

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208462Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208462

SUPPL #

HFD #

Trade Name Ninlaro

Generic Name Ixazomib

Applicant Name Millennium Pharmaceuticals, Inc.

Approval Date, If Known November 20, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

New Molecular Entity

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 year of exclusivity

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Jacquin Jones
Title: Regulatory Project Manager
Date: November 20, 2015

Name of Office/Division Director signing form: Ann T. Farrell, MD
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
11/20/2015

ANN T FARRELL
11/20/2015

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 208462 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A
Division Name: PDUFA Goal Date: Stamp Date: 7/10/2016
Division of Hematology Products March 10, 2016
Proprietary Name: Ninlaro
Established/Generic Name: ixazomib
Dosage Form: capsule
Applicant/Sponsor: Millennium Pharmaceuticals, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	<u> </u> wk. <u> </u> mo.	<u> </u> wk. <u> </u> mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	<u> </u> yr. <u> </u> mo.	<u> </u> yr. <u> </u> mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	<u> </u> yr. <u> </u> mo.	<u> </u> yr. <u> </u> mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	<u> </u> yr. <u> </u> mo.	<u> </u> yr. <u> </u> mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	<u> </u> yr. <u> </u> mo.	<u> </u> yr. <u> </u> mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)
- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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
11/20/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208462 BLA # N/A	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Ninlaro Established/Proper Name: ixazomib Dosage Form: 2.3, 3, and 4 mg capsule		Applicant: Millennium Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A
RPM: Jacquin Jones		Division: Division of Hematology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (notify CDER OND IO) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>March 10, 2016</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		N/A
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): proteasome inhibitor
 (confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: CST SharePoint)

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Approval: November 20, 2015
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	August 25, 2105 - Letter August 25, 2015 - Review
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: September 18, 2015 DMEPA: October 26, 2015 and September 30, 2015 DMPP/PLT: November 16, 2015 OPDP: November 10, 2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	September 4, 2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Orphan Drug Designation</u> 	N/A
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	November 19 (2), 18 (2), 13, 10, 3, and 2, 2015, October 30 (2), 29 (2), 28, 22, 21 (2), 16, 13, 8, 6, 5 (4), and 1 (2), 2015, September 28, 24 (2), 21, 17, 10 and 8, 2015, August 20 (2), 19 (2), 18, 17, 13, and 10, 2015, and July 30 (4), 28, and 15, 2015
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	April 1, 2015
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	November 14, 2011
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	October 13, 2015
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	November 5, 2015
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	CMC meetings: September 18, 2014 (prelim responses) and February 21, 2012 and

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	November 20, 2015
Division Director Summary Review (<i>indicate date for each review</i>)	November 19, 2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	November 17, 2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews • Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review, cosigned November 12, 2015 review
• Clinical review(s) (<i>indicate date for each review</i>)	November 12, 2015
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review dated November 12, 2015, page 76
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
• Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	N/A
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	N/A
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	DRISK: November 16, 2015
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	November 4, 2015 November 5, 2015– Letter
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review, cosigned October 31, 2015 review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review, cosigned October 31, 2014 review
Statistical Review(s) (<i>indicate date for each review</i>)	October 31, 2015

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review, cosigned November 5, 2015 review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review, cosigned November 5, 2015 review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	November 5, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	November 13, 2015
• Supervisory Review(s) <i>(indicate date for each review)</i>	November 9, 2015
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	November 9, 2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	Signed IQA October 29, 2015 review
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	October 30, 2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Methods Validation Report Summary November 12, 2015
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	October 30, 2015 see page 125 in review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable November 12, 2015

Day of Approval Activities

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> N/A
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input checked="" type="checkbox"/> N/A (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input checked="" type="checkbox"/> N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

Jones, Jacquin

From: Jones, Jacquin
Sent: Thursday, November 19, 2015 1:20 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ninlaro(ixazomib): FDA Proposed Labeling -Response due by 3 pm on Nov 19
Attachments: NDA 208462_Ninlaro Label_FDAProposedChanges_v11-19-15_FinalSnt.doc

Dear Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) submission dated July 10, 2015 (SN:0000), which provides for a New Application submission for NDA 208462 Ninlaro (ixazomib). We also, refer you to your November 19, 2015 labeling amendment submitted to the NDA.

The FDA team has reviewed Millennium's revisions and comments to the FDA proposed PI and has provided follow up revisions and comments for Millennium to review in the labeling attached. The revisions for the Patient Package Insert will be provided in a separate e-mail.

- Please review and accept all changes that you agree with.
- Please make proposed edits in tracked changes and provide rationale/comment for the new text.
- **Do not reject** any FDA changes or comments in the label, provide comments as needed.

Please provide a response via email **no later than 3pm, Thursday, November 19, 2015.**

As a reminder, please officially submit your response and revised label (tracked changed and clean) as an amendment to this NDA at the same time you send your response to this e-mail **no later than 3pm, Thursday, November 19, 2015.**

Thank you,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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

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
11/19/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Thursday, November 19, 2015 3:15 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ninlaro(ixazomib): FDA Proposed Labeling and PPI -Response due by 5 pm on Nov 19
Attachments: NDA 208462_Ninlaro LabelandPPI_FDAProposedChanges_v11-19-15_FinalSnt.doc

Dear Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) submission dated July 10, 2015 (SN:0000), which provides for a New Application submission for NDA 208462 Ninlaro (ixazomib). We also, refer you to your November 19, 2015 labeling amendment.

The FDA team has reviewed Millennium's revisions and comments to the FDA proposed Patient Package Insert (PPI) and has provided follow up revisions and comments for Millennium to review in the labeling attached. Also, additional revisions have been made to the PI from the previous version sent today.

- Please review and accept all changes that you agree with.
- Please make proposed edits in tracked changes and provide rationale/comment for the new text.
- **Do not reject** any FDA changes or comments in the label, provide comments as needed.

Please provide a response via email **no later than 5 pm, Thursday, November 19, 2015.**

As a reminder, please officially submit your response and revised label (tracked changed and clean) as an amendment to this NDA at the same time you send your response to this e-mail **no later than 5 pm, Thursday, November 19, 2015.**

Thank you,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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

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
11/19/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Wednesday, November 18, 2015 11:37 AM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ninlaro(ixazomib): FDA Proposed PPI Labeling -Response due by 12 pm on Nov 19
Attachments: NDA 208642_Ninlaro PPI_FDAProposedChangesv11-18-15_FinalSnt.doc

Dear Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) submission dated July 10, 2015 (SN:0000), which provides for a New Application submission for NDA 208462 Ninlaro (ixazomib).

The FDA team has reviewed the Patient Package Insert (PPI) and has provided proposed edits and comments for Millennium's review and feedback for the first round of changes in the attached PPI document.

In the attached document:

- Please review and accept all changes that you agree with in the attached document.
- Please make proposed edits in tracked changes and provide rationale/comment for the new text.
- **Do not reject** any FDA changes or comments in the PPI, provide comments as needed.

Please provide a response and revised document via email **no later than 12pm, Thursday, November 19, 2015.**

As a reminder, please officially submit your response and revised PPI (tracked changed and clean) as a labeling amendment to this NDA at the same time you send your response to this e-mail **no later than 12pm, Thursday, November 19, 2015.**

Thank you,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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

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
11/18/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Wednesday, November 18, 2015 12:19 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ninlaro(ixazomib): FDA Proposed Labeling -Response due by 12 pm on Nov 19
Attachments: NDA 208462_Ninlaro Label_FDAProposedChanges_v11-18-15_FinalSnt.doc

Dear Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) submission dated July 10, 2015 (SN:0000), which provides for a New Application submission for NDA 208462 Ninlaro (ixazomib). We also, refer you to your November 16, 2015 labeling amendment submitted to the NDA.

The FDA team has reviewed Millennium's revisions and comments to the FDA proposed PI and has provided follow up revisions and comments for Millennium to review in the labeling attached.

- Please review and accept all changes that you agree with.
- Please make proposed edits in tracked changes and provide rationale/comment for the new text.
- **Do not reject** any FDA changes or comments in the label, provide comments as needed.

Please provide a response via email **no later than 12pm, Thursday, November 19, 2015.**

As a reminder, please officially submit your response and revised label (tracked changed and clean) as an amendment to this NDA at the same time you send your response to this e-mail **no later than 12pm, Thursday, November 19, 2015.**

Thank you,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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

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
11/18/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Friday, November 13, 2015 6:05 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ninlaro(ixazomib): FDA Proposed Labeling -Response due by 3pm on Nov 16
Attachments: NDA 208462_Ninlaro Label_FDAProposedChangesv11-13-15_FinalSnt.doc

Dear Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) submission dated July 10, 2015 (SN:0000), which provides for a New Application submission for NDA 208462 Ninlaro (ixazomib). We also, refer you to your November 12, 2015 labeling amendment submitted to the NDA.

The FDA team has reviewed Millennium's revisions and comments to the FDA proposed PI submission dated November 12, 2015 and has provided follow up revisions and comments for Millennium to review in the labeling attached.

- Please review and accept all changes that you agree with.
- Please make proposed edits in tracked changes and provide rationale/comment for the new text.
- **Do not reject** any FDA changes or comments in the label, provide comments as needed.

Please provide a response via email **no later than 3pm, Monday, November 16, 2015.**

As a reminder, please officially submit your response and revised label (tracked changed and clean) as an amendment to this NDA at the same time you send your response to this e-mail **no later than 3pm, Monday, November 16, 2015.**

Thank you,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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

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
11/13/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Tuesday, November 10, 2015 2:21 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ninlaro(ixazomib): FDA Proposed Labeling -Response due by 11 am on Nov 12
Attachments: NDA 208462_Ninlaro Label_FDAProposedChanges_v11-10-15.doc

Dear Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) submission dated July 10, 2015 (SN:0000), which provides for a New Application submission for NDA 208462 Ninlaro (ixazomib). We also, refer you to your November 4, 2015 labeling amendment submitted to the NDA.

The FDA team has reviewed Millennium's revisions and comments to the FDA proposed PI submission dated November 4, 2015 and has provided follow up revisions and comments for Millennium to review in the labeling attached.

- Please review and accept all changes that you agree with.
- Please make proposed edits in tracked changes and provide rationale/comment for the new text.
- **Do not reject** any FDA changes or comments in the label, provide comments as needed.

Please provide a response via email **no later than 11 am, Thursday, November 12, 2015.**

As a reminder, please officially submit your response and revised label (tracked changed and clean) as an amendment to this NDA at the same time you send your response to this e-mail **no later than 11 am, Thursday, November 12, 2015.**

Thank you,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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

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
11/10/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Tuesday, November 03, 2015 8:43 AM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium-Clinical Information Request
Attachments: Ninlaro IR Nov 2.doc

Good morning Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer you to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). The Clinical review team has requested that the following tables be filled in with the requested data by **8 am on Thursday, November 5, 2015**. The attached document contains the same requested table information listed below for your reference.

Table A: Safety Population, Size and Denominators

Safety Database for the Study Drug ¹ Individuals exposed to the study drug in this development program N= (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=)	Active Control (n=)	Placebo (n=)
Normal Volunteers			
Controlled trials conducted for this indication ²			
All other than controlled trials conducted for this indication ³			
Controlled trials conducted for other indications ⁴			

¹ *study drug* means the drug being considered for approval.

² to be used in product's labeling

³ if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

⁴ include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Table B. Duration of Exposure

Number of patients exposed to the study drug
--

>=6 months*	>=12 months	>=18 months	>= 24 months or longer
N=	N=	N=	N=

Please submit responses to the information request via e-mail no later than **8 am on Thursday, November 5, 2015**; with a follow up of an official submission of the response information to the NDA file.

Thank you for your reply,

Jackie

Jacquie L. Jones, CDR, BSN, MS, USPHS
 Regulatory Health Project Manager
 Division of Hematology Products
 OHOP/CDER/FDA
 10903 New Hampshire Ave, Bldg 22, RM 2222
 Silver Spring, MD 20903
 Tel: 240-402-4590, Fax: 301-796-9909

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
11/05/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Friday, October 30, 2015 5:44 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ninlaro(ixazomib): FDA Proposed Labeling -Response due by COB Nov 4
Attachments: NDA 208462_Ninlaro_FDAProposedChangestoSpn_v10-30-15.doc

Dear Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) submission dated July 10, 2015 (SN:0000), which provides for a New Application submission for NDA 208462 Ninlaro (ixazomib).

The FDA review team has reviewed the new PI submission and has responded with the labeling attached.

- Please review and accept all changes that you agree with.
- Please make proposed edits in tracked changes and provide rationale/comment for the new text.
- **Do not reject** any FDA changes or comments in the label, provide comments as needed.

Please provide a response via email by **COB, Wednesday, November 4, 2015**.

As a reminder, please officially submit your response and revised label (tracked changed and clean) as an amendment to this NDA at the same time you send your response to this e-mail on **COB, Wednesday, November 4, 2015**.

Thank you,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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

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
10/30/2015

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Friday, October 30, 2015 5:52 PM
To: 'Wang, Li-Chun'
Subject: NDA 208462 Ixazomib Information Request

Hello Li-Chun,

Please see below for the FDA's information request.

This IR is in reference to Millennium's response dated October 22, 2015 to the information request from FDA dated October 16, 2015 as well as the teleconference held on October 30, 2015 at 3:30PM. Your proposal to

(b) (4)

FDA participants for teleconference:

Rabiya Laiq, Regulatory Business Process Manager
Janice Brown, Quality Assessment Lead
Diane Goll, Process and Microbiology Reviewer

MPI Meeting participants:

Li-Chun Wang (GRA CMC)
Satyam Upadrashta (GRA CMC)
Richard Yieh (Tech Ops)
Barry Robins (Commercial QA)
Clare Medendorf (Formulation)
Nick Yankauskas (Analytical)

Thanks,
Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov



Jones, Jacquin

From: Jones, Jacquin
Sent: Thursday, October 29, 2015 2:08 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- CMC Carton Container Information Request

Good afternoon Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer you to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). The CMC review team has an additional comment for the carton container label for ixazomib:

CMC Information Request:

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:

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.

Please submit responses to the information request via e-mail no later than **close of business on Friday October 30, 2015**; with a follow up of an official submission of the response information to the NDA file.

Thank you for your reply,

Jackie

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
10/29/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Thursday, October 29, 2015 5:27 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- Clinical Information Request

Good afternoon Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer you to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). The Clinical review team has the following information request concerning study C16010:

Clinical Information Request:

Regarding study C16010, please provide:

1. Total number of investigators.
2. Number of investigators who are sponsor employees (include both full and part time)
3. Number of investigators with disclosable financial interests/arrangements (Form FDA 3455)
 - Identify the number of investigators in each category (defined in 21 CFR 52.2 (a), (b), (c) and (f)).
 - Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study.
 - Significant payment of other sorts
 - Proprietary interest in the product tested held by investigator
 - Significant equity interest held by investigator in sponsor of covered study
4. Number of investigators with certification of due diligence (Form FDA 3454, box 3)

Please submit responses to the information request via e-mail no later than **Noon on Monday, November 2, 2015**; with a follow up of an official submission of the response information to the NDA file.

Thank you for your reply,

Jackie

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
10/29/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208462

INFORMATION REQUEST

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Director of Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ninlaro (ixazomib) Capsule.

We also refer to your July 10, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1.



(b) (4)

(Please acknowledge the following comments):

2. Regarding your comparability protocol and your (b) (4) and (b) (4) and minor adjustments to process parameters, you proposed the following acceptance criteria: average result is between (b) (4) % of label claim, relative standard deviation of individual results is (b) (4) %, all individual results are within (b) (4) % of the average result. We recommend that you revise the (b) (4) acceptance criteria used for assessing the supportive data to include a limit for the average values in line with the release assay, a fixed range for individuals, and a percentage RSD (i.e., Mean (b) (4) (b) (4) % of labeled amount, All Individuals within (b) (4) % of labeled amount, and (b) (4) % RSD) to assure your product meets the assay specification at release.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by COB October 29, 2015.

Sincerely,

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: 2015.10.28 15:08:01 -04'00'

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jones, Jacquin

From: Jones, Jacquin
Sent: Thursday, October 22, 2015 5:23 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium-Biometrics Information Request

Good afternoon Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer you to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). The Biometrics review team has the following information requests:

Biometric Information Requests:

Please check and resolve the data issues for the patients listed as follows (there are some overlap between two categories):

- Observed PFS (PFS2A) from 2nd interim analysis was smaller than observed PFS (PFS1A) from 1st IA.

USUBJID ARM	PFS2A PFS1A	CNSR2A	CNSR1A	
C16010-02004-003	2.8254620123	0 Ixazomib + LenDex	3.0226	0
C16010-18006-001	19.613963039	1 Ixazomib + LenDex	20.5996	0
C16010-37002-006	0.9199178645	0 LenDex	7.8193	1
C16010-43003-011	2.3983572895	0 LenDex	5.3224	0
C16010-45003-006	2.8254620123	1 Ixazomib + LenDex	4.6982	1
C16010-51002-008	9.4291581109	1 LenDex	10.3162	0
C16010-57006-003	0.0328542094	1 Ixazomib + LenDex	9.7906	1
C16010-57007-002	11.170431211	0 LenDex	11.3347	0
C16010-63027-002	0.0328542094	1 Ixazomib + LenDex	6.5708	1

- The subject already had an event at 1st IA, but the observed PFS was different between two interim analyses, and for some cases patients were even censored at 2nd IA.

USUBJID ARM	PFS2A PFS1A	CNSR2A	CNSR1A	
C16010-02004-003	2.8254620123	0 Ixazomib + LenDex	3.0226	0
C16010-18006-001	19.613963039	1 Ixazomib + LenDex	20.5996	0
C16010-18009-004	16	0 Ixazomib + LenDex	14.5544	0
C16010-22003-022	18.266940452	0 Ixazomib + LenDex	16.4271	0
C16010-27001-005	13.60164271	0 LenDex	13.0103	0
C16010-27002-003	13.371663244	0 Ixazomib + LenDex	12.9117	0
C16010-37001-004	19.613963039	0 Ixazomib + LenDex	18.6940	0

C16010-43003-011	2.3983572895	0 LenDex	5.3224	0
C16010-46002-005	15.704312115	0 LenDex	12.0246	0
C16010-46005-003	1.5770020534	0 LenDex	1.3470	0
C16010-51002-008	9.4291581109	1 LenDex	10.3162	0
C16010-51007-008	12.681724846	1 LenDex	11.0719	0
C16010-52002-001	25.823408624	0 Ixazomib + LenDex	21.4209	0
C16010-57001-006	17.478439425	1 LenDex	10.1191	0
C16010-57007-002	11.170431211	0 LenDex	11.3347	0

Please submit responses to the information request via e-mail no later than **close of business on Friday, October 23, 2015**; with a follow up of an official submission of the response information to the NDA file.

Thank you for your reply,

Jackie

Jacquie L. Jones, CDR, BSN, MS, USPHS
 Regulatory Health Project Manager
 Division of Hematology Products
 OHOP/CDER/FDA
 10903 New Hampshire Ave, Bldg 22, RM 2222
 Silver Spring, MD 20903
 Tel: 240-402-4590, Fax: 301-796-9909

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
10/22/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Wednesday, October 21, 2015 3:11 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- CMC Information Request

Good afternoon Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer you to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). The CMC review team has the following information request for Millennium's NDA 208462 ixazomib labeling:

CMC Information Request:

Ixazomib capsule imprinting for the 3 mg and 4 mg strengths (b) (4) and conflicts with the strength in sections 3 and 16 in the prescribing information. Provide a commitment with a implementation date to change the capsule imprinting from (b) (4) to 3 mg and 4 mg, respectively. Implement this change along with the revision to sections 3 and 16 to include the following:

- 4 mg strength: Light orange, size 3, imprinted with "Takeda" on the cap and (b) (4) mg on the body in black ink.
- (b) (4) mg strength: light grey, size 4, imprinted with "Takeda" on the cap and (b) (4) mg on the body in black ink.

These capsule imprinting and labeling changes can be implemented in your next annual report.

Please submit responses to the information request via e-mail no later than **close of business on Monday, October 26, 2015**; with a follow up of an official submission of the response information to the NDA file.

Thank you for your reply,

Jackie

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
10/21/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208462

INFORMATION REQUEST

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Director of Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ninlaro (ixazomib) Capsule.

We also refer to your July 10, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. [REDACTED]

(b) (4)

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by COB October 21, 2015.

Sincerely,

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: 2015.10.21 09:39:43 -04'00'

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA 208462

MID-CYCLE COMMUNICATION

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Director, Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ninlaro® (ixazomib) capsule, 2.3, 3, and 4 mg.

We also refer to the teleconference between representatives of your firm and the FDA on October 13, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, please call Jacquin Jones, Regulatory Project Manager, at (240) 402-4590.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: October 13, 2015, 8:30 am - 9:00 am (ET)

Application Number: NDA 208462
Product Name: Ninlaro® (ixazomib)
Indication: Treatment of patients with multiple myeloma who have received at least one prior therapy
Applicant Name: Millennium Pharmaceuticals, Inc.

Meeting Chair: Ann T. Farrell, MD
Meeting Recorder: Jacquin Jones, MS, BSN

FDA ATTENDEES

OHOP/Division of Hematology Products

Ann T. Farrell, MD, Director
Alexandria Schwarsin, MD, Medical Officer
Aviva Krauss, MD, Medical Officer
Qin Ryan, MD, PhD, Safety Reviewer
Diane Leaman, Safety Regulatory Project Manager
Amy Baird, Chief, Project Management Staff
Jacquin L. Jones, MS, BSN, Regulatory Project Manager

Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology (DCP) V

Bahru Habtemariam, PharmD, Acting Team Leader
Vicky Hsu, PhD, Clinical Pharmacology Reviewer

OCP/DCP I/Division of Pharmacometrics

Nitin Mehrotra, MPharm, PhD, Team Leader
Dinko Rekić, PhD, MSc (Pharm), Reviewer

Office of Biostatistics/ Division of Biometrics V

Lei Nie, PhD, Biostatistics Team Leader
Yun Wang, PhD, Biostatistics Reviewer

OHOP/Division of Hematology Oncology Toxicology (DHOT)

Christopher Sheth, PhD, Supervisory Pharmacologist
Emily Place, PhD, Pharmacology/Toxicology Reviewer

Office of Pharmaceutical Quality/Office of New Drug Products

Janice Brown, MS, Team Leader
Amit K. Mitra, PhD, Product Quality Reviewer

Office of Surveillance and Epidemiology/Division of Risk Management

Amarilys Vega, MD, Medical Officer

Office of Surveillance and Epidemiology /Division of Pharmacovigilance II

Tracy Salaam, PharmD, Safety Evaluator Team Leader
Regina Lee, PharmD, Safety Evaluator

EASTERN RESEARCH GROUP ATTENDEES

Christopher A. Sese, Independent Assessor

APPLICANT ATTENDEES

Melissa Anderson, RAC, Director, Global Regulatory Affairs
Eileen Bedell, MPH, Senior Director, Global Regulatory Affairs
Melody Brown, Vice President, Global Regulatory Affairs
Cory Ferguson, MHA, Manager, Global Regulatory Affairs
Asha Henderson, Senior Manager, Global Labeling
Pat Thomas, Director, Global Regulatory Affairs
Debbie Berg, RN, MSN, Scientific Director, Oncology Clinical Research
Dixie-Lee Esseltine, MD, Vice President, Oncology Clinical Research
Ai-Min Hui, MD, PhD, Senior Medical Director, Oncology Clinical Research
Helgi van de Velde, MD, Vice President, Oncology Clinical Research
Andy (Xuedong) Chi, PhD, Director, Statistics
Mingxiu Hu, PhD, Vice President, Global Biostatistics
Jianchang Lin, PhD, Senior Statistician, Global Statistics
Guohui Liu, PhD, Scientific Fellow, Global Statistics
Neeraj Gupta, PhD, Director, Clinical Pharmacology
Ben Exter, Director, Pharmacovigilance Sciences
Heather Stein, MD, MPH, Senior Medical Director, Pharmacovigilance
Ray Skwierczynski, PhD, Senior Director, Formulation Sciences
Li-Chun Wang, Director, Global Regulatory Affairs CMC
Alessandra Di Bacco, PhD, Director, Translational Medicine
Stephanie Powlin, PhD, DABT, Associate Scientific Fellow, Drug Safety Research and Evaluation
Cindy Xia, PhD, Director, Drug Metabolism and Pharmacokinetics

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we

may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

No significant approvability issues have been identified to date.

3.0 INFORMATION REQUESTS

3.1. Biostatistics

There are discrepancies in the data for the subgroups and submission of updated PFS results. The Applicant acknowledged the differences and stated that they will review the data further. The Applicant reported that they plan to submit a Topline Data Report around October 30 and requested to have a teleconference prior to the submission. The Agency agreed to the teleconference.

3.2. CMC

There are pending information requests related to issues with the drug product. The Applicant acknowledged the pending responses for the CMC information requests and asked for a date extension for Friday, October 16, 2015. The Agency agreed to the request.

3.3. Clinical and Clinical Pharmacology

The Agency has some concern regarding the safety of ixazomib in patients with renal Impairment and informed the Applicant that they may receive information requests regarding this concern.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

The Division is in the process of determining which safety issues warrant a Warning and Precaution. The Agency is determining how best to describe class effects of proteasome inhibitors in the labeling.

The Clinical Pharmacology team is currently reviewing drug-drug interactions (DDI) of concomitant administration of ixazomib with strong CYP3A4 or CYP1A2 inhibitors or inducers. PMRs may be requested based on the outcome of this review. The Agency informed the Applicant that they may receive information requests regarding DDI.

At this time, no major safety concerns have been identified that would require a REMs.

5.0 ADVISORY COMMITTEE MEETING

At this time, there are no plans for an AC meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for **November 5, 2015**. We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

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

/s/

ROMEO A DE CLARO
10/19/2015

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Friday, October 16, 2015 1:27 PM
To: 'Wang, Li Chun'
Cc: 'melissa.anderson@mpi.com'; Jones, Jacquin
Subject: RE: FDA Information Request NDA 208462-Please Respond by October 23, 2015

Hello Ms. Wang,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ninlaro (ixazomib) Capsule.

We also refer to your July 10, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Process:

(b) (4)

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by October 23, 2015.

Please send us a curtesy email copy of the responses followed by a formal submission through our gateway.

Kindly confirm receipt of this email.

Have a great day,
Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov

Jones, Jacquin

From: Jones, Jacquin
Sent: Tuesday, October 13, 2015 6:23 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- CMC Information Request

Good evening Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). During the NDA (ixazomib) review, the following additional information has been requested by the CMC review team:

[CMC IR](#)

Please submit a picture or graphical representation of each of the capsule strengths.

Please submit the requested information via e-mail no later than **10 am on Thursday, October 15, 2015**; with a follow up of an official submission of the response information to the NDA file.

Thank you for your reply,

Jackie

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
10/13/2015

From: Wall, Laura
To: melissa.anderson@takeda.com
Cc: [Jones, Jacquin](#); [Wall, Laura](#)
Subject: NDA 208462 - FDA Information Request - Please respond by COB Tuesday October 13, 2015
Date: Thursday, October 08, 2015 3:21:00 PM

Dear Melissa,

The clinical review team requests that you respond to the following Information Request:

Please send the total dose of lenalidomide per patient for subgroups of CrCl \geq 60 and CrCl < 60 at baseline.

To expedite the review, please send your response to Jackie via e-mail and officially to your application by **COB Tuesday October 13, 2015**.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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

/s/

LAURA C WALL
10/08/2015



NDA 208462

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Director Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ninlaro® (ixazomib) capsule, 2.3, 3, and 4 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 13, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, please call Jacquin Jones, Regulatory Project Manager, at (240) 402-4590.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: October 13, 2015, 8:30 am -9:00 am (ET)
Meeting Location: Teleconference

Application Number: NDA 208462
Product Name: Ninlaro® (ixazomib)
Indication: Treatment of patients with multiple myeloma who have received at least one prior therapy

Sponsor/Applicant Name: Millennium Pharmaceuticals, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review Letters have been issued to date.

2. Substantive Review Issues

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

There are no major safety concerns have been identified at this time that would need a REMS.

LCM AGENDA

1. Introductory Comments – RPM/CDTL

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Information Requests

We note the following information requests that are awaiting your response:

2.1. Biostatistics: Discrepancies in the subgroups and submission of updated PFS results

2.2. CMC: Issues related to drug product and drug substance.

2.3. Clinical and Clinical Pharmacology: Safety of ixazomib in patients with renal impairment.

3. Postmarketing Requirements/Postmarketing Commitments

The Clinical Pharmacology team is currently reviewing DDI regarding concomitant administration of ixazomib with strong CYP3A4 or CYP1A2 inhibitor. PMR(s) may be requested based on the outcome of this review.

4. Major labeling issues

The Agency is in the process of determining safety concerns that should be a Warning and Precaution. The Agency is determining how best to describe class effects of proteasome inhibitors.

5. Wrap-up and Action Items

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

/s/

ROMEO A DE CLARO
10/06/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Monday, October 05, 2015 9:57 AM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- Statistical Information Request

Good morning Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). During the NDA (ixazomib) review, the following additional information has been requested by the Statistical review team:

Statistical IR

The current data suggested small or no treatment effect on PFS in some subgroups, such as patients with creatinine level < 60 ml/min. Please perform further exploratory analyses to address the concern that Ninlaro may be ineffective for some patients, e.g. patients with renal impairment. When you submit 2nd interim analysis (final analysis for PFS) results, please also submit subgroup analyses of final PFS data, including subgroup analyses by creatinine level (<60 vs. ≥ 60), region (North America vs. Other), and prior therapy (1 vs. 2 or 3). In addition, discuss how you plan to address the lack of robustness of the treatment effect on PFS in these subgroups.

Please submit your response to the above information request in Millennium's proposed **October 8** submission based on the second interim analysis (final analysis for PFS). Please submit the requested information via e-mail with a follow up of an official submission of the response information to the NDA file.

Please confirm receipt of this email.

Have a wonderful day,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
10/05/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Monday, October 05, 2015 1:35 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- DMEPA and OPQ Carton and Container Recommendations

Good afternoon Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer you to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). The Division of Medication Error Prevention and Analysis (DMEPA) and Office of Product Quality (OPQ) have the following recommendations for Millennium's NDA 208462 ixazomib carton and container:

Carton & Container Recommendations:

- A. Outer Shell Pak Carton Labeling & Outer Shell Pak Carton Labeling—Sample
- a. The color scheme utilized in the Ninlaro 4 mg strength labels (orange) is identical to the font color (orange) used for the presentation of the proprietary name for all Ninlaro strengths. The use of the same orange color minimizes the difference between the strengths, which may lead to wrong strength selection errors.¹ Additionally, the limited use of the color only in the name on the container label does not adequately distinguish the strengths within the Ninlaro product line. Revise the labels to increase utilization of these colors throughout the label (such as highlighting the strength and name in the same color) to adequately differentiate the strengths (e.g., consider revising Ninlaro 3 mg to present the proprietary name, the strength statement, and the packaging color scheme all in blue) or alternatively use a unique color font for the presentation of the proprietary name that does not overlap with the font color of any of the strength presentations.
 - b. We recommend relocating the circular logo on principal display panel (PDP) away from the proprietary name as it competes for prominence and could be misinterpreted as the letter "O" and as part of the proprietary name.¹
 - c. Relocate the net quantity statement away from the product strength. Additionally, reduce the prominence of the net quantity statement as it has similar prominence to the strength statement. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.¹ Moreover, risk of confusion increased because the net quantity has the same numerical value as one of the product's strengths.
 - d. Relocate the "Rx Only" statement from the side panel to the PDP.
- B. Outer Shell Pak Labeling & Outer Shell Pak Labeling—Sample
- a. See recommendations A.a, A.b., and A.c. and revise accordingly.
 - b. Relocate the "Rx Only" statement from the back panel to the PDP.
 - c. If space permits, consider adding the statements (b) (4) " and (b) (4) to the side panels.
- C. Inner Shell Pak Label
- a. See recommendation A.a. and revise accordingly.
 - b. Revise the label to include the proprietary name, established name, strength, lot number and manufacturer per 21 CFR 201.10(i).

- c. Revise the statement (b) (4) to an affirmative statement such as, “Remove capsule right before taking your dose”. We recommend this revision due to post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word (b) (4) can be overlooked and misinterpret the warning as an affirmative action.²
- d. Modify the second sentence under Directions for Use to read “Unless otherwise instructed, take one capsule once a week on the same day and at approximately the same time for the first 3 weeks of a 4 week cycle.” This modification will increase clarity regarding the dosing regimen.
- e. 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.” This revision will help to improve the visibility of the primary storage statement.

References:

^[1] 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>.

² Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

Please submit responses to the recommendations via e-mail no later than **1 pm on Friday, October 9, 2015**; with a follow up of an official submission of the response information to the NDA file.

Thank you for your reply,

Jackie

Jacquie L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
10/05/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Monday, October 05, 2015 1:47 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- Clinical Pharmacology Information Request

Good afternoon Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). During the NDA (ixazomib) review, the following additional information has been requested by the Clinical Pharmacology review team:

[Clinical Pharmacology IR](#)

- Regarding your Phase 3 Study C16010, please provide a table showing the rates of Grade 3 or worse adverse events (AEs) AND the rates of dose reduction and discontinuation due to AEs for each agent in the placebo+LenDex or ixazomib+LenDex arm based on renal impairment category (normal, mild, moderate, severe according to FDA guidance).
- Please also confirm whether the patients who entered the Study with severe renal impairment at baseline received 4 mg ixazomib starting dose.

Please submit the requested information via e-mail no later than **10 am on Thursday, October 8, 2015**; with a follow up of an official submission of the response information to the NDA file.

Thank you for your reply,

Jackie

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
10/05/2015



NDA 208462

INFORMATION REQUEST

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Director of Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ninlaro (ixazomib) Capsule.

We also refer to your July 10, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. 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.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by October 13, 2015.

Sincerely,

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: 2015.10.05 18:59:44 -04'00'

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jones, Jacquin

From: Jones, Jacquin
Sent: Thursday, October 01, 2015 3:23 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- Clinical Information Request

Good afternoon Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). During the NDA (ixazomib) review, the following additional information has been requested by the Clinical review team:

Clinical Information Request

- Are there any reported cases of Posterior Reversible Encephalopathy Syndrome or Reversible Posterior Leukoencephalopathy Syndrome in the ixazomib development program. Provide a narrative and clinical context of all cases.

Please submit the requested information via e-mail no later than **10am on Wednesday, October 7, 2015**; with a follow up of an official submission of the response information to the NDA file.

Thank you for your reply,

Jackie

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
10/01/2015



NDA 208462

INFORMATION REQUEST

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Director of Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ninlaro (ixazomib) Capsule.

We also refer to your July 10, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Product

- 1) Discuss if lot-to-lot variability in talc and magnesium stearate properties (e.g. bulk density, particle size, surface area) impact drug product quality and what those impacts are. If there is an adverse impact, include appropriate mitigation steps including control strategies.
- 2) Discuss the impact of [REDACTED] ^{(b) (4)} gelatin capsules on stability of the drug product. If there is an adverse impact, adopt an appropriate control strategy.
- 3) For the assay and related substances assay method, include a justified resolution factor in the system suitability criteria.
- 4) Since the drug product [REDACTED] ^{(b) (4)} for the finished drug product in the blister pack.
- 5) Provide supplier's certificates of analysis, physical properties, and your acceptance criteria for the blister components including an identification test method. Provide CFR

citations for all blister pack components as indirect food additive. Provide USP <671>
test results for the blister pack [REDACTED] (b) (4)

- 6) Provide your acceptance criteria for bulk packaging components and include CFR citation for indirect food contact for individual components.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by October 15, 2015.

Sincerely,

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: 2015.10.01 17:46:45 -04'00'

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jones, Jacquin

From: Jones, Jacquin
Sent: Thursday, September 24, 2015 1:40 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- Clinical Information Request

Categories: REMINDER

Good afternoon Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). During the NDA (ixazomib) review, the following additional information has been requested by the Clinical review team:

Clinical IR

1. In the ADAE dataset for study C16010, there are two flags for dose adjustment, [REDACTED] ^{(b) (4)}. In simple language explain the difference between the two.
2. In the proposed Prescribing Information in Table 3 some preferred terms represent a pooling of terms. Please indicate which terms are pooled.

Please submit the requested information via e-mail no later than **3pm on Tuesday, September 29, 2015**; with a follow up of an official submission of the response information to the NDA file.

Thank you for your reply,

Jackie

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
09/28/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Monday, September 28, 2015 7:33 AM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- Clinical Pharmacology Information Request

Good morning Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). During the NDA (ixazomib) review, the following additional information has been requested by the Clinical Pharmacology review team:

Clinical Pharmacology IR

1. *Population PK report (#MIL-PKPD-MLN9708-021) indicates that the analysis dataset included 36 patients on strong CYP1A2-inhibitors (ciprofloxacin) and 16 patients on strong CYP3A4-inhibitors (9 clarithromycin, 4 itraconazole, 3 voriconazole) during the active ixazomib treatment period. However, we are not able to confirm the number of subjects on that received strong CYP1A2 inhibitors or strong CYP3A4 inhibitors in dataset mln9708-pk-20150331-csv.xpt.*
2. *Please provide unique subject identifier for each subject on strong CYP1A2-inhibitors and on strong CYP3A4-inhibitors. If needed submit an updated NONMEM dataset that includes all subjects on strong CYP1A2-inhibitors (ciprofloxacin) and strong CYP3A4-inhibitors.*
3. *Data should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.*

Please submit the requested information via e-mail no later than **1pm on Wednesday, September 30, 2015**; with a follow up of an official submission of the response information to the NDA file.

Thank you for your reply,

Jackie

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
09/28/2015



NDA 208462

INFORMATION REQUEST

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Director of Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ninlaro (ixazomib) Capsule.

We also refer to your July 10, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. 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.
2. 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.

Drug Product



If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by October 1, 2015.

Sincerely,

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: 2015.09.24 14:42:40 -0400'

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jones, Jacquin

From: Jones, Jacquin
Sent: Monday, September 21, 2015 9:19 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- Clinical Pharmacology Information Request

Good evening Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). During the NDA (ixazomib) review, the following additional information has been requested by the Clinical Pharmacology review team:

Clinical Pharmacology IR

- 1) *In Study C16009, you state a period effect was observed in Arm 2 (relative bioavailability study) and Arm 3 (food effect study), thereby confounding the results observed in Arm 1 (ketoconazole DDI study). Please clarify on what may have caused this period effect. If you have submitted documentations supporting the period effect in the NDA, please provide the locations of such files.*
- 2) *You state that non-CYP metabolism of ixazomib occurs at clinical concentration. Please provide additional detail regarding the non-CYP metabolic pathway of ixazomib. Similarly, if you have submitted documentations detailing the non-CYP metabolic pathway of ixazomib with the NDA, please indicate the locations of such files.*

Please submit the requested information via e-mail no later than **10 am on Thursday, September 24, 2015**; with a follow up of an official submission of the response information to the NDA file.

Thank you for your reply,

Jackie
Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
09/21/2015



IND104482

MEETING PRELIMINARY COMMENTS

Millennium Pharmaceuticals, Inc.
Attention: Li-Chun Wang, PhD
Director, Global Regulatory Affairs – CMC
40 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Wang:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MLN9708 (ixazomib citrate).

We also refer to your July 2, 2014, correspondence, received Millennium's development strategies, requesting a meeting to discuss Millennium's development strategies.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA, CMC

Meeting Date and Time: September 22, 2014, 2:00-3:00PM (EST)
Meeting Location: White Oak Building 21, Conference Room: 1415

Application Number: IND 104482
Product Name: MLN9708 (ixazomib citrate)
Indication: Treatment of Advanced Malignancies
Sponsor/Applicant Name: Millennium Pharmaceuticals, Inc.

FDA ATTENDEES (tentative)

Ali Al Hakim, Branch Chief, ONDQA
Janice Brown, CMC, Lead, ONDQA
William Adams, CMC Reviewer, ONDQA
Sandra Suarez, Biopharmaceutics Reviewer, ONDQA
Theresa Carioti, Regulatory Project Manager, DHP
Teicher Agosto, Regulatory Project Manager, ONDQA

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 22, 2014; 2:00-3:00PM (EST) between Sponsor and the Division of Division of New Drug Quality Assessment I. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Millennium Pharmaceuticals, Inc. ("Millennium") is currently developing MLN9708, a selective small molecule proteasome inhibitor, for the treatment of advanced

malignancies, including multiple myeloma. Millennium has requested a Pre-NDA, CMC, Type B meeting with the Office of New Drug Quality Assessment (“ONDQA”) to discuss the Millennium’s development strategies. The meeting packages were received on August 20, 2014.

2.0 DISCUSSION

Question 1:

A table of the previous quality recommendations from the End-Of-Phase 2 (EOP2) meeting, and subsequent follow-up meetings and their status is provided below. The minutes of these meetings are provided in Appendices A, B and C.

Does the FDA concur that all previous quality comments are adequately addressed?

FDA Response:

We have evaluated your submissions dated 12 January 2012 (serial number 148), 15 February 2012 (serial number 162), 29 October 2013 (serial number 423), 12 March 2014 (serial number 504) and 19 August 2014 (serial number 611); and have responded to the proposal on 08 February 2012, 02 March 2012, 19 February 2014, and 12 March 2014. The conclusion regarding the proposed regulatory starting materials has not changed. Designate the regulatory starting materials earlier in the drug substance manufacturing process.

Refer to FDA response to 5-c regarding dissolution.

Question2:

Reference is made to the position paper submitted to the FDA on 29 October 2013: Request for Feedback, *Justification for Proposed Regulatory Starting Materials for Ixazomib Citrate Drug Substance*, (b) (4). Reference is also made to the written advice received from the FDA on 19 February 2014 and from the clarification teleconference of 13 March 2014. The FDA discussed the residual concerns before possibly accepting the (b) (4) proposed regulatory starting materials. Based on this advice and subsequent clarification, Millennium is making the following commitments to the FDA regarding the proposed regulatory starting material (b) (4)

(b) (4)

(b) (4)

Does the FDA agree that the above commitments to the FDA now alleviate concerns regarding (b) (4) as a regulatory starting material?

FDA Response:

Refer to our response to question 1 regarding the proposed regulatory starting materials.

Question 3:

Reference is made to the position paper submitted to the FDA on 29 October 2013: Request for Feedback, *Justification for Proposed Regulatory Starting Materials for Ixazomib Citrate Drug Substance* (b) (4). Reference is also made to the written advice received from the FDA on 19 February 2014 and from the clarification teleconference of 13 March 2014. The FDA discussed the residual concerns before possibly accepting the (b) (4) proposed regulatory starting materials. Based on this advice and subsequent clarification, Millennium would like to confirm that the following commitments will be made and the appropriate information will be included in the NDA regarding the proposed regulatory starting material (b) (4)

(b) (4)

Does the FDA agree that the above commitments now satisfy the FDA's concerns regarding (b) (4) as a regulatory starting material?

FDA Response:

Refer to our response to question 1 regarding the proposed regulatory starting materials.

Question 4:

The proposed ixazomib citrate release and stability specifications to control the quality of the commercial drug substance are presented below (Table Q4-1). Tests and corresponding acceptance criteria are consistent with the relevant guidance documents, available safety information, stability data (including registration stability data and other representative stability data), and manufacturing process capability.

Question 4-a:

Does the FDA agree with Millennium's approach to setting the limit for the ixazomib citrate enantiomer in the final drug substance?

FDA Response:

We agree with the approach for setting the limit for ixazomib citrate enantiomer; however, a final determination regarding the proposed limit will be made during the review of your NDA submission.

Question 4-b:

(b) (4)

Does the FDA support Millennium's approach to use the ICH M7 guidance and extrapolate the TTC for setting the unspecified impurities limit in the drug substance?

FDA Response:

We agree with the approach for setting the unspecified impurities limit; however, a final determination regarding the proposed limit will be made during the review of your NDA submission.

Question 4-c:

(b) (4)

Does the FDA agree with the proposal to (b) (4) testing in drug substance for commercial batches?

FDA Response:

Your proposal to (b) (4) testing in the drug substance appears to be acceptable provided that the batches listed in table 3.2.S.4.4-2 of the amendment dated 19 August 2014 (serial number 0610) were produced using the proposed commercial manufacturing process. Include in your NDA the justification and batch data to support

your proposal. Note that the final determination of the drug substance specification is a review issue and will be based on the information provided in the NDA submission.

Question 4-d:

Ixazomib citrate has been monitored for microbiological attributes as per USP <61> and USP <62> at the time of release and on stability throughout development. The tests have included total aerobic microbial count, total yeasts and molds, and absence of *E. Coli*; all materials have complied with current specifications, to date. Drug substance characterization shows the drug substance (b) (4) and over the course of stability studies. Finally, the drug substance is used to make ixazomib capsules which are a non-sterile drug product.

Does the FDA agree to exclude microbiological testing in drug substance for commercial batches?

FDA Response:

(b) (4)

Question 4-e:

(b) (4)

Does the FDA agree to (b) (4) DMF in drug substance for commercial batches?

FDA Response:

Your proposal to (b) (4) DMF testing in the drug substance appears to be acceptable provided that the batches listed in table 3.2.S.4.4-2 (serial number 0610) were produced (b) (4) (b) (4)s. **Include in your NDA the justification and batch data to support your proposal. Note that the final determination of the drug substance specification is a review issue and will be based on the information provided in the NDA submission.**

Question 4-f:

Millennium has tested the final drug substance for heavy metals as per USP <231>II throughout development. (b) (4) (b) (4) Since the proposed specification limits for each element align with USP <232> and there is

limited process capability with this new method, does the FDA agree that the calculated ixazomib daily limit for each element are appropriate for control of drug substance quality?

FDA Response:

Your proposal is acceptable provided that retrospective testing for elemental impurities using ICP-MS cannot be performed on previously manufactured drug substance batches. Include in your NDA reasons why you were unsuccessful along with a commitment to evaluate the elemental impurity limits once enough drug substance batches are manufactured.

Question 4-g:

Does the FDA agree that the proposed attributes for release and stability testing included in Table Q4-1 are appropriate for controlling the quality of drug substance for commercial materials?

FDA Response:

The proposed tests appear to be adequate. The final conclusion regarding the proposed tests, analytical methods and acceptance criteria will be made at the time of NDA review. Refer also to the responses to questions 4-a through 4-f above.

Question 5:

The proposed ixazomib capsules release and stability test attributes and specifications to control the quality of proposed drug product for commercial use are presented below (Table Q5-1). Tests and corresponding acceptance criteria are consistent with relevant guidance documents, available safety information, stability data (including registration stability data and other representative stability data), and manufacturing process capability.

Question 5-a:



Does the FDA agree to exclude ixazomib testing in ixazomib capsules for commercial batches?

FDA Response:

Your proposal is acceptable as long as you control the three impurities/degradants of boronic acid (ixazomib) in the drug substance specification.

Question 5-b:

Millennium has tested ixazomib capsules for (b) (4) purity on all batches at release and on stability. The (b) (4) levels in the capsules have been consistently below the limit of quantitation (u) (4) % at release and on stability.

Based on the capsule data showing no change in (b) (4) levels after the manufacturing along with no increase observed on stability, does the FDA agree to exclude (b) (4) testing in ixazomib capsules for commercial batches?

FDA Response:

Your proposal to exclude (b) (4) testing in the drug product appears to be acceptable provided that the batches listed in table 3.2.S.4.4-2 (serial number 0610) were produced using the proposed commercial manufacturing process. The proposal to eliminate this test should be justified by supporting data and a discussion of how the (b) (4) could form over time. Include in your NDA the justification and batch data to support your proposal. Note that the final determination of the drug substance specification is a review issue and will be based on the information provided in the NDA submission.

Question 5-c:

Reference is made to the position paper submitted to the FDA on 29 October 2013: Request for Feedback, Appendix A – “Justification for Disintegration Testing In-Lieu of Dissolution Testing for Ixazomib Capsules.” (MLN9708, IND 104,482, Serial Number 0423) Reference is also made to the written advice received from the FDA on 12 February 2014, the clarification teleconference on 13 March 2014, and the email from FDA received on 21 March 2014. Does the FDA agree that Millennium may utilize disintegration testing in lieu of dissolution testing for ixazomib capsules for commercial batches?

FDA Response:

There is insufficient information on the meeting package to reach a conclusion on using disintegration testing in lieu of dissolution testing. Provide the following information/data:

(b) (4)



Additionally, please note that FDA’s acceptance of using disintegration in lieu of dissolution is a review issue under the NDA; therefore, both disintegration and dissolution profile data using an adequate dissolution test should be collected for the biobatches and primary stability batches and provided under the NDA. Also note that SUPAC changes under post-approval supplements should be supported with dissolution profile comparison data and the results from an appropriate statistical test demonstrating dissolution profile similarity (e.g., f2 test).

Question 5-d:

Millennium has conducted microbiologic examination of ixazomib capsules throughout development at release and on stability. Testing has followed USP <61> and <62> for total aerobic microbial count, total combined yeasts and molds count, and absence of *E. coli* with all results in compliance with specifications defined in USP <1111>.

(b) (4)

(b) (4)

Does the FDA agree to exclude microbiological testing in ixazomib capsules for commercial batches?

FDA Response:

(b) (4)

Question 5-e:

(b) (4)

(b) (4)

FDA Response:

The determination of the drug substance particle size limit in the drug substance specification is a review issue and will be based on the information provided in the NDA submission.

(b) (4)

- ii. Does the FDA agree with this approach to using an Arrhenius analysis to estimate the (b) (4) months storage at 30°C/75% RH?

FDA Response:

We agree with the approach for setting the limit for ixazomib citrate (b) (4); however, a final determination regarding the proposed limit will be made during the review of your NDA submission.

The NDA should include a discussion of factors that influence the degradation profile for drug substance and drug product. The use of drug substance particle size and models for estimating levels of product degradation are acceptable, but should be explained in detail and appropriately justified.

Question 5f:

Does the FDA agree that the proposed attributes for release and on stability in Table Q5-1 are appropriate for controlling the quality of drug product for commercial materials?

FDA Response:

The tests listed in table Q5-1 appear to be adequate in that they address identity, assay, purity, dosage uniformity and drug release. The final conclusion regarding the proposed tests, analytical methods and acceptance criteria will be made at the time of NDA review. Refer also to the responses to questions 5-a through 5-e above.

Question 6:

(b) (4)

FDA Response:

FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)]. However, FDA does not prescribe how that is to be

accomplished nor does it approve or review process validation plans/approaches used for process validation studies as it will depend on multiple factors. Some of these are specific to the complexity of the product manufacturing process and the batch scale. Full-scale process validation studies are required to be completed prior to distribution of the commercial product. Prior to marketed product distribution, it is necessary for firms to justify and confirm earlier process design and development work for their proposed scale down to commercial scale.

[Redacted] (b) (4)

Question 7:

[Redacted] (b) (4)

Does the FDA agree this is an acceptable approach for validation and the [Redacted] (b) (4)

[Redacted]

FDA Response:

[Redacted] (b) (4)

(b) (4)

For additional information, please refer to “Guidance for Industry, Process Validation: General Principles and Practices” posted at the following link.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>.

(b) (4)

Question 8:

Millennium will submit 18 months of registration stability data for the drug product in the NDA. In addition, Millennium would like to provide the 24-month registration stability update within 30 days of the NDA submission.

Will the FDA accept this additional stability update without jeopardizing the PDUFA NDA Review timelines?

FDA Response:

Yes, your proposal is acceptable.

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

/s/

JEWELL D MARTIN
09/18/2014

ALI H AL HAKIM
09/18/2014



NDA 208462

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC, Director, Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ixazomib citrate capsules (2.3, 3.0 and 4.0 mg).

We will also be performing methods validation studies on ixazomib citrate drug substance, as described in NDA 208462.

In order to perform the necessary testing, we request the following sample materials and equipment:

Method, current version

Test #	Test Name
MLN9708-29278 ver 1.0	Analytical Procedure for Assay and Impurities by HPLC

Samples and Reference Standards

(b) (4) of Ixazomib Citrate Drug Substance

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S. Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (michael.hadwiger@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael E. Hadwiger, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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

/s/

MICHAEL E HADWIGER
09/17/2015
Request for drug substance



NDA 208462

**METHODS VALIDATION
MATERIALS RECEIVED**

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC, Director, Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ixazomib citrate capsules (2.3, 3.0 and 4.0 mg) and to our 8/20/2015, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 9/10/2015, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (Michael.Hadwiger@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael E. Hadwiger, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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

/s/

MICHAEL E HADWIGER

09/10/2015

Sample receipt acknowledgement



NDA 208462

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Director Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) dated July 10, 2015, received July 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Ninlaro (ixazomib) capsule, 2.3, 3, and 4 mg.

We also refer to your amendments dated July 15 and 31, 2015, August 6, 7, 13, 20, 21, and 24, 2015 and September 1, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a) this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is March 10, 2016. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

We are reviewing your application according to the processes described in *the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 10, 2015. This date conforms to the 21st Century Review timeline for your application. If our

review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

In addition, the planned date for our internal mid-cycle review meeting is October 2, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, please call Jacquin Jones, Regulatory Project Manager, at (240) 402-4590.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

ANN T FARRELL
09/08/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208462

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

ATTENTION: Melissa Anderson, RAC
Global Regulatory Affairs, Director

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) dated and received July 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ixazomib Capsules, 2.3 mg, 3 mg, and 4 mg.

We also refer to your correspondence, dated and received July 15, 2015, requesting review of your proposed proprietary name, Ninlaro.

We have completed our review of the proposed proprietary name, Ninlaro, and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your July 15, 2015, submission(s) are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, Pharm.D., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Jacquin Jones, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4590.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

TODD D BRIDGES
08/25/2015



NDA 208462

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC, Director, Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ixazomib citrate capsules (2.3, 3.0 and 4.0 mg).

We will be performing methods validation studies on ixazomib citrate capsules (2.3 and 4.0 mg), as described in NDA 208462.

In order to perform the necessary testing, we request the following sample materials and equipment:

Method, current version

Test #	Test Name
MLN9708-29278 ver 1.0	Analytical Procedure for Assay and Impurities by HPLC
MLN9708-29280 Ver 1.0	Analytical Procedure for (b) (4)
MLN9708-29279 Ver. 1.0	Analytical Procedure for identification and Ixazomib Content by HPLC
MLN9708 (b) (4) Ver. 1.0	Analytical Procedure for Ixazomib citrate - (b) (4)
MLN9708 (b) (4) Ver. 1.0	Analytical procedure for ixazomib capsules - Identification, Assay, AND Related Substances BY HPLC
MLN9708-29290 Ver. 1.0	Analytical Procedure for Ixazomib capsules - Dissolution with HPLC

Samples and Reference Standards

- (b) (4) mg of Ixazomib Citrate Reference Standard
- (b) (4) mg Ixazomib Reference Standard (Test MLN9708-29279 Ver. 1.0)
- (b) (4) mg Ixazomib Citrate (b) (4)
- (b) (4) Ixazomib Citrate capsules, 2.3 mg strength
- (b) (4) Ixazomib Citrate capsules, 4 mg strength

Equipment

- (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S. Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (michael.hadwiger@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael E. Hadwiger, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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

/s/

MICHAEL E HADWIGER
08/20/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Thursday, August 20, 2015 12:46 PM
To: 'Anderson, Melissa'
Subject: FDA Response: NDA 208462 Ixazomib Millennium: 120-Day Safety Update/Data Submissions

Good afternoon Ms. Anderson,

Thank you for providing Millennium's responses to the NDA 208462 Ixazomib 120-Day Safety Update/Data Submissions information request. The review team has provided the below response to your question in Comment 3:

FDA Response:

- The Division recommends to proceed with the timeline as the Sponsor outlined in response to Question 3.
- For submission of tables and figures for the ITT population during the week of 19 October 2015, the Division recommends inclusion of PFS by investigator, in addition to the PFS by IRC and OS results.

Please let me know if your team has further questions.

Regards,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

From: Anderson, Melissa [<mailto:melissa.anderson@takeda.com>]
Sent: Thursday, August 20, 2015 11:36 AM
To: Jones, Jacquin
Subject: Response Attached: NDA 208462 Ixazomib Millennium: 120-Day Safety Update/Data Submissions
Importance: High

Dear Jackie,

Our response to this request is attached. The official submission will go through the gateway this afternoon.

Please note that we have included a question to the review team within our response to Comment 3.

Kind regards,
Melissa

Melissa Anderson, RAC

Director, Global Regulatory Affairs Development, Oncology
Ixazomib Global Regulatory Lead
Takeda Pharmaceuticals International Co., Inc.
Phone: 617-444-2209
Fax: 617-444-2399
melissa.anderson@takeda.com

From: Anderson, Melissa
Sent: Wednesday, August 19, 2015 11:57 AM
To: 'Jones, Jacquin'
Subject: RE: NDA 208462 Ixazomib Millennium: 120-Day Safety Update/Data Submissions

Dear Jackie,

I'm confirming receipt of this request. We will respond by tomorrow as requested.

Kind regards,
Melissa

Melissa Anderson, RAC

Director, Global Regulatory Affairs Development, Oncology
Ixazomib Global Regulatory Lead
Takeda Pharmaceuticals International Co., Inc.
Phone: 617-444-2209
Fax: 617-444-2399
melissa.anderson@takeda.com

From: Jones, Jacquin [<mailto:Jacquin.Jones@fda.hhs.gov>]
Sent: Wednesday, August 19, 2015 11:50 AM
To: Anderson, Melissa
Subject: NDA 208462 Ixazomib Millennium: 120-Day Safety Update/Data Submissions
Importance: High

Good morning Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). Your NDA (ixazomib) is currently under review and we have the following information request that require a **quick response time**:

FDA Requested Information:

1. What is the proposed submission date for the 120-day safety update? What is the data cut-off date for the 120-day safety update?
2. What is the proposed submission date for the datasets and results for the OS and PFS analysis based on interim analysis 2 for clinical trial C16010? What is the data cut-off date for interim analysis 2?
3. Discuss the feasibility of submitting items 1 and 2 by September 15, 2015, and comment whether any adjustments will need to be made on the data cut-off dates.

We respectfully request your response **no later than 12 pm on August 20, 2015 (tomorrow)**.

Please confirm receipt of this information request.

Thank you for your reply,

Jacquie L. Jones, CDR, BSN, MS, USPHS

Regulatory Health Project Manager

Division of Hematology Products

OHOP/CDER/FDA

10903 New Hampshire Ave, Bldg 22, RM 2222

Silver Spring, MD 20903

Tel: 240-402-4590, Fax: 301-796-9909

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
08/20/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Wednesday, August 19, 2015 11:50 AM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium: 120-Day Safety Update/Data Submissions

Importance: High

Good morning Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). Your NDA (ixazomib) is currently under review and we have the following information request that require a *quick response time*:

FDA Requested Information:

1. What is the proposed submission date for the 120-day safety update? What is the data cut-off date for the 120-day safety update?
2. What is the proposed submission date for the datasets and results for the OS and PFS analysis based on interim analysis 2 for clinical trial C16010? What is the data cut-off date for interim analysis 2?
3. Discuss the feasibility of submitting items 1 and 2 by September 15, 2015, and comment whether any adjustments will need to be made on the data cut-off dates.

We respectfully request your response **no later than 12 pm on August 20, 2015 (tomorrow)**.

Please confirm receipt of this information request.

Thank you for your reply,

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
08/19/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Wednesday, August 19, 2015 3:33 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 ixazomib: Internal Mock-up Package

Good afternoon Ms. Anderson,

The review team has said that an internal mock-up package sample from Millennium for NDA 208462 ixazomib, with a delivery date of September 1st or sooner, would be helpful during the review process.

The mock-up would be in addition to the product packaging sample requested for a September 9th delivery date. At the time of sending the samples, please provide 2 internal mock-ups and 2 product packages for review.

Please send the samples to my office address listed below:

- Jacquin Jones
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2222
10903 New Hampshire Avenue
Silver Spring, MD 20993

Please confirm receipt of this request.

Thank you for your reply,

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

From: Jones, Jacquin
Sent: Monday, August 17, 2015 10:20 PM
To: 'Anderson, Melissa'
Cc: Laiq, Rabiya
Subject: FDA Response: NDA 208462 ixazomib: Proposal for submitting secondary packaging change

Good evening Ms. Anderson,

The Agency agrees with Millennium's proposal to submit an alternative packaging design, along with the associated artwork, as an NDA amendment by September 1. Please provide samples of the product packaging and art design by September 9 for the FDA team to review.

Have a wonderful evening,

Jackie

Jacquie L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

From: Anderson, Melissa [<mailto:melissa.anderson@takeda.com>]
Sent: Friday, August 14, 2015 8:33 AM
To: Jones, Jacquie; Laiq, Rabiya
Subject: NDA 208462 ixazomib: Proposal for submitting secondary packaging change

Dear Jackie and Rabiya,

Per our conversation with Jackie after the Applicant Orientation Meeting this week, concerning our desire to accelerate, if possible, the review of the packaging components, we are providing the following details for your and the CMC reviewers' information. Please feel free to let us know if there is additional information required.

Background

Ixazomib capsules are packaged in a blister (b) (4)
(b) (4) The primary packaging component is PVC-aluminum/aluminum blister. The secondary packaging components include a blister card carrier which holds the blister strip (b) (4)
(b) (4) design has achieved F=1 results for (b) (4) testing for a number of currently marketed products; however, the ixazomib custom design has not achieved such results, yet. Redesign and testing is ongoing, but a second design for the secondary packaging is now being pursued on a parallel path. This alternative design has already passed (b) (4) testing.

Status and Request

As redesign and testing of the primary design may give way to the alternative design, Takeda proposes to submit this alternative design, along with its associated artwork, as an NDA amendment by September 1. The only changed NDA components will be packaging artwork in Module 1. Please note that the primary blister component remains unchanged; therefore, there is no change to product contact, blister size or any other attribute which could impact product quality.

In addition, we have been notified by our packaging site that it will take a minimum of 6 weeks to proof, review, print and deliver these specialized packaging components. We would greatly appreciate if the Agency could prioritize the review of the packaging components over other parts of the application and provide their comments and feedback on the packaging and artwork as early in the process as possible. It would enable us to incorporate any suggestions or edits during the review, thereby keeping our commercial launch readiness activities on track for quick delivery of product.

Is the Agency in agreement with the submission of changed packaging artwork by September 1 without impacting the PDUFA action date?

Kind regards,
Melissa

Melissa Anderson, RAC

Director, Global Regulatory Affairs Development, Oncology

Ixazomib Global Regulatory Lead

Takeda Pharmaceuticals International Co., Inc.

Phone: 617-444-2209

Fax: 617-444-2399

melissa.anderson@takeda.com

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
08/19/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Tuesday, August 18, 2015 11:54 AM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- FDA Request for Pharmacovigilance Plan
Attachments: FDA Guidance.Good PV Practices and PE Assessment.2005.pdf; FDA Guidance.E2E PV Planning.2005.pdf

Good morning Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). Your NDA (ixazomib) is currently under review and we have the following comment and request for additional information:

FDA Comment:

- FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with **ixazomib** following market approval. Guidance for pharmacovigilance planning is included in the *FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005)*, and the *FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005)*; guidance documents are attached. If the plan is available, please include it in the NDA application in the appropriate module so it can be reviewed accordingly.

We respectfully request your response **no later than 2pm on August 28, 2015.**

Please confirm receipt of this information request.

Thank you for your reply,

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
08/18/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Monday, August 17, 2015 10:20 PM
To: 'Anderson, Melissa'
Cc: Laiq, Rabiya
Subject: FDA Response: NDA 208462 ixazomib: Proposal for submitting secondary packaging change

Good evening Ms. Anderson,

The Agency agrees with Millennium's proposal to submit an alternative packaging design, along with the associated artwork, as an NDA amendment by September 1. Please provide samples of the product packaging and art design by September 9 for the FDA team to review.

Have a wonderful evening,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

From: Anderson, Melissa [<mailto:melissa.anderson@takeda.com>]
Sent: Friday, August 14, 2015 8:33 AM
To: Jones, Jacquin; Laiq, Rabiya
Subject: NDA 208462 ixazomib: Proposal for submitting secondary packaging change

Dear Jackie and Rabiya,

Per our conversation with Jackie after the Applicant Orientation Meeting this week, concerning our desire to accelerate, if possible, the review of the packaging components, we are providing the following details for your and the CMC reviewers' information. Please feel free to let us know if there is additional information required.

Background

Ixazomib capsules are packaged in a blister (b) (4)
(b) (4) The primary packaging component is PVC-aluminum/aluminum blister. The secondary packaging components include a blister card carrier which holds the blister strip (b) (4)
(b) (4) design has achieved F=1 results for (b) (4) testing for a number of currently marketed products; however, the ixazomib custom design has not achieved such results, yet. Redesign and testing is ongoing, but a second design for the secondary packaging is now being pursued on a parallel path. This alternative design has already passed (b) (4) testing.

Status and Request

As redesign and testing of the primary design may give way to the alternative design, Takeda proposes to submit this alternative design, along with its associated artwork, as an NDA amendment by September 1. The only changed NDA components will be packaging artwork in Module 1. Please note that the primary blister component remains unchanged; therefore, there is no change to product contact, blister size or any other attribute which could impact product quality.

In addition, we have been notified by our packaging site that it will take a minimum of 6 weeks to proof, review, print and deliver these specialized packaging components. We would greatly appreciate if the Agency could prioritize the review of the packaging components over other parts of the application and provide their comments and feedback on the packaging and artwork as early in the process as possible. It would enable us to incorporate any suggestions or edits during the review, thereby keeping our commercial launch readiness activities on track for quick delivery of product.

Is the Agency in agreement with the submission of changed packaging artwork by September 1 without impacting the PDUFA action date?

Kind regards,
Melissa

Melissa Anderson, RAC

Director, Global Regulatory Affairs Development, Oncology
Ixazomib Global Regulatory Lead
Takeda Pharmaceuticals International Co., Inc.
Phone: 617-444-2209
Fax: 617-444-2399
melissa.anderson@takeda.com

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
08/17/2015



NDA 208462

INFORMATION REQUEST

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Director of Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ninlaro (ixazomib) Capsule.

We also refer to your July 10, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

To facilitate our review of the proposed dissolution method and acceptance criterion for ixazomib oral capsules, address the following information requests:

1. For the dissolution data in Section 3.2.P.5.4 Batch Analyses, and Section 3.2.P.8.3 Stability Data, provide summary tables showing the mean, %RSD, min, max and n of the cumulative amount of drug released at each sampling timepoint.
2. It appears that the dissolution data for the clinical lots from Study C16010 were not included in Section 3.2.P.5.4 Batch Analyses, and Section 3.2.P.8.3 Stability Data. Provide also similar tables summarizing the dissolution data generated at the time of release and during in-use stability testing of the lots of the 3 strengths of ixazomib capsules used in Study C16010 (as listed in Table 9.1 of the study report). Table footnotes should specify the dissolution method parameters (e.g., Apparatus I or II, pH 1.2 or pH 5.5, and 900 mL or 500 mL dissolution medium).

3. Provide supporting analysis datasets in “.xpt” format, and their define files. The dataset should contain individual vessel data for all sampling timepoints, as well as relevant information such as capsule strength, drug product lot number, lot use (clinical - with study number, registration stability - with storage conditions), and dissolution method (i.e., historical pH 5.5 or proposed pH 1.2). Include a column flagging datapoints not included (and the reason for exclusion) in your statistical analysis as described in Section 3.2.P.5.6 Justification of Specifications (Dissolution acceptance criteria).

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by September 3, 2015.

Sincerely,

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Olen Stephens -S,
0.9.2342.19200300.100.1.1=2000558826
Date: 2015.08.13 15:38:39 -04'00'

Jones, Jacquin

From: Jones, Jacquin
Sent: Monday, August 10, 2015 9:12 AM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ixazomib Millennium- Efficacy Analyses Results Summarization

Good morning Ms. Anderson,

Please refer to Millennium Pharmaceuticals Inc.'s New Drug Application (NDA) 208462 Ninlaro (ixazomib). We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). Your NDA (ixazomib) is currently under review and we have the following additional requests for information:

- Please provide all the key efficacy analyses results (primary and key secondary efficacy endpoints) summarized in in-text tables/figures in section 11 of CSR body, in addition to refer to section 14.

Please submit requested information no later than **2 pm on August 13, 2015**.

Thank you for your reply,

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
08/10/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Tuesday, July 28, 2015 4:37 PM
To: 'Anderson, Melissa'
Subject: RE: NDA 208462 ixazomib: AOM attendees and Foreign Visitor Forms
Attachments: Millennium AOM LobbyGuard.pdf

Good afternoon Ms. Anderson,

Thank you for the list of names and Foreign Visitor Forms. Please find attached the LobbyGuard form for the meeting. You may also receive a system generated notification also.

I have confirmed that your team will be able to advance the slides yourselves from the FDA computer that will contain the presentation. Please let me know if I can assist further.

Have a wonderful day,

Jackie

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

From: Anderson, Melissa [<mailto:melissa.anderson@fda.hhs.gov>]
Sent: Tuesday, July 28, 2015 3:45 PM
To: Jones, Jacquin
Subject: NDA 208462 ixazomib: AOM attendees and Foreign Visitor Forms

Dear Jackie,

Attached are our two Foreign Visitor Forms, and following is the final attendee list:

- Melissa Anderson, RAC – Director, Global Regulatory Affairs
- Eileen Bedell, MPH – Senior Director, Global Regulatory Affairs
- Melody Brown – Vice President, Global Regulatory Affairs
- Debbie Berg, RN, MSN – Scientific Director, Oncology Clinical Research
- Dixie-Lee Esseltine, MD – Vice President, Oncology Clinical Research
- Ai-Min Hui, MD, PhD – Senior Medical Director, Oncology Clinical Research
- Helgi van de Velde, MD – Vice President, Oncology Clinical Research
- Nishith Jobanputra, DO – Medical Director, Pharmacovigilance
- Neeraj Gupta, PhD – Director, Clinical Pharmacology
- Jianchang Lin, PhD – Senior Statistician, Global Statistics
- Guohui Liu, PhD – Scientific Fellow, Global Statistics
- Alessandra Di Bacco, PhD – Director, Translational Medicine
- Li-Chun Wang – Director, Global Regulatory Affairs CMC

Can you please tell me if there will be a slide remote available for us to advance the slides ourselves, or if you will be advancing them for us? This will impact our final slide design.

Please let me know if you need anything else.

Kind regards,
Melissa

Melissa Anderson, RAC
Director, Global Regulatory Affairs Development, Oncology
Ixazomib Global Regulatory Lead
Takeda Pharmaceuticals International Co., Inc.
Phone: 617-444-2209
Fax: 617-444-2399
melissa.anderson@takeda.com

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

08/10/2015

Date Sent: July 28, 2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Thursday, July 30, 2015 8:05 AM
To: 'Anderson, Melissa'
Subject: FDA Response: NDA 208462 ixazomib: Proposal for CMC documents included in 30-day submission

Good morning Ms. Anderson,

The review team has confirmed that it is acceptable to include the additional CMC documents containing only editorial and formatting changes? Along with the submission of the CMC documents, you will need to include a document that indicates what changes were made in each of the CMC documents.

Regards,

Jackie

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

From: Anderson, Melissa [<mailto:melissa.anderson@takeda.com>]
Sent: Wednesday, July 29, 2015 12:11 PM
To: Jones, Jacquin
Subject: NDA 208462 ixazomib: Proposal for CMC documents included in 30-day submission
Importance: High

Dear Jackie,

Attached is a document summarizing the CMC documents that we propose to include in the upcoming 30-day submission. I would like to note that these are largely editorial and formatting changes intended to improve the ease of the review. One exception to this is updated stability data, which was pre-agreed with the Agency as part of the CMC pre-NDA meeting to be provided in the 30-day submission.

Can you please confirm with the review team if it is acceptable to include the additional documents containing only editorial/formatting changes?

I'm sorry to ask for this feedback on a short turnaround, but I've just learned that to have adequate publishing time we would greatly appreciate a response by mid-morning tomorrow, Thursday July 30.

Thanks very much for your help, and please let me know if you have any questions.

Kind regards,
Melissa

Melissa Anderson, RAC
Director, Global Regulatory Affairs Development, Oncology
Ixazomib Global Regulatory Lead
Takeda Pharmaceuticals International Co., Inc.

Phone: 617-444-2209
Fax: 617-444-2399
melissa.anderson@takeda.com

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

07/31/2015

Agency Response provided on 7/30/15.

Jones, Jacquin

From: Jones, Jacquin
Sent: Thursday, July 30, 2015 11:39 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ninlaro (ixazomib) Millennium -Clinical Trial Data Location

Good evening Ms. Anderson,

Please refer to your New Drug Application (NDA) 208462 Ninlaro (ixazomib) Millennium Pharmaceuticals Inc.. We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). Please confirm or provide a response to the following information:

FDA Information Request:

- Is the clinical trial data information located in Cambridge, MA?
- If not, where is the clinical trial data located?
- Please let me know if any of the clinical trials data is located overseas.

Please send **responses** that address the above information request via email no later than **1:00 PM ET on Friday, July 31, 2015**.

Also, **officially submit** the responses to your NDA file at the same time you send the e-mail response or provide a planned date for when the submission will be submitted, followed by a notification when the official submission has been sent.

Thank you for your reply,

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
07/30/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Thursday, July 30, 2015 4:12 PM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ninlaro (ixazomib) Millennium - Study Site Information

Good afternoon Ms. Anderson,

Please refer to your New Drug Application (NDA) 208462 Ninlaro (ixazomib) Millennium Pharmaceuticals Inc.. We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). Your NDA (ixazomib) is currently under review and we have the following additional requests for information:

Submit the study subject data listing information request below as pdf files, organized per clinical study investigator site separately. Provide the following the study subject data listings that should capture the following, as applicable for the following Principal Investigators: Norbert Grazsko, MD (Lublin, Poland), Tamas Masszi, MD (Budapest, Hungary), and David Siegel, MD (Hackensack, NJ).

- a. Subject discontinuations (If applicable application per treatment group: site subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).
- b. Subject assignment per treatment arm (randomization group, as applicable).
- c. Concomitant medication list (non-study medications).
- d. All adverse events (If applicable pretreatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no]).
- e. Primary study efficacy endpoint/s.
- f. Any protocol deviation/s or violation/s.

Submit requested information by **3pm on August 6, 2015**.

Thank you for your reply,

CDR Jacquin Jones

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
07/30/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Thursday, July 30, 2015 11:18 AM
To: 'Anderson, Melissa'
Subject: NDA 208462 Ninlaro (ixazomib) Millennium -Address Request

Good morning Ms. Anderson,

Please refer to your New Drug Application (NDA) 208462 Ninlaro (ixazomib) Millennium Pharmaceuticals Inc.. We also refer to the submission dated July 10, 2015 (SN:0000) containing the new application for Ninlaro (ixazomib). Please verify the following physical street addresses:

1. Sponsor: Millennium Pharmaceuticals, Inc.
Contact:
Melissa Anderson, RAC
Director, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA USA 02139
Telephone: 617-444-2209 E-mail: melissa.anderson@takeda.com
2. Please provide the physical address where the clinical trial data are located for inspection.

Please send **responses** that address the above information request via email no later than **10:00 AM ET on Friday, July 31, 2015**.

Also, **officially submit** the responses to your NDA file at the same time you send the e-mail response or provide a planned date for when the submission will be submitted, followed by a notification when the official submission has been sent.

Thank you for your reply,

Jacquin L. Jones, CDR, BSN, MS, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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
07/30/2015



NDA 208462

NDA ACKNOWLEDGMENT

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Director Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Ninlaro (ixazomib) capsule, 2.3, 3, and 4 mg

Date of Application: July 10, 2015

Date of Receipt: July 10, 2015

Our Reference Number: NDA 208462

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 8, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (240) 402-4590.

Sincerely,

{See appended electronic signature page}

Jacquie L. Jones, BSN, MS
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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
07/15/2015



IND 104482

MEETING MINUTES

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Associate Director, Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ixazomib (MLN9708).

We also refer to the meeting between representatives of your firm and the FDA on April 1, 2015. The purpose of the meeting was to discuss your plan to submit a NDA in July 2015 for ixazomib in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Rachel McMullen, Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Wednesday, April 1, 2015; 1:00 PM - 2:00 PM (EDT)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: IND 104482
Product Name: ixazomib (MLN9708)
Indication: Treatment of multiple myeloma in patients who have received at least one prior therapy

Sponsor/Applicant Name: Millennium Pharmaceuticals, Inc.

Meeting Chair: R. Angelo de Claro, MD, Clinical Team Leader
Meeting Recorder: Jessica Boehmer, MBA, Senior Regulatory Project Manager

FDA ATTENDEES:

OHOP/Division of Hematology Products

Ann Farrell, MD, Director
R. Angelo de Claro, MD, Clinical Team Leader
Jessica Boehmer, MBA, Senior Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology

Pedro Del Valle, PhD, Acting Team Leader
Brenda Gehrke, PhD, Pharmacologist

Office of Clinical Pharmacology/Division of Clinical Pharmacology V

Gene Williams, PhD, Clinical Pharmacology Team Leader
Olanrewaju Okusanya, PharmD, MS, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality/Office of New Drug Products

Olen Stephens, PhD, Branch Chief

Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK)

Carolyn L. Yancey, MD, Reviewer

Jueli Li, Pharmacy Student

Natalia Gut, Pharmacy Student

EASTERN RESEARCH GROUP ATTENDEE

Patrick J. Zhou, Analyst

SPONSOR ATTENDEES

Millennium Pharmaceuticals, Inc.

Melissa Anderson, RAC, Associate Director, Global Regulatory Affairs

Melody Brown, Vice President, Global Regulatory Affairs

Eileen Bedell, MPH, Senior Director, Global Regulatory Affairs

Cory Ferguson, MHA, RAC, Manager, Global Regulatory Affairs

Dixie-Lee Esseltine, MD, Vice President, Global Clinical Development

Helgi van de Velde, MD, Vice President, Global Clinical Development

Ai-Min Hui, MD PhD, Senior Medical Director, Global Clinical Development

Neeraj Gupta, PhD, Director, Clinical Pharmacology

Guohui Liu, PhD, Scientific Fellow, Global Statistics

Jianchang Lin, PhD, Senior Statistician, Global Statistics

Nishith Jobanputra, DO, Medical Director, Pharmacovigilance

1.0 BACKGROUND

Ixazomib (research name MLN2238) is an orally bioavailable, small molecule inhibitor of the 20S proteasome. The Sponsor's proposed indication is "Ixazomib in combination with lenalidomide and dexamethasone is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy".

The Sponsor has previously obtained advice on selected topics related to the NDA content and format from the Agency through two Type C requests for written feedback. With reference to Millennium's first Type C, the Agency provided written feedback on April 25, 2014. The topics for this first Type C interaction included the Integrated Summary of Efficacy, Integrated Summary of Safety, submission of data for the renal and hepatic impairment studies, categories and format of individual patient narratives, and format of clinical and nonclinical datasets. The Agency provided written feedback received on November 20, 2014 for Millennium's second Type C request. The topics for this second Type C interaction included individual patient narratives and case report forms, adverse events of clinical importance for individual patient narratives, Summary of Clinical Efficacy, marginal structural models for the primary analysis of overall survival, content and format of site-level clinical data for submission to the Office of Scientific Investigations, financial disclosure information, and Question-Based Review Clinical Pharmacology Summary.

FDA sent Preliminary Comments to Millennium Pharmaceuticals Inc. on March 26, 2015.

2. DISCUSSION

CLINICAL

Question 1

Does the Agency agree that the results from pivotal Study C16010 are adequate to support the filing and review of ixazomib for the treatment of patients with multiple myeloma who have received at least 1 prior therapy?

FDA Response:

Your general submission plan for the clinical efficacy and safety sections of the NDA appears reasonable. The Agency will determine the adequacy of the NDA for filing and review at the time of NDA submission.

Discussion:

The Agency clarified that narratives for deaths that occur within 30 days of study treatment should be submitted in order to evaluate concurrent medical conditions in that timeframe. The Sponsor's proposal to include safety narratives for studies that have CSRs is acceptable to the Agency.

Regarding submission of narratives for grade 1 or 2 AEs of special interest, the Agency clarified that the Sponsor should prioritize the narratives that would be important in making dosing modifications. The proposal to submit aggregate summary information for AESI not relevant to dosing modification appears reasonable. The Agency may require submission of additional narratives upon request.

Question 2

Does the Agency agree with the Applicant's proposed content and data cut-off date for the 120-day safety update?

FDA Response:

No. The 120 safety update with cut-off date of 27 March 2015 should be submitted by September 2015.

Discussion:

The Agency agrees with the Sponsor's proposal to submit the DSUR to the IND. The Agency also agrees with the submission of unblinded updated safety analysis for clinical trials C16010 and requests a submission earlier than November 2015, if feasible.

Question 3

Does the Agency agree with the Applicant's plan for submission of the C16009 (drug-drug interaction, food effect, relative bioavailability) study data to the NDA?

FDA Response:

The Agency agrees with the submission of arm 5 of study C16009 during the first 30 days following the original NDA submission, as a late submission under PDUFA V. Submission of the completed drug interaction study should be accompanied by an updated package

insert that includes the new results, if the new results are appropriate for inclusion in the package insert.

Discussion:

No discussion occurred.

Additional Comment:

Refer to the following website for details on how to submit the population PK modeling and results.

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDE/ucm180482.htm>

The population PK analysis of the DDI must be time-dependent. That is, when subjects are not taking the concomitant medication their DDI parameter is off. You will need to document the number of subjects on the particular concomitant medication that had their PK sampled during administration of the concomitant medication. Also report 1) whether this sampling was at steady-state of both drugs 2) the dose of the concomitant medication and 3) the timing of administration relative to each other. Each interaction should be evaluated for individual compounds and not for therapeutic classes of drugs (e.g. aminoglycosides, sulfonamides). Proton-pump inhibitors may be considered an exception if the mechanism of interaction is on the absorption of the drug.

You should also conduct dose/exposure –response analyses for both efficacy and safety to support the selection of the dose.

Discussion:

No discussion occurred.

Question 4

Does the Agency agree with the Applicant's assessment that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary for ixazomib?

FDA Response:

No. At this time, the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of ixazomib outweigh the risks, and if it is necessary, what the required elements will be. It will be important to consider the benefit-risk profile of ixazomib, in combination with lenalidomide and dexamethasone, proposed for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Discussion:

No discussion occurred.

REGULATORY

Question 5

It is anticipated that the data from the second IA for pivotal Study C16010 will become available during the review period for the proposed NDA. Does the Agency agree to discuss the submission strategy (content/format and timing) for these data, and consideration for possible inclusion in the label, with the Applicant by teleconference when the top-line second IA data become available?

FDA Response:

Yes. Please indicate the anticipated timing for the availability of the topline second interim analysis (IA) data.

Discussion:

The Sponsor noted that the topline second IA data may become available by August/September 2015. The Agency clarified that the primary interest of the review team with the second IA data is the updated OS results. The Agency recommended that the Sponsor discuss with the Agency the results of the second IA during the review of the application.

Question 6

Can the Agency please confirm whether an Applicant Orientation Meeting will be requested of the Applicant?

FDA Response:

Yes.

Discussion:

No discussion occurred.

Question 7

The Applicant plans to submit the draft Structured Product Labeling (SPL) within 30 days of the NDA submission. Does the Agency agree with this proposal?

FDA Response:

Structured Product Labeling (SPL) should be submitted with your NDA submission as described in 21 CFR 314.50(l)(1)(i). However, if necessary, you may submit the SPL within 30 days of the NDA submission.

Discussion:

No discussion occurred.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

The late submission components will be as follows:

- C16015 (Renal impairment) CSR and dataset
- C16018 (Hepatic impairment) CSR and dataset
- C16016 (ADME) dataset (CSR will be in NDA)
- C16009 Arm 5 (Drug-drug interaction with clarithromycin) CSR addendum and dataset
- Draft Structured Product Labeling
- Dataset in standard format for exposure / response analysis report (report will be in NDA)

The Sponsor clarified that the additional time was to create a definition file for the ER dataset and the Agency requests the dataset be provided with the NDA and the defined file be provided within a 30 day period. The Sponsor agreed. The Agency requested that the dataset name correspond with the NONMEM control stream. For ER analysis the dataset name should correspond with the SAS code. The Sponsor agreed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that the need for a REMS will be determined during the review of the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
 - C16015 (Renal impairment) CSR and dataset
 - C16018 (Hepatic impairment) CSR and dataset
 - C16016 (ADME) dataset (CSR will be in NDA)
 - C16009 Arm 5 (Drug-drug interaction with clarithromycin) CSR addendum and dataset
 - Draft Structured Product Labeling
 - Dataset in standard format for exposure / response analysis report (report will be in NDA)

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - BIOMETRICS

NDA NUMBER: LATE COMPONENT - CLINICAL

NDA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY

NDA NUMBER: LATE COMPONENT - NONCLINICAL
NDA NUMBER: LATE COMPONENT - QUALITY

In addition, we note that a chemistry pre-submission meeting was scheduled for September 22, 2014, and then withdrawn after preliminary comments were received. We refer you to the preliminary comments dated September 18, 2014 for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site

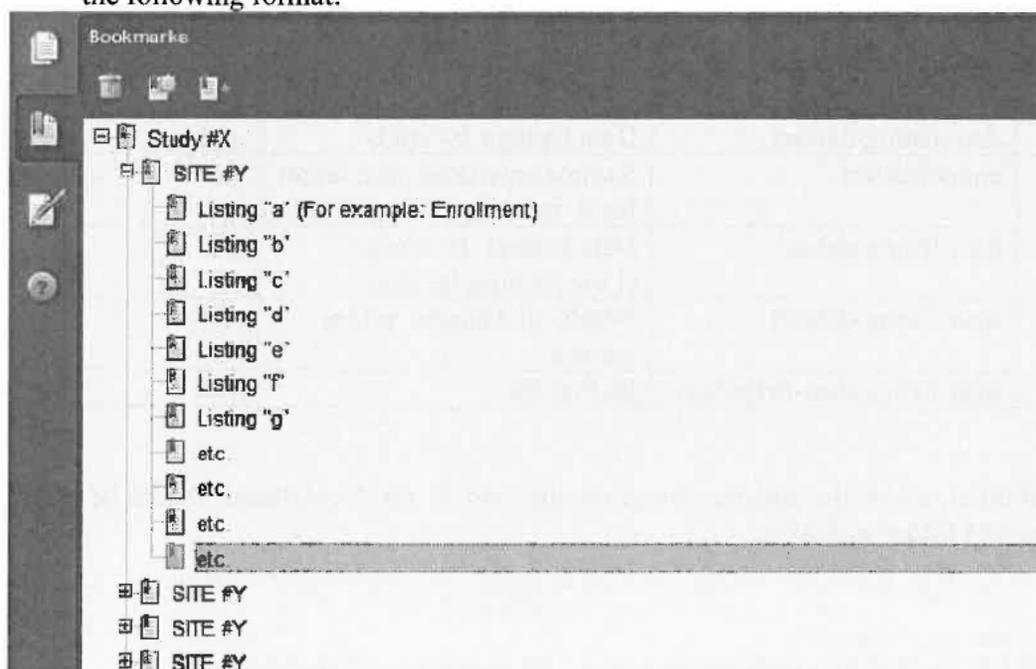
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor’s slides are attached to these minutes.

4 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ROMEO A DE CLARO
04/02/2015



IND 104482

MEETING MINUTES

Millenium Pharmaceuticals, Inc.
Attention: Katherine Barton, MS
Manager, Worldwide Regulatory Affairs - CMC
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Barton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MLN9708.

We also refer to the meeting between representatives of your firm and the FDA on Tuesday, February 21, 2012. The purpose of the meeting was to discuss your CMC development program to date and to identify any additional information needed to support initiation of Phase 3 clinical trials and the NDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any *significant* differences in understanding regarding the meeting outcomes.

If you have any questions, call Jewell D. Martin, Product Quality Regulatory Project Manager at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, PhD
Senior Regulatory Health Project Manager for Product
Quality
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2, Chemistry, Manufacturing and Controls (CMC)

Meeting Date and Time: Tuesday, February 21, 2012, 10:30 – 11:00 ET
Meeting Location: Food and Drug Administration
White Oak Campus, Building 21 Room 1421

Application Number: IND 104482
Product Name: MLN9708
Indication: Treatment of advanced malignancies, including multiple myeloma.
Sponsor/Applicant Name: Millennium Pharmaceuticals, Inc.

Meeting Chair: Sarah Pope Miksinski, Ph.D.
Meeting Recorder: Scott N. Goldie, Ph.D.

FDA ATTENDEES

Janice T. Brown, M.S.	CMC Lead
Angelica Dorantes, Ph.D.	Biopharmaceutics Team Lead
Brenda Gehrke, Ph.D.	Pharmacology/Toxicology Reviewer
Scott N. Goldie, Ph.D.	Senior Regulatory Health Project Manager for Product Quality
Jewell D. Martin, MA, MBA, PMP	Product Quality Regulatory Project Manager
Sarah Pope Miksinski, Ph.D.	CMC Branch Chief
Haleh Saber, Ph.D.	Pharmacology/Toxicology Supervisor

SPONSOR ATTENDEES

Satyam Upadrashta, PhD, RAC	Senior Director, Worldwide Regulatory Affairs CMC
Ramani Raghavan, MS, RAC	Associate Director, Worldwide Regulatory Affairs CMC
Katherine Barton, MS	Manager, Worldwide Regulatory Affairs CMC
Raymond Skwierczynski, PhD	Senior Director, Analytical Development – Small Molecules
Eric Elliot, PhD	Scientist II, Process Chemistry R & D
Elizabeth Hewitt, MS	Scientist II, Analytical Development – Small Molecules
Heather Damon	Manager II, Quality Control

Meeting Minutes
[Insert Meeting Type]
DATE

[Insert Office/Division]

Peter Zawaneh, PhD Scientist II, Formulation Sciences

1.0 BACKGROUND

Millennium Pharmaceuticals, Inc. ("Millennium") is currently developing MLN9708, a selective small molecule proteasome inhibitor, for the treatment of advanced malignancies, including multiple myeloma. Millennium has requested an End-of-Phase 2 (EOP2), Type B meeting with the Office of New Drug Quality Assessment ("ONDQA") to discuss the Chemistry, Manufacturing, and Controls (CMC) development plan, the data generated to initiate the phase 3 program, and identify any additional requirements needed to support the marketing application. The minutes of the face to face meeting, held on February 21, 2012, are recorded below.

2.0 DISCUSSION

2.1. **Question 1:** MLN9708 drug substance is manufactured via a (b) (4)

(b) (4)

Does the FDA agree that (b) (4) are appropriate regulatory starting materials for MLN9708 drug substance?

FDA Response to Question 1: We agree that the proposed starting materials are (b) (4)

(b) (4)

Millennium Response: Upon reviewing the FDA response, Millennium has thoroughly assessed the appropriateness of the proposed regulatory starting materials (RSM's). Specifically, the choice of (b) (4)

(b) (4) Based on the demonstration of adequate control strategy for the control of impurities in the drug substance as summarized below, Millennium believes that the proposed RSM's are appropriate and ensure the desired quality attributes in MLN9708 drug substance. Further, (b) (4)

(b) (4)

established based on relevant guidance documents, available safety information, stability data, and manufacturing experience to date.

Does the FDA agree that the proposed test attributes for release and on stability are appropriate for monitoring the quality of MLN970S drug substance in pivotal phase 3 clinical trials?

FDA Response to Question 2: We concur that the proposed tests are acceptable in that they address identity, assay, purity and key physical attributes. Also refer to the response to Question 3. It is understood that the tests for impurities may change with the change in designated starting material (see response to Question 1). The analytical methods will be evaluated at the time of NDA submission. Based on the submitted batch analysis data, the proposed acceptance criterion are acceptable for the intended use. To support the proposed criteria and product stability, your test results should include a determination of all impurities at or above the limit of detection for the HPLC method. All aspects of the drug substance specification will be evaluated at the time of NDA submission.

Millennium Response: Millennium acknowledges the division's comments on the MLN9708 drug substance specification and agree to fully evaluate the specification prior to the NDA submission. Regarding the division's comment on the determination of all impurities at or above the limit of detection for the HPLC method, Millennium commits to adhere to the reporting, identification, and qualification thresholds per ICH Q3A. All impurities above the ICH reporting threshold ($\geq 0.05\%$) will be combined and reported as total impurities, and those exceeding the reporting threshold will be individually listed in the certificate of analysis and submitted in the NDA.

Discussion: When submitted, the application will be evaluated based on the impurity information submitted. The thresholds presented in the ICH guidance's represent the minimum required. The FDA requests that sufficient data be provided to permit evaluation of the application in a single review cycle based on the timelines specified under GRMP. Unresolved issues will be addressed in an information request letter as appropriate.

2.2. **Question 3:**



Does the FDA agree that [REDACTED] (b) (4)

FDA Response to Question 3: It is premature to determine if [REDACTED] (b) (4) to be controlled in the drug substance. We recommend that you supply sufficient scientific justification and batch analysis data to support your proposal. Based on your calculated [REDACTED] (b) (4) of the genotoxic intermediate compound, [REDACTED] (b) (4) would be below the TTC limit of (b) (4) $\mu\text{g}/\text{day}$. We have a flexible approach for the levels of genotoxic impurities in drugs used for advanced malignancies (see ICH S9); therefore, the presence of genotoxic impurities are generally not an approval issue. However in your initial NDA submission, you will need to demonstrate the actual levels of all impurities in the drug substance and in the drug product.

Millennium Response: Pursuant to the division's request, Millennium is offering the following scientific justification regarding the presence of genotoxic impurity and its control.

Initially, Millennium would like to correct an error in the briefing book. [REDACTED]

The correct half life should have been listed as [REDACTED] seconds.

Discussion: Your proposal to not include additional controls, based on the data provided appears to be acceptable; however, the adequacy and applicability of the studies is a review issue, and its determination will be based on data included in the NDA submission. Justifications provided on February 15, 2012 should be also provided with the NDA.

- 2.3. **Question 4:** The proposed MLN9708 capsules release and stability specifications to control the quality of capsules in pivotal phase 3 clinical trial supplies are presented below. Tests and corresponding acceptance criteria are consistent with the stage in development and have been established based on relevant guidance, stability, nonclinical data, and manufacturing experience to date. Millennium will continue to evaluate the drug product specifications based on critical quality attributes, such as safety and stability data, as defined during development.

Does the FDA agree that the proposed test attributes for release and on stability are appropriate for monitoring the quality of MLN970S capsules in pivotal phase 3 clinical trials?

FDA Response to Question 4: We concur that the proposed tests are acceptable in that they address appearance, identity, assay, purity, dosage uniformity and drug release. However, the analytical methods and the justification for using disintegration test in place of the dissolution will be evaluated at the time of NDA submission. Therefore, until we approve this change, the dissolution test should be included in the product's specification table and dissolution profile data from the PK, clinical, and stability batches should be collected and submitted under the NDA. Based on the submitted batch analysis data, the proposed acceptance criteria are acceptable for the intended use, provided a criterion for the dissolution test is included. To support the proposed criteria and product stability, your test results should include a determination of all impurities at or above the limit of detection for the HPLC method. All aspects of the drug product specifications will be evaluated at the time of NDA submission.

Millennium Response: Millennium acknowledges the division's comments on the MLN9708 drug product specification and agree to fully evaluate the specification prior to the NDA submission. Regarding the division's comment on the determination of all impurities at or above the limit of detection for the HPLC method, Millennium commits to adhere to the reporting, identification, and qualification thresholds per ICH Q3B. All impurities above the ICH reporting threshold (b)(4)0%) will be combined and reported as total impurities, and those exceeding the reporting threshold will be individually listed on the certificate of analysis and submitted in the NDA.

Millennium acknowledges that the proposed disintegration test will be evaluated for its adequacy in lieu of dissolution method during the NDA review process. Based on the data gathered to date, it is Millennium's view that disintegration has served as a reliable test in assessing the product performance. Millennium has a validated, quantitative dissolution test that has been used throughout development and is also currently being

used for information only testing of the capsules at release and on stability. Dissolution data and profiles using this test method were provided in Appendix B of the briefing booklet. Therefore, going forward, Millennium will agree to include the current dissolution test method on the Phase 3 Capsules specification with acceptance criterion to report the individual and mean %dissolved at 15, 30, 45 and 60 minutes, during which an asymptote will have been reached. In order to compare future dissolution data to the existing dissolution data, Millennium proposes using the current test method and the time points specified above. Dissolution profile data from PK, clinical and stability batches will be collected and submitted under the NDA.

Millennium believes reporting a Q value at this time for the dissolution specification is not meaningful based on the following:

- MLN9708 is a highly soluble and rapidly dissolving drug substance in the drug product according to BCS guidance. (b) (4)
- (b) (4)
- The dissolution method utilizes only (b) (4) mL of dissolution media. Dissolution studies to date confirm that (b) (4)% drug dissolved in 30 minutes across physiological pHs in 500mL of media. Dissolution profiles using this test method for a (b) (4)mg development batch at pH 1.2, 4.5, and 6.8 were provided in Figure 3-B in Appendix B of the briefing booklet. The (b) (4) mg development batch is much higher than the highest clinical commercial dosage strength of 5.5 mg.
- The intrinsic solubility of the drug is (b) (4) The concentration of the API in a (b) (4)-mg capsule, the highest dose strength, dissolved in 500-mL dissolution medium is at least (b) (4) times below the solubility of the drug.
- The rapidly dissolving behavior is similar across dosage strengths (0.2 mg to 12 mg) at release and on stability at 25°C/60%RH for 18 months. The range of dosage strengths tested is wider than the range of clinical commercial dosage strengths (2.3 mg to 5.5 mg).
- Only one batch of CTM dosage strengths has been produced to date. Thus, very limited batch history data are available to provide justification for a Q-value. Long-term stability studies on these formulations have just started.

All Phase 3 clinical trial material utilizes the commercial dosage strengths produced by our commercial manufacturing site at full commercial scale. Prior to NDA submission, Millennium will have applicable dissolution and disintegration data for comparison purposes on representative commercial material to justify the use of a disintegration test for commercial use. (b) (4)

Millennium proposes (b) (4) clinical trial material at the proposed commercial scale (composite of multiple dosage

strengths) via dissolution and disintegration. If the data are consistent, aligned with development data, and show no benefit for dissolution over disintegration, Millennium will plan to use only disintegration for commercial launch. The data will be available at the time of NDA submission.

Millennium is currently assessing the biopharmaceutical properties of MLN9708, and the data will be available in the NDA submission. Millennium has assessed the solubility profile of MLN9708 throughout the physiological pH range (1.2 to 6.8) and provided the data in Figure B-1 of the briefing booklet. Millennium will complete dissolution profile data of representative commercial dosage strengths at pH (1.2, 4.0, and 6.8). Millennium is planning on using dissolution to test the formulation and process factors that impact dissolution/disintegration during process robustness studies. Millennium is planning on testing the raw material attributes (i.e, drug substance particle size) to see the dissolution/disintegration impact. These data will be available at the NDA submission.

Attempts to date have not been successful to identify a discriminating dissolution method. During the pivotal trials, dissolution method development at all pHs will continue to be investigated to determine if a discriminating dissolution method is feasible. Since the API rapidly dissolves, a discriminating method may not be achievable. Furthermore, since the rate of dissolution of MLN9708 is faster than the rate of absorption, there will not be a relationship between the dissolution and the in-vivo exposure.

Millennium will continue to gather dissolution and disintegration data throughout development to determine the relationship between the two test methods. Millennium will follow the selection criteria defined in ICH Q6A (Decision Tree # 7), to show that disintegration is at least as discriminating as dissolution and that disintegration is the appropriate performance test.

Discussion: FDA proposed that Millennium submit the package with complete data supporting the use of a disintegration test instead of a dissolution test to the IND at least three months prior to the submission of the NDA, to provide an opportunity for review and feedback. Also, FDA mentioned that Millennium could submit the package at least 3 months before the Pre-NDA meeting to allow enough time to review the data and provide a response during the Pre-NDA meeting. FDA stated that if their proposal is accepted under the IND, the dissolution test and Q value would not be needed for the NDA. Otherwise, the dissolution method development report with complete information/data and a proposal for the dissolution Q value with justification should be submitted in the NDA, and this information will be a review issue under the NDA.

Millennium asked FDA, if was acceptable not to report at this time the dissolution Q value for their product. FDA responded that as long they continue collecting complete dissolution profile data for their product, it was acceptable not to report the dissolution Q value.

2.4. **Additional Biopharmaceutics Comments:**

To support your proposal of using disintegration testing instead of dissolution testing to control the quality of your product, please provide in your NDA submission a report with the following key information/data;

1. The biopharmaceutical properties of MLN9708,
2. Data on the relationships between dissolution and the in-vivo exposure (if available),
3. Data showing a relationship between dissolution and disintegration,
4. Information on the formulation and process factors that impact dissolution/disintegration (e.g., amount of lubricant, etc.),
5. Understanding of raw material attributes (i.e., drug substance particle size) and process parameters that impact dissolution/disintegration.
6. Complete solubility profile data on MLN9708, throughout the physiological pH range (1.2 to 6.8).
7. Complete dissolution profile data (i.e., individual, mean, plots) of MLN9708 capsules at pH 1.2, 4.0 and 6.8.
8. Relationship data between dissolution and disintegration of MLN9708 capsules considering at least two of the initial sampling points (i.e., % drug dissolved at 10 min and at 15 min) using a discriminating dissolution method.

The above report may also be submitted under your IND for review and comments.

Discussion: Millennium acknowledged receipt of FDA's comments. No further discussion occurred during the meeting.

3.0 **ISSUES REQUIRING FURTHER DISCUSSION**

There are no specific issues requiring further discussion at this time.

4.0 **ACTION ITEMS**

There are no specific due dates or time lines for submission of information or other action items. General agreements and commitments are included in the Discussion section (2.0) above.

5.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Senior Regulatory Health Project Manager for Product Quality
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I (DNDQA I)
Office of New Drug Quality Assessment (ONDQA)
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

There were no slides or handouts distributed by Millennium during the meeting.



IND 104482

MEETING MINUTES

Millennium Pharmaceuticals
Attention: Melissa Anderson, RAC
Associate Director, Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MLN 9708 (ixazomib citrate).

We also refer to the meeting between representatives of your firm and the FDA on Monday, November 14, 2011. The purpose of the meeting was to discuss the design of proposed phase 3 trial Study C16010, entitled "A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral Ixazomib Citrate (MLN9708) plus Lenalidomide and Dexamethasone versus Placebo plus Lenalidomide and Dexamethasone in Adult Patients with Relapsed and/or Refractory Multiple Myeloma" and the overall clinical development program to support registration of this drug.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Theresa Ferrara, Regulatory Project Manager at (301) 796-2848.

Sincerely,

{See appended electronic signature page}

Virginia E. Kwitkowski, MS, RN, ACNP-BC
Lead Clinical Analyst
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: Monday, November 14, 2011 9:00 – 10:00 am
Meeting Location: FDA White Oak campus, Bldg 22 Room 1313

Application Number: IND 104482
Product Name: MLN 9708 (ixazomib citrate)
Indication: treatment of patients with (b) (4) multiple myeloma who have received at least 1 prior therapy

Sponsor/Applicant Name: Millennium Pharmaceuticals
Meeting Chair: Virginia Kwitkowski, MS, RN, ACNP-BC
Meeting Recorder: Theresa Ferrara, MPH

FDA ATTENDEES

Edvardas Kaminskas, MD, Deputy Director, DHP
Virginia Kwitkowski, MS, RN, ACNP-BC, Lead Clinical Analyst, Clinical Team Leader, DHP
R. Angelo de Claro, MD, Clinical Reviewer, DHP
Julie Bullock, PharmD, Clinical Pharmacology Team Leader, Office of Clinical Pharmacology
Bahru Habtemariam, PharmD, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Mark Rothmann, PhD, Statistics Team Leader, Office of Biostatistics
Kyung Yul Lee, PhD, Statistics Reviewer, Office of Biostatistics
Theresa Ferrara, MPH, Regulatory Project Manager, DHP

SPONSOR ATTENDEES

Melissa Anderson, RAC Associate Director, Regulatory Affairs (*via telecon*)
Eileen Bedell, MPH Director, Regulatory Affairs
Debbie Berg, RN MSN Senior Clinical Scientist
Dixie-Lee Esseltine, MD Vice President, Global Clinical Development
Neeraj Gupta, PhD Associate Director, Clinical Pharmacology
Steven Hamburger, PhD Senior Director, Regulatory Affairs
Ai-Min Hui, MD PhD Medical Director
Hnin Hnin Ko, MD MSc MPH Director, Pharmacovigilance
Huamao Mark Lin, PhD Senior Manager, Health Economics
George Mulligan, MD Director, Translational Medicine (*via telecon*)
Hongliang Shi, MS Associate Director, Biostatistics
Melody Brown, Vice President, Worldwide Regulatory Affairs

1.0 BACKGROUND

Ixazomib is an oral proteasome inhibitor currently under investigation in Phase 1 and 2 clinical trials under IND 104482 (oral formulation) and IND 103577 (IV formulation). Orphan designation was granted by FDA for patients with multiple myeloma (MM) in February 2011.

Clinical development of ixazomib is ongoing for MM, AL amyloidosis, and advanced solid tumors. Type C meeting was held for AL amyloidosis indication on October 13, 2010, and follow-up T-con on April 5, 2011. There are no previous meetings for the MM indication.

The purpose of this End of Phase 2 meeting is to seek advice on the design of the Phase 3 randomized trial study C16010 comparing lenalidomide and dexamethasone with and without oral ixazomib citrate (MLN9708) in patients with relapsed and/or refractory MM. Millennium is also seeking advice on the adequacy of the overall clinical development program to support regular approval for the proposed indication of treatment of relapsed and/or refractory MM.

2. DISCUSSION

Questions on Clinical Protocol

Question 1

Does the Agency agree that PFS is an appropriate primary efficacy endpoint in this single randomized, controlled, double-blind study (C16010 Protocol Synopsis) to support a marketing authorization for the proposed combination treatment of ixazomib citrate plus LenDex in patients with RRMM who have received at least 1 prior therapy?

FDA Response: In general, a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision. However, you should be aware that PFS may be influenced by any imbalance in assessment dates or missing data between treatment arms. You should be aware that toxicities due to ixazomib could unblind treatment assignments and introduce bias.

Whether a PFS HR 0.75 (median PFS of 11 months in control arm versus 14.7 months in active arm) represents clinical benefit in the absence of a benefit on OS will be a review issue.

For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide clinically meaningful and statistically persuasive efficacy findings with an acceptable risk benefit profile. We strongly suggest that you conduct two adequate and well-controlled trials to support the proposed indication.

Sponsor Response 1

Some statistical aspects of Study C16010 have been modified, as detailed in Table 1.

Table 1 Statistical Design Modifications to Protocol C16010

	Original	Update
Sample size	586	703
Primary endpoint		
PFS hypothesis	HR 0.75 (11 vs. 14.7 mos)	HR 0.66 (11 vs. 16.8 mos)
PFS power	80%	90%
PFS analysis	Group sequential with 2 interim analyses and 1 final analysis	1 final analysis
Secondary endpoints		
OS hypothesis	NA	HR 0.77 (30 vs. 39 mos)
OS power	NA	80%
OS analysis	When PFS significant	Group sequential with 2 interim analyses (one at PFS analysis, one at 2/3 information), and 1 final analysis
Key secondary endpoints	4 ORR, OS in overall population, OS in del(17), pain response rate	2 OS in overall population, OS in del(17)
Key secondary endpoints type I error control	Closed sequential testing, and Hochberg procedure	Closed sequential testing

To summarize, the primary changes to the statistical design are as follows:

- PFS remains the primary endpoint; however, there will only be 1 planned analysis for PFS (no early evaluation). Power for this PFS analysis has been increased to 90%.
- OS in the overall population and OS in patients with del(17) will be the only 2 key secondary endpoints: ORR and pain response rate will be calculated but under the category of other secondary endpoints. Therefore, closed sequential testing procedure will be used to ensure strong control of type I error and a Hochberg procedure will not be performed.
- Sample size has been increased to 703 patients to provide 80% power to detect an OS benefit.

The plan is to enroll 703 patients into this randomized, double-blind, placebo-controlled study, with PFS as the primary endpoint and 2 key secondary endpoints, namely OS in the entire study population and OS in high-risk patients carrying del(17). The power for PFS is now 90% and for OS is 80%. A larger treatment effect (hazard ratio of 0.66, assuming median PFS of 11 months for control versus 16.8 months for treatment) is assumed in the PFS power estimation. PFS will only be tested once with 0.05 2-sided type I error rate. The closed sequential testing procedure

will be used to test OS in the entire study population and OS in high-risk patients carrying del(17) only after PFS is statistically significant to ensure strong type I error control for the study. Analyses for primary and key secondary endpoints will be conducted in the ITT population.

The primary analysis for this study is PFS. However, the study will not be stopped after the PFS analysis, even if a significant PFS effect is observed, to obtain an adequate statistical power for OS.

There will be an independent data monitoring committee that will review 2 planned interim analyses before the planned final analysis for OS. Assuming a hazard ratio of 0.77 (median survival of 30 months in the control arm versus 39 months in the treatment arm), the number of death events needed for the final OS analysis is 482 (80% power and 2-sided alpha of 0.05). A total of approximately 703 patients will need to be randomized in a 1:1 ratio into the 2 treatment arms (stratified by: 1 versus 2 or 3 prior therapies; proteasome-inhibitor exposed versus proteasome-inhibitor naïve; and tumor with del[17] versus without del[17]), assuming an average enrollment rate of approximately 13 patients/month for the first 6 months, approximately 30 patients/month thereafter, and approximately 10% dropout rate. The final analysis of OS is estimated to occur approximately 81 months from the enrollment of the first patient, including a 27-month randomization period and an additional 54-month follow-up from the last patient enrolled. With an observed hazard ratio of 0.833 (eg, median OS of 30 months for control versus 36 months for treatment, 20% improvement), the test for OS will be statistically significant at the final analysis with 482 death events.

The first interim analysis will be performed when approximately 234 PFS events have occurred. This will be the final analysis for PFS, with the opportunity to claim PFS benefit. With 234 PFS events, it will have 90% power to detect a hazard ratio of 0.66 (median PFS of 11 months for control versus 16.8 months for treatment) using a 2-sided log-rank test at a 2-sided alpha level of 0.05. Assuming enrollment of approximately 13 patients/month for the first 6 months and 30 patients/month thereafter, the first interim analysis is expected to occur at approximately 24.5 months after the first patient is enrolled and approximately 633 patients have been enrolled.

With an observed hazard ratio of 0.775 (eg, median PFS of 11 months for control versus 14.2 months for treatment, 29% improvement), PFS will be statistically significant at the analysis with 234 progression/death events. If the test for PFS is not statistically significant, the study

will be claimed as unsuccessful and no further testing will be conducted. If the test for PFS is significant, the OS will be tested with the opportunity to stop the trial for overwhelming evidence of efficacy or futility. At the time of the PFS analysis, enrollment in the study will continue if 703 patients have not been achieved. The PFS results will not be reported until the study has been fully enrolled.

The second interim analysis will be for OS and will be performed when approximately 322 deaths (two-thirds of the total expected deaths) have occurred, with the opportunity to stop the study for overwhelming evidence of efficacy or futility. This interim analysis is expected to occur approximately 48 months after the first patient is enrolled.

Based on the O'Brien-Fleming stopping boundary (the Lan-DeMets method), the alpha levels at the 2 planned OS interim analyses and final analysis would be 0.0002, 0.0121, and 0.0376, respectively, if the number of events at these analysis time points are exactly 118, 322, and 482.⁽¹⁾ Correspondingly, if the nominal p-value is less than 0.0002, 0.0121, and 0.0463 at the first interim analysis, the second interim analysis, and the final analysis, the test for OS will be claimed to be statistically significant.

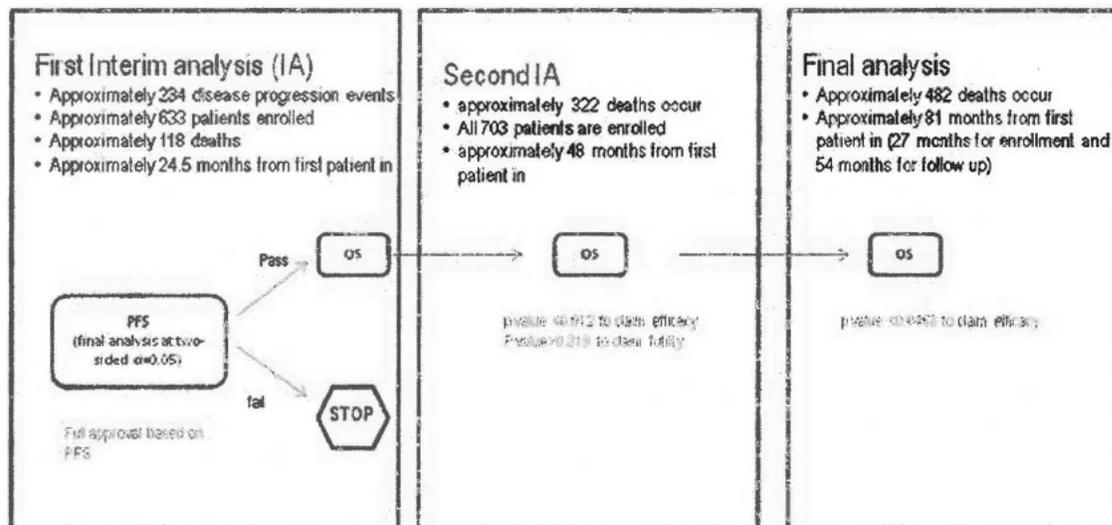
OS in high-risk patients carrying del(17) will only be tested if the test of OS in the entire study population is statistically significant at any of the planned analyses at the same significance level as OS in the entire population at that time point. This is to ensure strong type I error control for both key secondary endpoints.

Since the testing of any key secondary endpoints is gated by the significance of the primary endpoint PFS, and the type I error rate for all key secondary endpoints is controlled at 2-sided 0.05 level, the overall type I error rate for both primary and key secondary endpoints is also strongly controlled at the 2-sided 0.05 level.

Table 2 Assumption for the Study Design

Parameter	Sample size calculation					Statistical significance		
	Alpha (full)	Power	HR	Median (month)	Number of events	Sample size	HR	Median (month)
PFS	0.05	90%	0.66	11 vs 16.8	234		0.775	11 vs 14.2
OS	0.05	80%	0.77	30 vs 39	482	703	0.833	30 vs 36

Figure 1 Study Schema



With respect to MLN9708-associated toxicities that could potentially unblind treatment assignments, there are no adverse events that have been identified at this time that are unique to MLN9708. In particular, the emerging data suggest a low rate of peripheral neuropathy and a very low rate of Grade 3 or 4 neuropathy as opposed to VELCADE. MLN9708 and lenalidomide have overlapping adverse event profiles with respect to common adverse events such as fatigue, rash, thrombocytopenia, neutropenia, and GI toxicities; and treatment of these adverse events should be conducted irrespective of study group allocation such that there should be no need to unblind to study group. We therefore feel the potential bias is minimized due to these overlapping toxicities and plans to maintain the blind. Furthermore, we will additionally enforce the blind through frequent site monitoring and education.

Meeting Discussion for Question 1: The magnitude of PFS improvement will remain a review issue. FDA encourages Millennium to continue efficacy evaluations until central confirmation occurs. The proposal provided by Millennium appears to control for the type 1 error rate. The Agency recommended conducting a non-inferential post-final analysis on PFS at the time of second interim OS analysis.

Question 2

Does the Agency agree that the overall response rate (ORR), OS, and OS in high risk patients positive for the del(17) biomarker are appropriate key secondary endpoints? In addition, PFS and OS in cytogenetic subgroups including translocations t(4;14) and t(14;16), +1q, and del(17) are secondary endpoints. Does the agency consider these subset analyses to be reasonable secondary endpoints in patients with RRMM? It is the sponsor's assumption that if the statistical

requirements are met for these key secondary endpoints, statements regarding the treatment effect in these secondary objectives can be included in the US prescribing information.

FDA Response: Yes.

Sponsor Response 2

As the sponsor has eliminated one of the key secondary endpoints addressed in this question, we assume this response is still valid for the two remaining key secondary endpoints, OS in the entire study population and OS in high risk patients positive for the del(17) biomarker.

Question 3

Does the Agency agree that pain response rate as measured by the Brief Pain Inventory – Short Form (BPI-SF) and analgesic use, the quality of life (QOL) as measured by patient-reported outcome (PRO) questionnaires including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), and the multiple myeloma specific module (QLQ-MY-20), are appropriate endpoints for this trial? It is the sponsor's assumption that if the statistical requirements are met for the pain response rate key secondary endpoint, statements regarding the treatment effect in this key secondary objective can be included in the US prescribing information.

FDA Response: For the pain response endpoint, you have not yet provided the measurement properties of the BPI-SF for this context of use. However, we concur with your proposal to analyze the item which evaluates the worst pain over the past 24 hours, as opposed to the average pain over the past 24 hours. Additionally, we recommend that you include a daily analgesic diary in the protocol and that changes in analgesic use are taken into account when constructing the pain response definition for use in your key secondary endpoint.

Your likelihood of success in this patient population (not selected for pain) seems low.

We do not have documentation that the EORTC QLQ C30 and QLQ-MY-20 are well-defined and reliable assessments of MM symptoms, functioning and global health status for use in clinical trials to support efficacy claims. Please refer to the *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

Briefly, we have the following concerns.

- Distal health concepts found in the EORTC-QLQ C30 and other health-related QoL instruments (e.g., patient report of interference with family life or worry about future events) extend beyond the central domains of importance for understanding and describing the effect of an investigational treatment for regulatory purposes. Such concepts are subject to influence by a variety of factors that are external to the condition, and measures of these concepts are generally inadequately defined to support

labeling claims. Instead, we recommend focusing on the specific core set of symptoms and functional decrements of MM in the targeted patient population.

- The global health status scale is ill-defined and combines harms and benefits in an overall measure; therefore, it should not be used to support a key study endpoint measure. We generally do not recommend global questions for use as key study endpoints.
- The instrument's instructions are imprecise and do not specify whether patients are to respond based on their average or usual severity, the worse symptoms, or the frequency of the symptoms.
- The 7-day recall period may not be appropriate for all the concepts being measured (e.g., pain or dyspnea).
- Documentation of patient input in the development of the instrument was not provided.

We recommend that you consider developing/utilizing an instrument based upon patient input that represents an appropriate and complete measure of the core symptoms for the target population of patients.

Sponsor Response 3

Thank you for your feedback. Your comments have given us valuable guidance for consideration, and we would like an opportunity to further refine our plan. Because it is important that we come to agreement on how to capture this aspect, we would like to request an opportunity to discuss this in a subsequent meeting with the appropriate FDA personnel.

Meeting Discussion for Question 3: The Agency would welcome a meeting request to further discuss the patient-reported outcomes evaluation plan for the pivotal trial. A separate briefing package would be needed.

Question 4

Does the Agency agree with the choice of comparator?

FDA Response: Yes. The proposed treatment arms of ixazomib+lenalidomide+dex versus placebo+lenalidomide+dex are acceptable.

Sponsor Response 4 (part 1)

Agreed. No further discussion needed.

Further, does the Agency agree that the availability of new therapies subsequent to program initiation will not negate this proposed comparator as a suitable choice for the pivotal study to support registration?

FDA Response: Yes.

Sponsor Response 4 (part 1)

Agreed. No further discussion needed.

Question 5

Does the Agency agree with the proposed dose, schedule, and treatment duration for both the test regimen and the comparator, as outlined below?

FDA Response: No. You have not provided adequate information to justify the ixazomib dose for your Phase 3 clinical trial. Your meeting package describes clinical experience in only 3 patients treated at the proposed Phase 3 treatment regimen. Additional data from the Phase 2 cohort of the ongoing C16005 clinical trial should be provided.

In addition, we recommend that you complete your food effect study prior to initiating your phase 3 trial to better inform appropriate dosing of your drug.

Sponsor Response 5

The phase 2 cohort of the ongoing C16005 clinical trial will be fully enrolled with 46 patients by March 2012, which is prior to initiation of the C16010 clinical trial. This additional data will be available to justify the phase 3 dose.

Table 3 Projected Number of Patients Dosed at Recommended Phase 2 Dose in Ongoing Study C16005 Before Start of Study C16010

Date	Patients enrolled at RP2D	Patients completed ≥ 4 cycles	Range of cycle number
Now (Nov 2011)	10	3	1 - 9
Jan 2012	32	3	1 - 10
March 2012	46	20	1 - 13

RP2D = recommended phase 2 dose.

In Study C16010, patients will be advised to take their blinded oral capsules weekly on an empty stomach (at least 1 hour before or more than 2 hours after a meal). This is similar to dosing instructions for earlier phase 1 and 2 studies after weekly or twice weekly dosing.

Approximately 115 patients in these phase 1 and 2 studies have been orally dosed with MLN9708.

However, Millennium recognizes the need to evaluate the effect of food and this has been planned to be evaluated in Study C16009, arm 3, with first patient enrollment planned for 2012. The data from the food effect study will be available as part of the NDA submission.

Meeting Discussion for Question 5: The proposed plan for justifying the phase 3 dose appears reasonable. When the data are available, it should be submitted to the IND prior to the start of the phase 3 trial. The plan to evaluate the effect of food in parallel to phase 3 appears reasonable. The food effect study can be conducted using the investigational formulation as long as it does not differ significantly from the commercial formulation.

Questions on Clinical Pharmacology

Question 6

The need for dedicated hepatic and renal dysfunction studies will be assessed based on a review of all available data including clinical and nonclinical data on the clearance mechanisms of ixazomib citrate along with the results from the proposed clinical mass balance study. Does the Agency agree with the proposal?

FDA Response: No, you have already identified hepatic metabolism as the major elimination route of ixazomib citrate. Therefore, you should plan and conduct a hepatic impairment study. The need for renal impairment study should be determined based on your ADME study.

Sponsor Response 6

Agreed. No further discussion needed.

Question 7

Does the Agency agree that the proposed DDI program that includes completed in vitro studies and a planned clinical DDI study with ketoconazole are adequate to support a marketing application for ixazomib citrate?

FDA Response: No, in addition to your proposed DDI study, you need to address the following:

1. You will also need to conduct a DDI study using CYP3A4 inducer.
2. *In vitro* study results show 31% of the drug is metabolized by CYP1A2. Therefore, you should also address the issue of drug-drug interaction when ixazomib citrate is administered concomitantly with CYP1A2 inhibitors/inducers.

Sponsor Response 7

Agreed. No further discussion needed.

Question 8

The sponsor proposes to develop a strategy for a definitive clinical QTc evaluation based on interactions with the Interdisciplinary Review Team (IRT) guided by the data collected in four ongoing phase 1 studies. Does the Agency agree?

FDA Response: Yes. Submit your proposed QTc plan for review and concurrence by the Agency.

Sponsor Response 8

Agreed. No further discussion needed.

Questions on Statistical Analyses

Question 9

Does the Agency agree that type I error rate is strongly controlled for the primary endpoint and for the 4 key secondary endpoints by the closed testing procedure?

FDA Response: No. A Hochberg procedure, while likely to control the type 1 error rate, does not strongly control the type 1 error rate. Please also see additional comment #7.

Sponsor Response 9

See Sponsor Response 1 regarding recent changes to the study design. Since there are only 2 key secondary endpoints, OS in the overall population and OS in high risk patients carrying del(17), we do not plan to utilize the Hochberg procedure. Type 1 error control for the primary endpoint and 2 key secondary endpoints is described in Sponsor Response 1.

Question 10

Does the Agency agree with the proposed sample size, including the estimated effect size?

FDA Response: The sample size appears appropriate. An improvement in PFS should be both statistically persuasive and clinically meaningful. Please also refer to Question 1.

Sponsor Response 10

The combination of lenalidomide and low-dose dexamethasone is recognized as an effective treatment for patients with RRMM, with a demonstrated median PFS of 11.1 months obtained in studies that were the basis for the FDA approval.⁽²⁾ The control arm in our proposed pivotal phase 3 clinical study (C16010) will include oral placebo dosing along with LenDex and will serve as the comparator to the combination of oral ixazomib citrate plus LenDex. Our expectation is that the LenDex control arm in C16010 will replicate the 11-month PFS previously reported.

A total of approximately 234 disease progression/death events is required to provide 90% power at a 2-sided alpha of 0.05 to detect a hazard ratio of 0.66 (median PFS of 11 months in the control arm versus 16.8 months in the treatment arm). This 5.8-month difference in PFS targets a 52% improvement in PFS. With an observed hazard ratio of 0.775 (eg, median PFS of 11 months for control versus 14.2 months for treatment, 29% improvement), statistical

significance can be claimed at the analysis for PFS with 234 progression/death events. The sponsor considers these results both statistically and clinically meaningful.

While the sponsor considers PFS is sufficient to support registration, we believe treatment effect in OS should be adequately estimated. Therefore, OS in the entire study population is the first key secondary endpoint, and the total sample size is calculated based on maintaining 80% power to test OS. Group sequential design is used with 2 interim analyses and 1 final analysis that allows early stopping for efficacy and/or futility using O'Brien-Fleming stopping boundary (the Lan-DeMets method). The first interim analysis will occur when PFS is analyzed, and the second interim analysis will occur when approximately 322 deaths (two-thirds of the total expected deaths) have occurred.

A total of approximately 482 death events is required to provide 80% power at a 2-sided alpha of 0.05 to detect a hazard ratio of 0.77 (median OS of 30 months in the control arm versus 39 months in the treatment arm). This 9-month difference in OS targets a 30% improvement in OS. A total of approximately 703 patients will need to be randomized in a 1:1 ratio into the 2 arms. This assumes an average enrollment rate of approximately 13 patients/month for the first 6 months, approximately 30 patients/month thereafter, and approximately 10% dropout rate. The final analysis of OS is estimated to occur approximately 81 months from the enrollment of first patient, including a 27-month randomization period and an additional 54-month follow-up from the last patient enrolled. With an observed hazard ratio of 0.833 (eg, median OS of 30 months for control versus 36 months for treatment, 20% improvement), statistical significance can be claimed at the final analysis with 482 death events.

Questions on Regulatory Strategy

Question 11

Does the Agency agree that the size of the overall safety database is adequate to support registration?

FDA Response: The adequacy of your safety database to support filing and approval of an application will be a review issue based on the results of your clinical trial.

Sponsor Response 11

Agreed. No further discussion needed.

Additional Comments:

- 1. The Agency recommends that you submit Protocol C16010 for Special Protocol Assessment once you have adequately justified the ixazomib dose. See FDA response to Question 5.**

Sponsor Response to Comment 1

Millennium would like to understand the Agency's request for a SPA. Since the study design has been updated, we would like to discuss this at the meeting.

Meeting Discussion to Comment 1: The Agency advised that SPA is optional and may be considered by Millennium. If a SPA were submitted, it would need to contain the final statistical analysis plan.

- 2. Due to the safety signal reported with lenalidomide, we recommend that you propose a plan to prospectively monitor for second primary malignancies during the trial and for at least 5 years after last dose.**

Sponsor Response to Comment 2

We plan on incorporating this into our routine surveillance, and it will be ongoing at the time of the NDA submission.

- 3. We discourage a submission based on a rather early evaluation of PFS as estimated effects will be less precise and the comparison will be weighted towards early events.**

Sponsor Response to Comment 3

Please refer to Sponsor Response 1. Per our updated study design, there will be no early evaluation of PFS.

- 4. We require the intent-to-treat (ITT) population, which includes all subjects as randomized, for the primary and secondary endpoint analysis. Randomization fairly distributes patients to arms.**

Sponsor Response to Comment 4

Please refer to the Sponsor Response 1. The ITT population will be used for the primary and the 2 key secondary endpoint analyses.

- 5. All patients should be followed for PFS until a PFS event has occurs (progression or death) or until the data cutoff. Missing data/assessments of progression should be kept to a minimum. Patients should be followed for PFS until an IRC assessment of a PFS event (progression or death). A substantial amount of missing data or events could undermine confidence in the PFS results of the trial and may prevent a labeling claim on PFS.**

Sponsor Response to Comment 5

We agree and will work to operationally ensure there is a minimum of missing data/assessments.

- 6. Sensitivity analyses should be performed to account for the limitations of the data and to examine the potential impact of any missing data. For further advice on missing data see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials.**

Sponsor Response to Comment 6

Comprehensive sensitivity analyses based on FDA and EMA guidelines will be performed for PFS analysis.

- 7. Testing the OS and other key secondary endpoints at the overall desired two-sided significance level whenever the PFS reaches statistical significance (interim or final analysis) will inflate the strong study-wise type I error rate. For further information see the reference: H. M. James Hung, Sue-Jane Wang, Robert O'Neill. Statistical Considerations for Testing Multiple Endpoints in Group Sequential or Adaptive Clinical Trials *Journal of Biopharmaceutical Statistics*, 17: 1201–1210, 2007.**

Sponsor Response to Comment 7

Please refer to Sponsor Response 1.

- 8. Please specify the number of events for the analysis for OS. We recommend that any analysis be based on a pre-specified number of events in order to isolate the power and the amount of information in the comparison. The timing of the analyses of all secondary endpoints should be pre-specified.**

Sponsor Response to Comment 8

Please refer to Sponsor Response 1.

- 9. Please provide a detailed statistical analyses plan.**

Sponsor Response to Comment 9

The statistical components of the study will be detailed in the protocol. The final SAP will be submitted prior to the PFS analysis.

References

1. Lan K, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659-63.
2. Dimopoulos MA, Chen C, Spencer A, Niesvizky R, Attal M, Stadtmauer EA, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. *Leukemia* 2009;23(11):2147-52.

3.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

FDA recommended Patient Reported Outcome endpoints to be discussed during a separate meeting with SEALD. A future meeting request to be submitted by Millennium for this discussion.

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Millennium provided slides to facilitate discussion during the meeting. Slides attached.

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

/s/

VIRGINIA E KWITKOWSKI
11/15/2011

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 208462

LATE-CYCLE MEETING MINUTES

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Director Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) dated July 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ninlaro® (ixazomib) capsule, 2.3, 3, and 4 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on November 5, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Jacquin Jones, Regulatory Project Manager, at (240) 402-4590.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: November 5, 2015, 11:30 am -12:00 pm (ET)
Meeting Location: Teleconference

Application Number: NDA 208462
Product Name: Ninlaro® (ixazomib)
Applicant Name: Millennium Pharmaceuticals, Inc.

Meeting Chair: R. Angelo de Claro, MD, Clinical Team Leader, CDTL

Meeting Recorder: Jacquin Jones, MS, BSN, Regulatory Project Manager

FDA ATTENDEES

OHOP/Division of Hematology Products

Ann T. Farrell, MD, Director
R. Angelo de Claro, MD, Clinical Team Leader, Cross Discipline Team Leader (CDTL)
Alexandria Schwarsin, MD, Medical Officer
Qin Ryan, MD, PhD, Safety Reviewer
Diane Leaman, Safety Regulatory Project Manager
Amy Baird, Chief, Project Management Staff
Jacquin L. Jones, MS, BSN, Regulatory Project Manager

Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology (DCP) V

Bahru Habtemariam, PharmD, Acting Team Leader
Vicky Hsu, PhD, Reviewer

OCP/DCP I/Division of Pharmacometrics

Jee Eun Lee, PhD, Reviewer

Office of Biostatistics/ Division of Biometrics V

Lei Nie, PhD, Team Leader
Yun Wang, PhD, Reviewer

OHOP/Division of Hematology Oncology Toxicology (DHOT)

Christopher Sheth, PhD, Supervisory Pharmacologist
Emily Place, PhD, MPH, Reviewer

Office of Pharmaceutical Quality/Office of New Drug Products

Janice Brown, MS, Team Leader

Office of Surveillance and Epidemiology (OSE)/Division of Risk Management
Amarilys Vega, MD, Medical Officer

OSE/Division of Pharmacovigilance II
Regina Lee, PharmD, Safety Evaluator

OSE/Division of Medication Error Prevention and Analysis
Ebony Ayres, PharmD, Reviewer

Office of Medical Policy/Division of Medical Policy Programs
Sharon Mills, BSN, RN, CCRP, Reviewer

EASTERN RESEARCH GROUP ATTENDEES

Christopher A. Sese, Independent Assessor

APPLICANT ATTENDEES

Melissa Anderson, RAC, Director, Global Regulatory Affairs
Eileen Bedell, MPH, Senior Director, Global Regulatory Affairs
Melody Brown, Vice President, Global Regulatory Affairs
Cory Ferguson, MHA, Manager, Global Regulatory Affairs
Asha Henderson, Senior Manager, Global Labeling
Debbie Berg, RN, MSN, Scientific Director, Oncology Clinical Research
Dixie-Lee Esseltine, MD, Vice President, Oncology Clinical Research
Ai-Min Hui, MD, PhD, Senior Medical Director, Oncology Clinical Research
Helgi van de Velde, MD, Vice President, Oncology Clinical Research
Jianchang Lin, PhD, Senior Statistician, Global Statistics
Guohui Liu, PhD, Scientific Fellow, Global Statistics
Neeraj Gupta, PhD, Director, Clinical Pharmacology
Ben Exter, Director, Pharmacovigilance Sciences
Heather Stein, MD, MPH, Senior Medical Director, Pharmacovigilance
Ray Skwierczynski, PhD, Senior Director, Formulation Sciences
Satyam Upadrashta, Senior Director, Global Regulatory Affairs CMC
Li-Chun Wang, Director, Global Regulatory Affairs CMC
Alessandra Di Bacco, PhD, Director, Translational Medicine
Stephanie Powlin, PhD, DABT, Associate Scientific Fellow, Drug Safety Research and Evaluation
Cindy Xia, PhD, Director, Drug Metabolism and Pharmacokinetics
Julie Batal, Senior Director, Global Labeling
Mingxiu Hu, PhD, Vice President, Global Biostatistics
Nishith Jobanputra, DO, Medical Director, Pharmacovigilance

1.0 BACKGROUND

NDA 208462 was submitted on July 10, 2015 for Ninlaro® (ixazomib)

Proposed indication: Treatment of patients with multiple myeloma who have received at least one prior therapy.

PDUFA goal date: March 10, 2016

FDA issued a Background Package in preparation for this meeting on November 2, 2015.

2.0 DISCUSSION

1. Introductory Comments

Discussion: Welcome, Introductions, Ground Rules, Objectives of the meeting:

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

2. Discussion of Substantive Review Issues

Discussion: The Agency informed the Applicant that there are no substantive review issues that have been identified to date.

3. Discussion of Minor Review Issues

Discussion: No minor review issues have been identified at this time.

4. Additional Applicant Data

Discussion: No additional application data has been requested at this time.

5. Information Requests

Discussion: The Applicant has responded to outstanding information requests.

6. Discussion of Upcoming Advisory Committee Meeting

Discussion: The Agency informed the Applicant that an Advisory Committee meeting is not planned.

7. REMS or Other Risk Management Actions

Discussion: The Agency informed the Applicant that no major safety concerns have been identified at this time that would need a REMS.

8. Postmarketing Requirements/Postmarketing Commitments

Discussion: The Agency informed the Applicant that no PMRs/PMCs are anticipated at this time.

9. Major Labeling Issues

Discussion: The Agency acknowledge receipt of the Applicant's draft labeling edits and informed the Applicant that FDA proposed labeling will be provide at the early part of next week.

Non-Clinical:

The Applicant was asked to provide AUC values used to calculate exposure multiples for the labeling.

10. Review Plans

The Agency plans to send the second draft of the proposed labeling edit to the Applicant by next week, with a requested 1-2 day Applicant review turn-around. The Agency informed the Applicant that the Burst materials will be provided next week for their review.

The Agency informed the Applicant that two manufacturing site inspections are still pending.

Discussion: The Applicant acknowledged the Agency's plans.

11. Wrap-up and Action Items

This application has not yet been fully reviewed by the Signatory Authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

ROMEO A DE CLARO
11/06/2015



NDA 208462

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Millennium Pharmaceuticals, Inc.
Attention: Melissa Anderson, RAC
Director Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ninlaro[®] (ixazomib) capsule, 2.3, 3, and 4 mg.

We also refer to the Late-Cycle Meeting Package dated October 6, 2015. This document is an updated version and replaces that document for the Late-Cycle Meeting (LCM) scheduled for November 5, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, please call Jacquin Jones, Regulatory Project Manager, at (240) 402-4590.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: November 5, 2015, 11:30 am -12:00 pm (ET)
Meeting Location: Teleconference

Application Number: NDA 208462
Product Name: Ninlaro[®] (ixazomib)
Indication: Treatment of patients with multiple myeloma who have received at least one prior therapy

Sponsor/Applicant Name: Millennium Pharmaceuticals, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review Letters have been issued to date.

The Division is awaiting final reports for clinical site and manufacturing site inspections.

2. Substantive Review Issues

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

There are no major safety concerns have been identified at this time that would need a REMS.

LCM AGENDA

1. Introductory Comments – RPM/CDTL

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Postmarketing Requirements/Postmarketing Commitments

No PMRs/PMCs are anticipated at this time.

3. Labeling issues

Refer to draft labeling that the Division sent to the Applicant on 30 October 2015.

4. Wrap-up and Action Items

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

/s/

ROMEO A DE CLARO
11/02/2015