015

P.3 Manufacture

Batch Formula

The proposed commercial batch size for the 2.3- and 3.0-mg ixazomib capsules is (b) (4)
 (b) (4)
 The batch formulas for the 2.3-, 3.0-, and 4.0-mg ixazomib capsules are presented low.

Component	2.3 mg Capsule (g)	3.0 mg Capsule (g)	4.0 mg Capsule (g)
Ixazomib citrate ^{a,e}	(b) (4)		
Microcrystalline cellulose ^{b,f}			
Talc ^f			
Magnesium stearate ^f			
Target batch size			
Imprinted ^c hard gelatin capsule shell ^{d,e}	(b) (4)		
Units			

	Size, Color	(b) (4)	4, Light grey	3, Light orange
--	--------------------	---------	---------------	-----------------

a (b) (4)

(b) (4)

(b) (4)

Imprinted with dose strength and Takeda (b) (4) logo.

^d All of the components of the capsule shell are compliant with USP/NF, Ph.Eur., and JP.

^e See Module 3.2.P.4.1 for the non-compendial specifications.

^f USP/NF, Ph.Eur., and JP

Reviewer's Assessment: Satisfactory

(b) (4)

Weight percentages are checked and calculated below.

	2.3 mg Capsule		3.0 mg Capsule		4.0 mg Capsule	
Ingredient	(g)	% w/w	(g)	% w/w	(g)	% w/w
Ixazomib citrate	(b) (4)					
Microcrystalline cellulose	(b) (4)					
Talc	(b) (4)					
Magnesium stearate	(b) (4)					
Target batch size	(b) (4)					

Commercial Process Flow Diagram

The ixazomib capsules are manufacture (b) (4)

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(b) (4)



OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature:

Approvable

Diane Goll 30-Oct-2015

Secondary Review Comments and Concurrence:

Concur.

Jennifer Maguire 30-Oct-2015

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

27. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

TABLE 1: DS Manufacturing and Testing Sites

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
(b) (4)					

Reviewer's Assessment:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)								

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

The overall manufacturing inspection recommendation is pending as of 10/27/15.

Steven Hertz, M.S.

Consumer Safety Officer

OPF Division of Inspectional Assessment, Branch 1

10/27/15

Secondary Review Comments and Concurrence:

I concur with the primary reviewer's inspectional assessment.

Steven Fong, Ph.D.

Acting Quality Assessment Lead and Microbiologist

OPF Division of Inspectional Assessment, Branch 1

10/30/2015

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

29. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Yes, the proposed dissolution method and acceptance criterion are suitable as a routine quality control test for ixazomib oral capsules.

The drug substance is highly soluble. At 37°C, 0.61 mg/mL (as ixazomib) dissolves at pH 1.2; solubility increases as pH increases.

a. *What are the proposed dissolution method parameters?*



(b) (4)

Table 38-1. Dissolution Method for ixazomib oral capsules (2.3, 3, and 4 mg)

Table 1.a Dissolution Conditions

Apparatus	(b) (4)
Speed of rotation:	(b) (4)
Dissolution medium:	(b) (4)
Volume:	(b) (4)
Bath temperature:	(b) (4)
Sampling time point:	(b) (4)
Number of test units:	(b) (4)
Sampling volume	(b) (4)

(b) (4)

b. *Why were these dissolution method parameters selected?*

- 

(b) (4)

In two Design of Experiment (DOE) studies conducted, the Applicant investigated the influence of various formulation and process parameters (b) (4)

(b) (4)

(u) (4)

see Table 38-3.

Table 38-3. Formulation, Process, and Raw Material Parameters studied in Design of Experiment Studies

Parameter	Magnesium Stearate (%)	Talc (%)	Mixing (# of revolutions)	Fill weight (mg)
Manufacturing target	(b) (4)			
Lower value studied				
Upper value studied				

Parameter	Dose (mg)	% Drug Load	Drug substance Particle Size	MCC Particle Size d ₅₀	MgSt (%)	Talc (%)	Mixing (revolutions)
Manufacturing Target	(b) (4)						
Low value studied							
High value studied							

Source: Biopharmaceutics review of IND104482 (S-0423)

(b) (4)

d. Does the dissolution method have discriminating capability?

Yes, the proposed dissolution method has adequate power to discriminate drug product batches with unacceptable (b) (4) as well as raw material attributes, specifically drug substance particle size.

- (b) (4)

quality control test for batch-to-batch uniformity, for highly soluble and rapidly dissolving drug products (BCS classes 1 and 3).

Reviewer’s Assessment:

Dissolution Method

The reviewer agrees that the proposed dissolution method has sufficient discriminating power, as it was able to distinguish batches of ixazomib capsules with unacceptably high moisture content. Excessively high moisture content of the drug product could lead to incomplete drug dissolution and increased formation of impurities or degradants. The proposed dissolution method also showed discriminating capability for drug substance particle size distribution but only for % drug released at the early sampling timepoints (\leq 20 minutes).

Dissolution Acceptance Criteria

Based on the Applicant’s capability analysis including representative batches of ixazomib

(b) (4)

In response to the Biopharmaceutics Information Request dated 08/13/2015, the Applicant submitted on 08/31/2015 the requested analysis dataset of individual vessel dissolution data. In this submission, the multiple timepoint dissolution data at Month 24 of long-term storage (n=12) of four pivotal clinical lots [with blister lot numbers 102323, 102329, 102335, 102336 corresponding to six finished goods lot numbers 102740, 102741, 103118, 102742, 103119, 103267] were included. Based on the reviewer’s analysis of the Month 24 data for these pivotal clinical lots (Figure 38-5), the USP Stage 2

(b) (4)

Disintegration

Disintegration was routinely tested for the clinical and registration stability batches; however, the Applicant is proposing to remove the test from the Drug Product Specifications. Previously, the Biopharmaceutics reviewer (Dr. Sandra Suarez) did not accept the sponsor’s proposal to use disintegration in lieu of dissolution testing due to insufficient information provided (see IND 104482/S-0423). Dr. Suarez concluded (and this reviewer agrees) that disintegration is less sensitive than dissolution testing in detecting differences in drug substance particle size, (b) (4) and capsule age.

Figure 38-5.

(b) (4)

30. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

(b) (4)

a. Which batches of ixazomib oral capsules were used in the pivotal Phase 3 clinical trial?

In the 08/31/2015 response to the Biopharmaceutics Information Request dated 08/13/2015, the Applicant clarified that all capsule lots used in Study C16010 were included in Section 3.2.P.5.4 Batch Analyses. The Applicant also clarified that the capsule lots in the clinical study report of Study C16010 were referenced by their respective finished goods lot numbers, whereas the capsule lot numbers in Batch Analyses were referenced by their bulk drug product lot numbers. Table 39-1 provides a lot genealogy, linking the finished goods lot numbers to the bulk drug product lot numbers.

Table 39-1. Lot Genealogy for Ixazomib Capsule Lots Used in Clinical Study C16010

(b) (4)



(b) (4)

Reviewer's Assessment:

The reviewer agrees that in vitro and/or in vivo bridging studies between the drug product used in the pivotal clinical trial and the proposed commercial product are not necessary.

Risk Assessment Table

Initial Risk Assessment			Final Risk Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments**
Dissolution	Drug Product (b) (4)	Low	(b) (4)	Acceptable	None. The drug product is rapidly dissolving.
	Substance Particle Size				

**OVERALL ASSESSMENT AND SIGNATURES:
 BIOPHARMACEUTICS**

Reviewer’s Assessment and Signature:

The proposed dissolution method [consisting of USP Apparatus I (basket) agitated at 100 rpm speed, and 500 mL of 0.1 N HCl (pH 1.2)] is deemed adequate for the routine quality control of ixazomib oral capsules. Based on the review of dissolution data available for the batches of ixazomib 2.3, 3.0, and 4.0 mg capsules used in the pivotal clinical study, the proposed dissolution acceptance criterion (Q $\frac{(b)}{(4)}$ % dissolved in 20 minutes) is acceptable.

USP Apparatus	Spindle Rotation	Medium/ Volume/Temperature	Acceptance Criterion
1, Basket (40 mesh)	100 rpm	500 mL 0.1 N HCl, pH 1.2 at 37 ± 0.5 °C	Q = $\frac{(b)}{(4)}$ % at 20 min

From a Biopharmaceutics perspective, NDA 208-462 for ixazomib oral capsules is recommended for APPROVAL.

10/23/2015

Gerlie Gieser, Ph.D.

Biopharmaceutics Reviewer

Division of Biopharmaceutics/OPQ

Secondary Review Comments and Concurrence:

I concur with Dr. Gieser’s assessment and approval recommendation for NDA 208462.

10/23/2015

Okpo Eradiri, Ph.D.

Acting Biopharmaceutics Lead

Division of Biopharmaceutics/OPQ

ASSESSMENT OF MICROBIOLOGY

31. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

Reviewer's Assessment:

See Assessment of the Process for Microbiology evaluation

2.3.P.7 Container/Closure System

32. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Reviewer's Assessment:

See Assessment of the Process for Microbiology evaluation

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

33. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

(b) (4)



(b) (4)

Reviewer's Assessment: Satisfactory.

(b) (4)

34. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment:

Not applicable.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

See Assessment of the Process for Microbiology evaluation

Secondary Review Comments and Concurrence:

See Assessment of the Process for Microbiology evaluation

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

35. Is the applicant's claim for categorical exclusion acceptable?

36. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

Reviewer's Assessment: The applicant claimed a categorical exclusion based on the EIC which was calculated to be (b)(4) ppb. Therefore, the EA can be categorically excluded according to 21CFR §25.31(b).

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: EA is satisfactory to the reviewer
Amit K. Mitra, Ph.D/29-OCT-2015

Secondary Review Comments and Concurrence: I concur

Olen Stephens, Ph.D. OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII
29-Oct-15

**I. Review of Common Technical Document-Quality (Ctd-Q) Module 1
Labeling & Package Insert**

For NDA only

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))
NINLARO[®] (ixazomib) capsules, for oral use
Capsules: 4 mg, 3 mg, and 2.3 mg (3)

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Ninlaro [®]	Acceptable
Dosage form, route of administration	Capsules for oral use	Acceptable
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Capsules: 4 mg, 3 mg, and 2.3 mg	Acceptable

Conclusion: This section of the label is acceptable

(b) “Full Prescribing Information” Section

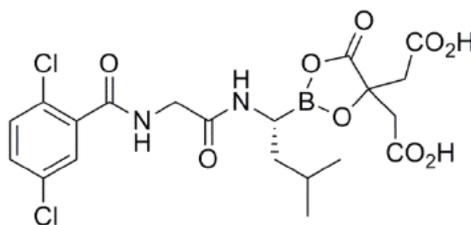
3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Capsules	Acceptable
Strengths: in metric system	Yes	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	<p>4 mg: Light orange gelatin capsule imprinted with “Takeda” on the cap and 4.0 mg on the body in black ink. NINLARO 4 mg capsules contain 4 mg of ixazomib equivalent to 5.7 mg of ixazomib citrate.</p> <p>3 mg: Light grey gelatin capsule imprinted with “Takeda” on the cap and 3.0 mg on the body in black ink. NINLARO 3 mg capsules contain 3 mg of ixazomib equivalent to 4.3 mg of ixazomib citrate.</p> <p>2.3 mg: Light pink gelatin capsule imprinted with “Takeda” on the cap and 2.3 mg on the body in black ink. NINLARO 2.3 mg capsules contain 2.3 mg of ixazomib equivalent to 3.3 mg of ixazomib citrate</p>	Acceptable

Conclusion: This section of the label is acceptable; Salt equivalence statements also provided in current version of edited label.

#11: Description (21CFR 201.57(c)(12))

NINLARO (ixazomib) is an antineoplastic agent. Ixazomib citrate, a prodrug, rapidly hydrolyzes under physiological conditions to its biologically active form, ixazomib. The chemical name of ixazomib citrate is 1,3,2-dioxaborolane-4,4-diacetic acid, 2-[(1*R*)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]-5-oxo- and the structural formula is:



The molecular formula for ixazomib citrate is $C_{20}H_{23}BCl_2N_2O_9$ and its molecular weight is 517.12. Ixazomib citrate has one chiral center and is the *R*-stereoisomer. The solubility of ixazomib citrate in 0.1N HCl (pH 1.2) at 37°C is 0.61 mg/mL (reported as ixazomib). The solubility increases as the pH increases.

NINLARO (ixazomab) capsules for oral use contain 4, 3 or 2.3 mg of ixazomib equivalent to 5.7, 4.3 or 3.3 mg of ixazomib citrate, respectively. Inactive ingredients include microcrystalline cellulose, magnesium stearate, and talc. Capsule shells contain gelatin and titanium dioxide. The 4 mg capsule shell contains red and yellow iron oxide, the 3 mg capsule shell contains black iron oxide and the 2.3 mg capsule shell contains red iron oxide. The printing ink contains shellac, propylene glycol, potassium hydroxide, and black iron oxide.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Ninlaro	Acceptable
Dosage form and route of administration	Capsules	Implied oral use
Active moiety expression of strength with equivalence statement for salt (if applicable)	Yes	Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Acceptable
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	Antineoplastic agent	Acceptable
Chemical name, structural formula, molecular weight	provided	Acceptable
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)		Acceptable

Conclusion: This section of the label is acceptable

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

13.1 How Supplied

NINLARO is supplied as:

4 mg gelatin capsule: Light orange, size 3, imprinted with “Takeda” on the cap and 4.0 mg on the body in black ink. NINLARO 4 mg capsules contain 4 mg of ixazomib equivalent to 5.7 mg of ixazomib citrate.

- One 4 mg capsule in a single blister pack (NDC 63020-080-01)
- Three 4 mg single packs in a carton (NDC 63020-080-02)

3.0 mg gelatin capsule: Light grey, size 4, imprinted with “Takeda” on the cap and 3.0 mg on the body in black ink. NINLARO 3 mg capsules contain 3 mg of ixazomib equivalent to 4.3 mg of ixazomib citrate.

- One 3 mg capsule in a single blister pack (NDC 63020-079-01)

- Three 3 mg single packs in a carton (NDC 63020-079-02)

2.3 mg gelatin capsule: Light pink, size 4, imprinted with “Takeda” on the cap and 2.3 mg on the body in black ink. NINLARO 2.3 mg capsules contain 3 mg of ixazomib equivalent to 3.3 mg of ixazomib citrate.

- One 2.3 mg capsule in a single blister pack (NDC 63020-078-01)
- Three 2.3 mg single packs in a carton (NDC 63020-078-02)

Capsules are individually packaged in a PVC-Aluminum/Aluminum blister.

13.2 Storage

NINLARO may be stored at room temperature. Do not store above 30°C (86°F). Do not freeze.

Store capsules in original packaging until immediately prior to use.

13.3 Handling and Disposal

NINLARO is cytotoxic¹. Capsules should not be opened or crushed. Direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid (b) (4) [redacted]. If contact occurs, wash thoroughly with soap and water.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

Item	Information Provided in NDA	Reviewer’s Assessment
Strength of dosage form	4, 3, 2.3 mg capsules	Acceptable
Available units (e.g., bottles of 100 tablets)	3-pack	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Acceptable
Special handling (e.g., protect from light, do not freeze)	Disposal language provided	Acceptable
Storage conditions	Provided	Acceptable

Manufacturer/distributor name listed at the end of PI, following Section #17

Distributed and Marketed by:

Takeda Pharmaceutical Company Limited
Cambridge, MA 02139

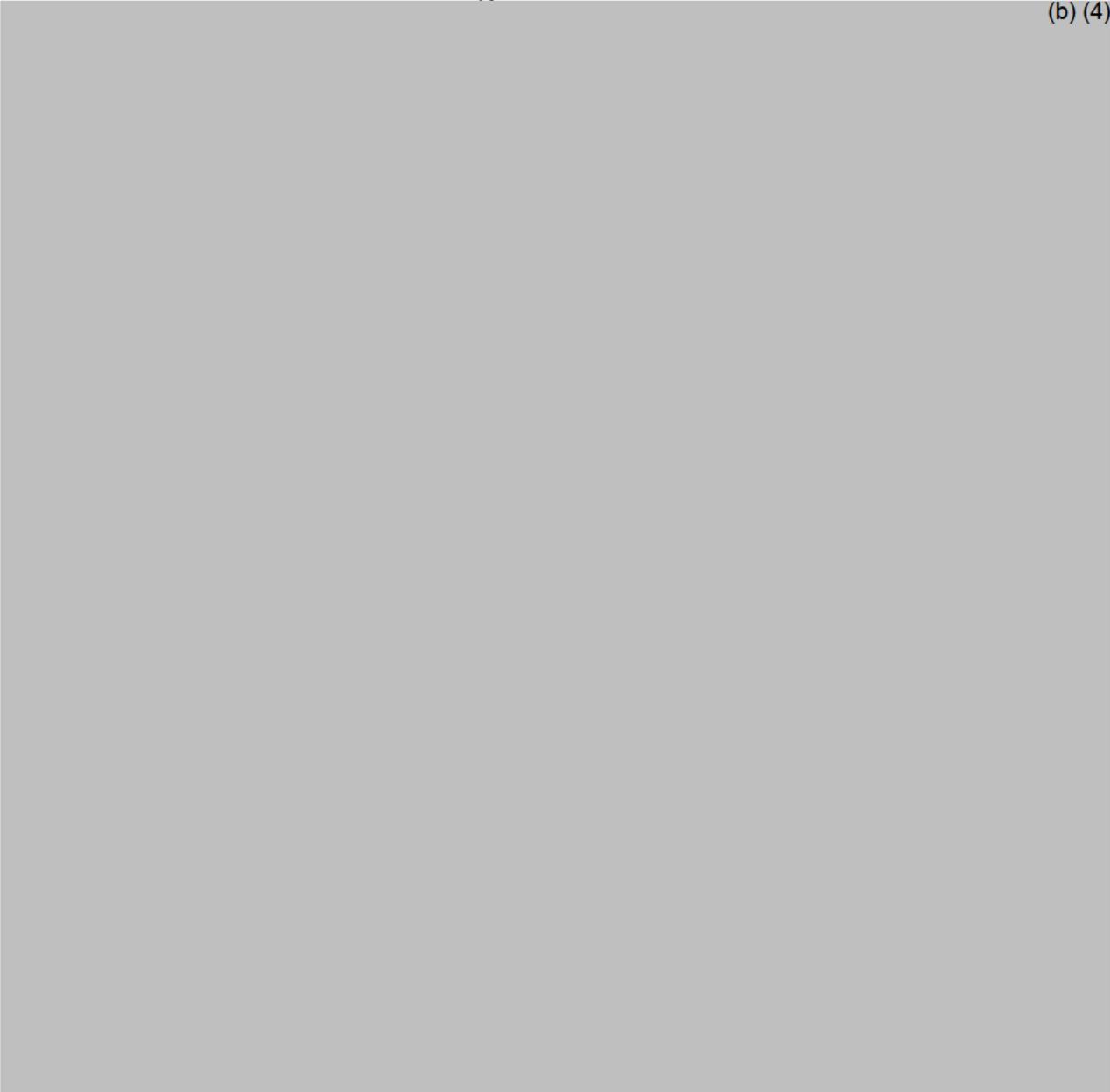
Issued: MMMM YYYY

Item	Information Provided in NDA	Reviewer’s Assessment
Manufacturer/distributor name (21 CFR 201.1)	Provided	Acceptable

Conclusion: Labeling meetings are on-going with the clinical division

2. Container and Carton Labeling

(b) (4)



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Provided	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Provided	Acceptable
Route of administration (21.CFR 201.100(b)(3))	Orally	Acceptable
Net contents* (21 CFR 201.51(a))	3-Pack	Acceptable
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	NA	Acceptable
Lot number per 21 CFR 201.18	Space provided	Acceptable
Expiration date per 21 CFR 201.17	Space provided	Acceptable
“Rx only” statement per 21 CFR 201.100(b)(1)	Provided	Acceptable
Storage (not required)	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)	Provided	Acceptable
Bar Code per 21 CFR 201.25(c)(2)***	Space provided	Acceptable
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Acceptable
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label



CHEMISTRY REVIEW

NDA 208462, NINLARO (ixazomib) capsules



(b) (4)

Conclusion: The DMEPA made a statement on the storage conditions as follows: Consider revising the storage information by listing the statement “capsules may be stored at room temperature before the statement: Do not store above 30°C(86 ° F). Do not freeze”. The CMC reviewer agrees with this comment on storage conditions since the long term stability data were generated at 30 ° C/75%RH.

2) Carton Labeling

(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Provided	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Provided	Acceptable
Net contents (21 CFR 201.51(a))	3-Pack	Acceptable
Lot number per 21 CFR 201.18	Space Provided	Acceptable
Expiration date per 21 CFR 201.17	Space Provided	Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	NA	Acceptable
Sterility Information (if applicable)	NA	Acceptable
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided	Acceptable
Storage Conditions	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)	Not provided	Not required
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Acceptable
Name of manufacturer/distributor	Provided	Acceptable
“See package insert for dosage information” (21 CFR 201.55)	Provided	Acceptable
“Keep out of reach of children” (optional for Rx, required for OTC)	Provided	Acceptable
Route of Administration (not	Not provided	Not required

required for oral, 21 CFR 201.100(d)(1) and (d)(2))		
Salt Equivalence Statement	<p>The applicant should edit the outer containers to comply with the preferred formatting of the salt equivalence statement:</p> <p>The outer dosepak, outer dosepak carton, outer shellpak carton, and outer shellpak have the incorrect salt equivalence statements. Revise the outer dosepak as follows for each strength:</p> <ol style="list-style-type: none">1. Each capsule contains 2.3 mg of ixazomib equivalent to 3.3 mg of ixazomib citrate.2. Each capsule contains 3 mg of ixazomib equivalent to 4.3 mg of ixazomib citrate.3. Each capsule contains 4 mg of ixazomib equivalent to 5.7 mg of ixazomib citrate.	Comment to be conveyed by the clinical PM

Conclusion: Label is adequate

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Labeling section is satisfactory to the reviewer.

Amit K. Mitra, Ph.D/29-OCT-2015

Secondary Review Comments and Concurrence: I concur

Olen Stephens, Ph.D. OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII
29-Oct-15

II. List of Deficiencies To Be Communicated: None

III. Attachments

A. Lifecycle Knowledge Management



CHEMISTRY REVIEW
NDA 208462, NINLARO (ixazomib) capsules



a) Drug Product

Product attribute/CQA	Factors that can impact the CQA	Failure Mode	Initial Risk Ranking	Risk Mitigation	Final Risk Ranking	Lifecycle considerations
Assay, stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	(b) (4)	Low	(b) (4)	Low	(b) (4)
Physical stability (solid state)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 		Medium		Medium	
Content Uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 		Medium		Medium	
Microbial Limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 		Low		Low	
Dissolution – BCS Class: (b) (4)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 		Low		Low	



NDA 208462-Orig1-New - User Fee - Form 3674/HDA - Coversheet(1) » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

Task Summary **Task Details** Issues Updates More

Overview **Facility Inspection - Overall Application Recommendation**

Edit Custom Form

Custom Form

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation

Approve

Navigation Links

Form Link

http://panorama.fda.gov/task/view?ID=55a4a8ce01c41fde7589ee74777045fb&activeTab=content-dashboard__5418eab10003b6cd5fd5f929c4fa823

Assigned To



OPF Reviewer



Steven Hertz



IM - OPF Reviewer

Edit Assignment

This was done on

Nov 12, 2015

(4 days ago)

Status

Complete

Requested by



DARRTS Integration

This task is waiting on

Facilities

Last Update

Nov 12, 2015

Submitted On

Jul 14, 2015

Reference Number

5134756