CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208462Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 16, 2015
To:	Ann Farrell, M.D. Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Nisha Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	NINLARO (ixazomib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 208642
Applicant:	Millennium Pharmaceuticals, Inc.

1 INTRODUCTION

On July 10, 2015, Millennium Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 208462 for NINLARO (ixazomib) capsules. The proposed indication for NINLARO (ixazomib) capsules is in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on July 17, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for NINLARO (ixazomib) capsules.

MATERIAL REVIEWED

- Draft NINLARO (ixazomib) capsules PPI received on July 10, 2015 and further revised throughout the review cycle, and received by DMPP and OPDP on November 9, 2015.
- Draft NINLARO (ixazomib) capsules Prescribing Information (PI) received on July 10, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 5, 2015, November 9, 2015, and November 10, 2015.

2 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

3 CONCLUSIONS

The PPI is acceptable with our recommended changes.

4 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
11/16/2015

NISHA PATEL
11/16/2015

BARBARA A FULLER
11/16/2015

LASHAWN M GRIFFITHS
11/16/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 10, 2015

To: Jacquin Jones, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for Ninlaro® (ixazomib) capsules, for oral use
NDA 208462

In response to your consult dated July 14, 2015, we have reviewed the draft Package Insert (PI) for Ninlaro® (ixazomib) capsules, for oral use (Ninlaro) and offer the following comments. Please note that OPDP has made these comments using the version e-mailed to OPDP on November 10, 2015.

Section	Statement from draft	Comment
6 Adverse Reactions	Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 26% in patients in the NINLARO regimen and 16% of patients in the placebo regimen. (b) (4) the most common (b) (4) blurred vision (6% in the NINLARO regimen and 3% in the placebo regimen), dry eye (b)% in the NINLARO regimen and (b)% in the placebo regimen), (b) (4)	(b) (4)

Section	Statement from draft	Comment
6 Adverse Reactions	The following serious adverse (b) (4) acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura. (b) (4)	(b) (4)
11 Description	Ixazomib citrate, a prodrug, **rapidly** hydrolyzes under physiological conditions to its biologically active form, ixazomib. (b) (4)	Please consider deleting "rapidly" as it is promotional in tone.

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/s/

NISHA PATEL
11/10/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 3, 2015

TO: Jacquin Jones, B.S.N., M.S., Regulatory Project Manager
Alexandria Schwarsin, M.D., Medical Officer
R. Angelo de Claro M.D., Cross Discipline Team Leader
Division of Hematology Products

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D. for
Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 208462

APPLICANT: Millenium Pharmaceuticals, Inc.

DRUG: ixazomib

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Priority

INDICATION: Treatment of (b) (4) multiple myeloma

CONSULTATION REQUEST DATE: August 4, 2015

INSPECTION SUMMARY GOAL DATE (extended): November 3, 2015

DIVISION ACTION GOAL DATE: November 20, 2015

PDUFA DATE: March 10, 2016

I. BACKGROUND:
Clinical data for the treatment of multiple myeloma support the combination of a proteasome inhibitor, an immune-modulator (i.e., thalidomide analog), and a glucocorticosteroid (i.e., dexamethasone). Ixazomib (MLN9708) is a modified dipeptide boronic acid proteasome inhibitor similar to bortezomib (Velcade®), proposed by the sponsor for the treatment of multiple myeloma.

Treatment options for subjects with primary resistant or relapsed multiple myeloma may include combination therapies with glucocorticoids and cytotoxic chemotherapeutic agents, more recently combined with autologous stem transplantation (ASCT).

A double-blind randomized clinical trial study was submitted in support of the applicant's NDA. For this NME NDA under the PDUFA V program review with priority therapy designation, CDER DHP requested that a single domestic site and two international sites be inspected. The sites enrolled large numbers of patients and showed good response to study drug treatment.

Study C16010
Study C16010 was a Phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of ixazomib (MLN9708) versus placebo in patients with relapsed and/or refractory multiple myeloma (MM) who were treated with lenalidomide and dexamethasone as their standard therapy. The primary study objective was to determine whether the addition of oral ixazomib (MLN9708) to the background therapy of lenalidomide and dexamethasone improves progression-free survival (PFS) in patients with relapsed and/or refractory multiple myeloma. The primary study efficacy endpoint was defined as the time from the date of randomization to the date of first documentation of disease progression based on central laboratory results and International Myeloma Working Group (IMWG) criteria as evaluated by an independent review committee (IRC), or death due to any cause as a competing risk.

II. RESULTS:

Name of CI / Location	Study Site/Study Protocol/Number of Subjects Enrolled	Inspection Date	Classification*
David S. Siegel, M.D., Ph.D. John Theurer Cancer Center Hackensack University Medical Center 92 Second Street Hackensack, NJ 07601	Site #58011 Protocol C16010 Subjects=5	September 8-18, 2015	Preliminary: VAI
Norbert Grzasko, M.D., Ph.D. Department of Haematooncology and Bone Marrow Transplantation, Medical University of Lublin Staszica 11 Lublin, Poland 20-081	Site #42002 Protocol C16010 Subjects=20	Pending	Pending
Tamas Masszi, M.D., Ph.D. St. István and St. Laszlo Hospital Dept. of Hematology & Stem Cell Transplantation Albert Flórián út 5-7 Budapest, Hungary 1097	Site #22003 Protocol C16010 Subjects=27	October 12-16, 2015	Preliminary:VAI
Sponsor: Millennium Pharmaceuticals, Inc. 40 Landsdowne Street Cambridge, MA 02139	Protocol C16010	October 19-23, 2015	Preliminary: NAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI =No Response Requested = Deviations(s) from regulations. Data acceptable.
OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.
Preliminary=The Establishment Inspection Report (EIR) has not been received; findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATORS

1. David S. Siegel, M.D., Ph.D./Study Protocol C16010/Site #58011
Hackensack, NJ 07601

a. What was inspected:

The inspection was conducted from September 8 to 18, 2015. A total of five subjects were screened and enrolled, one patient died, one patient discontinued during the study, and three subjects completed the study. An audit of three enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (Inspectional Observations) was issued at the end of the inspection for the following regulatory deficiencies:

1) Failure to maintain accurate case histories and records. Specifically these were not captured in the e-CRF for the following enrollees as examples: (a) Subject 001 in the "no ixazomib" group had low grade edema, (b) Subject 003 in the "ixazomib" ("peeling in the mouth", Cycle 4); sore tongue (Cycle 5); confusion (Cycle 9), gum recession (Cycle 10), "itchy body" (Cycle 12), and (c) Subject 005 in the "no ixazomib" group (malaise/fatigue/myalgia on July 7, 2015 study visit).

   Reviewer's Comment:
   The above adverse events are regulatory deficiencies and sporadically occurred throughout the study (namely, Cycle 1 through Cycle 12). These adverse events are unlikely to have a significant impact on the safety analyses for this NDA.

2) The study was not conducted in accordance to the investigational plan. Specifically, there is no documentation of which reference thermometers were used to calibrate the subject refrigerators where the investigational product was stored. The drug product was required to be stored between two and eight degrees Centigrade.

   Reviewer's Comment:
   According to the study protocol, "patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle."

   The applicant has stability data to support the storage of ixazomib capsules at 5 degrees °C for 24 months (b) (4) 25 °C) and the results met the proposed specification. However, this does not directly address the issue of indefinite storage outside the protocol-indicated temperature range, since the information as to how the subjects stored the medication is not available. OSI cannot verify that the medication was stored at the correct protocol specified temperature. DHP will have to consider whether possible improper storage could affect efficacy outcome at this site.

c. Assessment of data integrity:
OSI defers the regulatory deficiency item regarding lack of documentation of the reference thermometers to DHP. Otherwise, data submitted by this clinical site appear acceptable in support of this specific indication.

Dr. Siegel responded adequately in a letter dated October 7, 2015.

2. Norbert Grzasko, M.D., Ph.D./Study Protocol C16010/Site #42002
Lublin, Poland

NOTE: The field inspection is pending. DHP excluded this study site from analyses.

3. Tamas Masszi, M.D., Ph.D./Study Protocol C16010/Site #22003
Budapest, Hungary 1097

a. What was inspected:
The inspection was conducted from October 12 to 16, 2015. A total of 33 subjects were screened and 27 subjects enrolled. Twenty three subjects completed the study. The study is still ongoing, with six subjects participating. An audit of 20 enrolled subjects' records was conducted. A review of 19 subjects' records with progressive disease was also conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (Inspectional Observations) was issued at the end of the inspection for the following regulatory deficiencies:

I. The study was not conducted in accordance to the investigational plan. Specifically, the response assessment calendar dates for progressive disease in e-CRF records for three subjects did not match the progressive disease notification document. Thus, (a) Subject 007's progressive disease notification was January 15, 2014, but the e-CRF was March 19, 2014, (b) Subject 027's progressive disease notification was February 5, 2014, but the e-CF was March 5, 2014, and (c) Subject 016's progressive disease notification was June 3, 2013, but the e-CRF was May 27, 2013.

Comments:
While these were considered regulatory deficiencies, the above observations were not be the final calendar dates considered by DHP (the final arbiter of tumor response assessment status) as progressive disease status.

DHP stated that the primary endpoint of the trial is independent review committee (IRC)-assessed, and hence will use the IRC-determined evaluation of the primary data for regulatory decision making, so the above observation should not impact study outcome.

II. The Master Drug Accountability log inventories had (a) eight cartons of Lot #221003, but the clinical study site inventory revealed six cartons, and (b) one carton of Lot 103112, but the clinical study site inventory revealed three cartons.

Reviewer's Comment:
The above field observations were considered regulatory deficiencies. There was no evidence from the NDA submission that patients were overdosed or harmed.

c. Assessment of data integrity:
Notwithstanding the regulatory deficiencies which were not considered critical, data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR
4. Millennium Pharmaceuticals, Inc.
Cambridge, MA 02139

a. What was inspected:
The inspection was conducted from October 19 to 23, 2015. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:
Monitoring deficiencies, in terms of initiating interim monitoring visits within a timely manner, were identified. There was no evidence of under-reporting of adverse events.

A Form FDA 483 was not issued at the end of the sponsor inspection.

c. Assessment of data integrity:
Data submitted by this sponsor appear acceptable in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

A single domestic and two international clinical sites were inspected in support of this NDA. The sponsor (Millennium Pharmaceuticals, Inc.) was also inspected.

The preliminary classification for Dr. Siegel and Dr. Masszi is Voluntary Action Indicated (VAI). The preliminary classification for the sponsor is No Action Indicated (NAI). In summary, the study data derived from these clinical sites are considered reliable in support of the requested indication. Lack of documentation of the reference thermometers makes OSI confirmation of product stability impossible; DHP will make the judgment as to product storage impact.

Note: *The inspectional observations noted above are based on preliminary communication with the field investigator, the Form FDA 483, and written response to the 483. A clinical inspection summary addendum will be generated if conclusions change significantly upon receipt of the Establishment Inspection Report (EIR).*

{See appended electronic signature page}

Anthony Orencia, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D. for
Janice K. Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.
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/s/

ANTHONY J ORENCIA
11/03/2015

SUSAN D THOMPSON
11/03/2015

KASSA AYALEW
11/04/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 26, 2015
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 208462
Product Name and Strength:	Ninlaro (ixazomib) capsules 4 mg, 3 mg, 2.3 mg
Submission Date:	October 9, 2015
Applicant/Sponsor Name:	Millennium Pharmaceuticals
OSE RCM #:	2015-1584-1
DMEPA Primary Reviewer:	Ebony Ayres, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised carton labeling and container labels for Ninlaro (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSION

The revised carton labeling and container labels for Ninlaro are acceptable from a medication error perspective. We have no further recommendations at this time.

[1] Ayres E. Label and Labeling Review for Ninlaro (NDA 208462). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 SEP 29. 21 p. OSE RCM No.: 2015-1584.

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/s/

EBONY J AYRES
10/26/2015

YELENA L MASLOV
10/26/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 29, 2015
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 208462
Product Name and Strength:	Ninlaro (ixazomib) capsules 4 mg, 3 mg, 2.3 mg
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Millennium Pharmaceuticals
Submission Date:	July 10, 2015 and September 1, 2015
OSE RCM #:	2015-1584
DMEPA Primary Reviewer:	Ebony Ayres, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD
DMEPA Associate Director:	Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

As part of the approval process for Ninlaro (NDA 208462), the Division of Hematology Products (DHP) requested that we review the proposed label, labeling, and Prescribing Information, submitted on July 10, 2015 and September 1, 2015, for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E(N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed container labels, carton labeling, and Prescribing Information (PI) for Ninlaro, NDA 208462. Ninlaro is an oral antineoplastic agent supplied as 2.3 mg, 3 mg, and 4 mg capsules. With regards to the carton labeling and container labels, the Applicant uses the same font color for the presentation of the proprietary name for all strengths. Additionally, the color used on the label of the 4 mg strength is identical to the color utilized in the proprietary name presentation. (b) (4) Additionally, the logo and net quantity statement on the carton labeling should be relocated to decrease the risk of misinterpretation of important prescribing information. As a result, we recommend revisions to the labels and labeling.

(b) (4)

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels and labeling can be improved to increase the readability and prominence of information on the label and labeling and to help mitigate the risk of medication errors.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Ninlaro Prescribing Information

a. Section 2 Dosage and Administration

(b) (4)

ii. 2.1 Dosing and Administration Guidelines

1. Revise the sentence (b) (4) to read "The recommended starting dose of NINLARO is 4 mg administered…" (b) (4)
2. Revise the sentence (b) (4) to read "NINLARO should be taken at approximately the same time (b) (4) at least one hour…". This modification will increase clarity regarding the dosing regimen.
3. Label the table entitled "Dosing Schedule: NINLARO taken with Lenalidomide and Dexamethasone" as Table 1 and renumber subsequent tables accordingly.

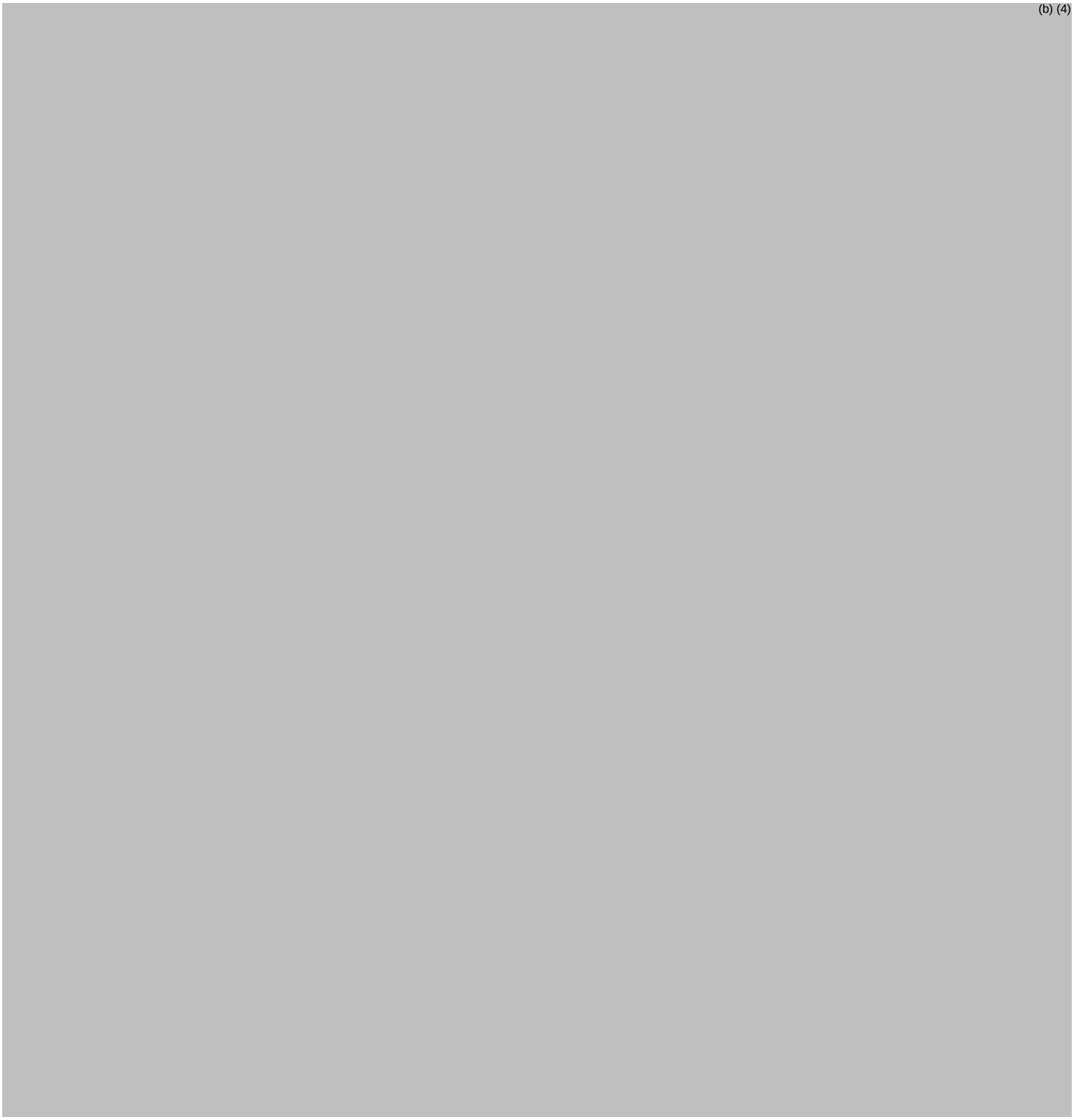
iii. 2.2 Dose Modification Guidelines

1. Revise the title of Table (b) (4) to read "Ninlaro Dose Reductions due to Adverse Reactions". This revision will help to clarify when the information in the table should be used.
2. Add the statement "See Sections 2.3 and 2.4." after the statement "Recommended starting dose of 3 mg in patients with moderate or

[1] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2015 JUL 21]. Available from: http:www.ismp.org/tools/errorproneabbreviations.pdf.

severe hepatic impairment, severe renal impairment or end-stage renal disease requiring dialysis." listed below Table 1.

(b) (4)



[2] See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2015 JUL 21]. Available from: http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

[3] Institute for Safe Medication Practices. Affirmative warnings (b) (4) may be better understood than negative warnings (b) (4) ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ninlaro that Millennium Pharmaceuticals submitted on July 10, 2015.

Table 2. Relevant Product Information for Ninlaro	
Initial Approval Date	N/A
Active Ingredient	Ixazomib
Indication	Treatment of patients with multiple myeloma who have received at least one prior therapy
Route of Administration	Oral
Dosage Form	Capsule
Strength	4 mg, 3 mg, and 2.3 mg
Dose and Frequency	4 mg once a week on Days 1, 8 and 15 of a 28-day treatment cycle
How Supplied	Capsule; each carton contains three single blister packs
Storage	May be stored at room temperature. Do not store above 30°C (86°F). Do not freeze.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 14, 2015, we searched the L:drive and AIMS using the terms, Ninlaro and ixazomib, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous labels and labeling reviews.

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/s/

EBONY J AYRES
09/29/2015

YELENA L MASLOV
09/30/2015

LUBNA A MERCHANT
09/30/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 208462

Application Type: New NDA

Name of Drug/Dosage Form: Ninlaro (ixazomib) Capsule

Applicant: Millennium Pharmaceuticals, Inc.

Receipt Date: July 10, 2015

Goal Date: March 10, 2016

1. Regulatory History and Applicant's Main Proposals

Ninlaro® (Ixazomib) has been submitted as an Original NDA under NDA 208462 for the indication of the treatment of patients with multiple myeloma who have received at least one prior therapy. The Applicant has Orphan Drug Designation for the proposed indication.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant during labeling negotiations.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There is white space between the product title and Initial US Approval.*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required

Selected Requirements of Prescribing Information

• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

N/A 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"[see Warnings and Precautions (5.2)]"*.

Comment:

N/A

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUIN L JONES
09/18/2015

MARA B MILLER
09/18/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 208462 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Ninlaro® Established/Proper Name: ixazomib Dosage Form: Capsule Strengths: 2.3, 3, and 4 mg		
Applicant: Millennium Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: July 10, 2015 Date of Receipt: July 10, 2015 Date clock started after UN: n/a		
PDUFA/BsUFA Goal Date: March 10, 2016	Action Goal Date (if different): November 20, 2015	
Filing Date: September 8, 2015	Date of Filing Meeting: August 14, 2015	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of patients with multiple myeloma who have received at least one prior therapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 104482 and (b) (4)	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** *http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm* ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** *http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm*	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf*	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ N/A ☐ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☒		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm* **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: **5 years exclusivity** ***Note:*** *An applicant can receive exclusivity without requesting it;*	☒	☐	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single [redacted] (b) (4) drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the [redacted] (b) (4) not be considered the same active ingredient as that contained in an already approved [redacted] (b) (4) drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☒	☐		Orphan Designation Granted and therefore exempt from PREA requirements.

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Orphan Designation Granted and therefore exempt from PREA requirements.
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		Submitted on 8/7/15
Is the PI submitted in PLR format?[4]	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

[4]

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☒	☐	☐	
Has a review of the available pregnancy and lactation data been included?	☒	☐	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to Patient Labeling? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	

http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

If no, request in 74-day letter.				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** November 15, 2011 and March 2, 2012 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** September 22, 2014 (prelim responses) and April 1, 2015 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 14, 2015

BACKGROUND: Ninlaro® (ixazomib) Capsule is an orally bioavailable small molecule inhibitor of the 20S proteasome indication for the treatment of patients with multiple myeloma who have received at least one prior therapy. This Original NDA for Ninlaro (Ixazomib) capsule has been submitted under NDA 208462.

IND 104482 is the associated IND.

The Applicant is requesting a Priority review designation. Also, the Applicant has Orphan Drug Designation for the proposed indication.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jacquin Jones	Y
	CPMS/TL:	Amy Baird/Mara Miller	Y
Cross-Discipline Team Leader (CDTL)	Angelo de Claro		Y
Division Director/Deputy	Ann Farrell/Edvardas Kaminskas		Y
Office Director/Deputy	Richard Pazdur		Y
Clinical	Reviewer:	Alexandria Schwarsin	Y
	TL:	Angelo de Claro	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Vicky Hsu	Y

	TL:	Bahru Habtemariam	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Jee Eun Lee/Nitin Mehrotra	Y
Biostatistics	Reviewer:	Yun Wang	Y
	TL:	Lei Nie/Yuan Li Shen	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Emily Place	N
	TL:	Christopher Sheth	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Janice Brown	N
	RBPM:	Rabiya Laiq	Y
• Drug Substance	Reviewer:	Katherine Windsor	N
• Drug Product	Reviewer:	Amit Mitra	Y
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:	Steven Hertz	N
• Biopharmaceutics	Reviewer:	Gerlie Giesser	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	Olen Stephens- Branch Chief		Y
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Sharon Mills	N
	TL:	Barbara Fuller	Y
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Nisha Patel	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Ebony Ayers	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		

	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orencia	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☐ ☒ NO ☐ To be determined Reason: ***the application did not raise significant safety or efficacy issues***
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☐ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☒ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	None
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **October 2, 2015** **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): Expedited review timeline attached. Planned Goal Date: November 20, 2015; PDUFA Action Date: March 10, 2016. **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

Attachment: Expedited Review Timeline

NDA 208462- TIMELINE

Applicant: Millennium Pharmacueticals, Inc.
Drug: ixazomib (Ninlaro)
Receipt Date: July 10, 2015
NME, The Program; Expedited Review

TASK	PRIORITY/EXPEDITED
Application Orientation Meeting	**August 10, 2015**
Filing Meeting	**August 14, 2015**
Filing Date (Day 60)	**September 8, 2015**
Day 74 Letter	**September 22, 2015**
Mid-Cycle/Late Cycle Planning Meeting (Internal)	**October 2, 2015**
Mid-Cycle Communication with Applicant/Late Cycle Meeting	**October 13, 2015**
Labeling Meetings	**October 6, 13, 20 , and 30, 2015**
Primary Reviews Completed	**October 30, 2015**
Secondary Reviews Completed	**October 30, 2015**
Wrap-up Meeting/Label Meeting	**November 3, 2015**
Send Labeling/PMR/PMC	**October**
Complete CDTL Review	**November 6, 2015**
Complete Division Director Review	**November 10, 2015**
Complete Office Director Review and Sign-off **Action Goal Date: November 20, 2015**	**Possibly as early as November 13, 2015**
	Notes: Priority/Expedited Review, No AC meeting

TASK	PRIORITY/EXPEDITED

Review Team

Clinical : Alexandria Schwarsin (Angelo de Claro, TL and CDTL)
Stats : Yun Wang (Lie Nie
Clin Pharm– Vicky Hsu (Bahru Habtemariam, TL)
Pharmacometrics: Jee Eun Lee (Nitin Mehrotra, TL)
CMC: Janice Brown, ATL and Rabia Laqia , RBPM

- Drug Product: Amit Mitra
- Drug Substance: Katherine Windsor
- Facility: Steven Hertz
- Biopharmacueticals: Gerlie Giesser (Okpo Eradiri, TL)

Pharm/Tox– Emily Place (Christopher Sheth, TL)

Labeling

- CMC: CMC Team
- DMEPA: Ebony Ayers (Yelena Maslov, TL)
- DHP RPM: Jacquin Jones

OSE

- RPM: Kevin Wright (Sue Kang, TL)
- DPV: Shaily Arora (Tracy Salaam, TL)
- DMEPA: Ebony Ayers (Yelena Maslov, TL)
- DRISK: Amarilys Vega (Naomi Redd, TL)
- DEpi: Steven Bird

Consults

- OSI (Clinical Site Inspection): Anthony Orencia (Janice Pohlman, TL)
- OPDP: Nisha Patel
- DMPP: Sharon Mills (Barbara Fuller, TL)

NME Program

- Azada Hafiz

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUIN L JONES
09/03/2015

MARA B MILLER
09/04/2015