

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205353Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 205353 BLA #	NDA Supplement # N/A BLA Supplement #	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: FARYDAK [®] Established/Proper Name: panobinostat Dosage Form: Capsule Strengths: 10 mg, 15 mg, and 20 mg		Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable):
RPM: CAPT Diane Hanner		Division: Division of Hematology Products (DHP)
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><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></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) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) <p>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>February 24, 2015</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 type="checkbox"/>
❖ 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 _____		<input checked="" type="checkbox"/> January 23, 2015 Received by OPDP
❖ 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

- Fast Track Rx-to-OTC full switch
 Rolling Review Rx-to-OTC partial switch
 Orphan drug designation Direct-to-OTC
 Breakthrough Therapy designation

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

BLAs: Subpart E

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

Subpart H

- 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

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

Comments: Two INDs related to NDA- IND 067091 (intravenous formulation) and IND 069862 (oral capsule)

❖ 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)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> 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"/> Other BURST-ASCO
❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? If so, specify the type 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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>	February 23, 2014 Approval
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 March 24, 2014-Original
❖ 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 checked="" type="checkbox"/> January 9, 2015 Medication Guide <input checked="" type="checkbox"/> July 11, 2014 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 January 9, 2015 Medication Guide July 11, 2014 Patient Package Insert
❖ 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 March 24, 2014-Original
❖ Proprietary Name	June 18, 2014 Proprietary Name Conditionally Accepted Letter-
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	June 18, 2014 Proprietary Name Review (DMEPA)
❖ Labeling reviews <i>(indicate dates of reviews)</i>	OPDP: January 23, 2015 DMPP/PLT (DRISK): October 10, 2014 DMEPA: September 18, 2014 RPM: May 22, 2014 SEALD: None CSS: None Other: None

Administrative / Regulatory Documents

<ul style="list-style-type: none"> ❖ RPM Filing Review⁴/Memo of Filing Meeting (<i>indicate date of each review</i>) ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee 	<p>May 22, 2014</p> <p><input checked="" type="checkbox"/> Not a (b)(2)</p>
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<p><input checked="" type="checkbox"/> Included</p>
<ul style="list-style-type: none"> ❖ 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 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<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>) 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not an AP action</p>
<ul style="list-style-type: none"> ❖ 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 designation</u> 	<p>Orphan Designation (MM granted August 20, 2012)</p>
<ul style="list-style-type: none"> ❖ 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, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	<p>February 20, 19, 13, 12, 11, 10, 9, and 2, 2015</p> <p>January 30, 29, 26, 23, 21, 20, 16, 14 (2), and 7, 2015;</p> <p>December 31, 19, 12, and 4, 2014;</p> <p>November 24, and 21, 2014;</p> <p>October 24, 14, 10 (2), and 9, 2014;</p> <p>September 29, 16 (2), and 11, 2014;</p> <p>August 29 (4), 26 (2), 25 (2), 24, 22, 20, 19, 18(2), 17, 15, 14, 13, 11, 8, 4, and 1, 2014;</p> <p>July 31(3), 29 (2), 22, 14, and 7, 2014;</p> <p>June 26, 25 (2), 19, 16, 12, and 10, 2014;</p> <p>May 27, 23, 20, 19, 14, 12, 9, 5, 2 (2), and 1 (2), 2014;</p> <p>April 25, 24, and 22, 2014;</p> <p>March 28 (2), and 27, 2014</p>

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

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)	Telecons: November 19, and 3, 2014; July 7, 2014;
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	February 5, 2014
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> None
• Mid-cycle Communication (<i>indicate date of mtg</i>)	June 11, 2014
• Late-cycle Meeting (<i>indicate date of mtg</i>)	October 23, 2014
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/>
• Date(s) of Meeting(s)	November 6, 2014
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 23, 2015
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 20, 2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> January 25, 2015
PMR/PMC Development Templates (<i>indicate total number</i>)	2 PMRs
Clinical	
Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Co-signed reviews dated August 26, and 27, 2014
• Clinical review(s) (<i>indicate date for each review</i>)	February 19, 2015 January 22, 2015(Addendum) August 27, 2014 (Safety) August 26, 2014 (Efficacy)
• 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 page 15 of Clinical Review Dated: August 27, 2014
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	IRT June 30, 2014
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management	February 22, 2015 DRISK Review
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	February 11, 2015
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	OPDP Review August. 28, 2014
• 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>)	Sponsor submitted
	February 4, 2015

	REMS Notification letter February 19, 2015 REMS Memo August 28, 2014 DRISK Review
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	September. 11, 2014
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review Co-signed review dated August 26, 2014 and December 22, 2014
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review Co-signed review dated August 26, 2014 and November 21, 2014
Statistical Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> December 22, 2014 Addendum August 26, 2014
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review Co-signed review dated January 24, 22, and 20, 2015; September 26, 2014
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review Co-signed review dated January 24, 22, and 20, 2015 September 26, 2014
Clinical Pharmacology review(s) (indicate date for each review)	<input checked="" type="checkbox"/> January 24, 22, and 20, 2015 Addendum September 26, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<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>	September. 2, 2014
• Supervisory Review(s) <i>(indicate date for each review)</i>	August 28, 2014
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	August 28, 2014
❖ 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 Included in P/T review, page
❖ 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	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review Co-signed review dated October 7, 2014; August 27, 2014; May 10, 2014
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	October 7, 2014 September 22, 2014 Biopharm Addendum August 27, 2014 August 27, 2014 Biopharm
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> May 29, 2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ 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>	See page 7 of CMC review dated October 7, 2014
<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"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵</i>)	Date completed: September 11, 2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<input checked="" type="checkbox"/> NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested June 13 and 18, 2014 <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

...e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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 type="checkbox"/> Done
❖ 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

EXCLUSIVITY SUMMARY

NDA # 205353

SUPPL #

HFD # 161

Trade Name FARYDAK®

Generic Name panobinostat

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known February 23, 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

505(b)(1)

c) 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

d) Did the applicant request exclusivity?

YES NO

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

The sponsor did not specify the number of years.

e) 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?

N/A

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 #2 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: CAPT Diane Hanner
Title: Regulatory Project Manager
Date: February XX, 2015

Name of Office/Division Director signing form: Edvardas Kaminskas, MD
Title: Deputy Director, Division of Hematology

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/

DIANE C HANNER
02/23/2015

EDVARDAS KAMINSKAS
02/23/2015

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 205353 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DHP PDUFA Goal Date: 2/24/15 Stamp Date: 3/24/14

Proprietary Name: FARYDAK

Established/Generic Name: Panobinostat

Dosage Form: Oral Capsule, 10, 15, and 20 mg

Applicant/Sponsor: Novartis

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

(1) Treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.

(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: Treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.

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	__ 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**

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

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 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 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,

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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 †
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 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 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/

DIANE C HANNER
02/19/2015

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Bcc: [Robottom, Suzanne Berkman](#)
Subject: NDA 205353(Farydak) REMS documents
Date: Friday, February 20, 2015 5:46:00 PM
Importance: High

Hi Jeannie,

Please address the following regarding NDA 205353 (Farydak) REMS comments.

REMS Document:

- Page 1: "Initial REMS Approval XX/2015" revise to include the month "2/2015"
- There is one instance each on pages 1 and 3 to include the initial approval date. Please include the date as directed by Diane Hanner.

REMS Supporting Document - 1.6.5 Target healthcare provider audience for REMS communication:

- Delete (b) (4) in the following statement as these risks may occur regardless of the mitigation efforts. "(b) (4)"

Webpage:

- The pdf of the REMS website includes 6 pages, 3 with error message and 3 with various formats. Include only page 1 in your final REMS submission.

Factsheet:

- Hyphenate "ST-segment" and "T-wave"

Journal information piece:

- Revise the following statement to remove 'detailed'.
"Refer to Factsheet for (b) (4) diarrhea management information available at www.FARYDAK-REMS.com"

We have no edits or comments on the following materials

- Letters/emails

Submission Instructions

Once these edits have been incorporated, submit final version of the REMS Document, materials, and REMS Supporting Document in MS Word and PDF formats through the Gateway and provide a courtesy copy to Diane Hanner via email. Please indicate in that email that the email REMS package is identical to what was submitted through the Gateway.

If possible, include the REMS Document and all the communication materials as a single MS Word Document. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. If certain documents such as enrollment forms are only

in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document. Please note – submit the REMS Supporting Document as a separate document.

Please remember to submit both the print and email versions of the REMS Letters for both HCPs and Professional Societies (a total of 4 documents) in both MS Word and PDF format(8 documents total).

Thank you,
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@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/

DIANE C HANNER
02/20/2015

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: NDA 205353 (panobinostat) rems-support 2-19-15.docx
Date: Thursday, February 19, 2015 12:06:00 PM
Attachments: [rems-support 1 13 15 revised 2-19-15.docx](#)
Importance: High

Hi Jeannie,

Attached please find NDA 205353 (panobinostat) REMS support document.

Please send the entire REMS – REMS Document, materials, Supporting Document (marked with any changes and clean) via email by noon, tomorrow 2-20-15.

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
02/19/2015

Hanner, Diane

From: Hanner, Diane
Sent: Friday, February 13, 2015 3:44 PM
To: Shen, Jeannie (jeannie.shen@novartis.com)
Subject: NDA 205353 Proposed_Farydak draft label 13Feb15.doc

Importance: High

Hi Jeannie,
Please click on the attachment and view the NDA 205353 (panobinostat) revised label.
Please return your revised version a.s.a.p. in tracked changes.
Thank you.
Regards,
Diane



Attachment sent to
sponsor/Proposer...

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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/s/

DIANE C HANNER
02/13/2015

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Bcc: [Robottom, Suzanne Berkman](#)
Subject: NDA 205353 Panobinostat REMS Materials
Date: Thursday, February 12, 2015 5:37:00 PM
Attachments: [2-12-15 sent to spon -02 10 15 REMS letter to Prof Soc FDA revised 1 \(2\).doc](#)
[2-12-15 sent to spon-Farydak REMS Factsheet v5 \(2\) \(2\).doc](#)
[2-12-15- sent to spon - 02 10 15 Farydak REMS webpage FDA revised 1 \(2\).docx](#)
[2-12-15 sent to spon -REMS JournalInformationPiece FDA revised v4 \(2\).docx](#)
[2-12-15- sent to spon 02 10 15 REMS letter to HCP FDA revised 1 \(2\).doc](#)

Hi Jeannie,

Attached please find the following revised NDA 205353 (panobinostat) REMS documents.

- REMS Letters (Professional Society and HCP)
- Factsheet
- Journal information piece
- Webpage

The REMS Supporting Document is not attached!! We will be sending this document to you separately.

Please wait and send all REMS Materials back at one time.

Additional Comments to Novartis:

REMS Materials

1. Please note: We have transferred your .PDF files to WORD in order to edit the formatting better. When transferring files to WORD format, some text appearance is inadvertently altered. Please ignore text formatting changes from the conversion from .PDF format to WORD format, unless it is related to font size or color.

In addition, please note that precise shade of burgundy in our revisions may not match the Farydak trademark color. Please use the colors consistent with the Farydak color scheme.

2. Revise the headings to a darker color. The proposed (b) (4) color is light and difficult to read in document. We have modified color to burgundy to match Novartis's color scheme for Farydak. We recommend that Novartis use the burgundy shade from your color scheme in headings and text as appropriate throughout all REMS communication materials.
3. We have modified the content of the hard copy version of both REMS Letters. Please include similar content for the emailed versions for each audience with the following exceptions:
 - For emailed version of both REMS Letters, please include hyperlink to the REMS Factsheet at www.FARYDAK-REMS.com.
 - Remove the word "enclosed" where the enclosure of the Factsheet is referenced in both letters.

REMS Document

4. We have one comment (a typo from our version) on the REMS Document submitted to Diane Hanner via email on Tuesday, February 10, 2015.

Please revise the following statement with regard to the distribution of the factsheet in conjunction with the REMS Letters. The Factsheet should accompany both the Letter to HCPs *and* the Letter to Professional Societies. Revise the last sentence as follows (edit in red and underlined):

1. REMS Letters
... "A copy or link to the Prescribing Information (PI) and *REMS Factsheet* will accompany each *REMS Letter for Healthcare Providers*. A copy or link to the *REMS Factsheet* will accompany each *REMS Letter for Professional Societies*.

General Comment

5. Once all documents and materials are revised, please resend them to Diane Hanner via email. We will provide any additional edits then direct you to submit the REMS Document, materials, and REMS Supporting Document to the Gateway.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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Silver Spring, Maryland 20993
(301) 796-2330
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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
02/12/2015

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, February 10, 2015 4:30 PM
To: Shen, Jeannie (jeannie.shen@novartis.com)
Subject: NDA 205353 (Medication Guide) DRAFT
Attachments: DMPP proposed revisions_NDA 205353_panobinostat_3 FEB 2015.doc

Hi Jeannie,

Please address the changes to the NDA 205353 (panobinostat) Medication Guide and return it to me a.s.a.p.

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
02/11/2015

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Bcc: [Kwitkowski, Virginia](#)
Subject: NDA 205353 (panobinostat) Revised version of the PMRs -time sensitive - Please respond by Friday -2-13-15
Date: Wednesday, February 11, 2015 10:24:00 AM
Attachments: [02-11-15 PMRs sent to Novartis.doc](#)

Hi Jeannie,

Please click on the attachment and view the revised NDA 205353 (panobinostat) PMRs, and please respond by Friday, February 13, 2015.

Thank you.

Regards,

Diane

CAPT Diane Hanner

Senior Program Management Officer

FDA/CDER/OHOP/DHP

10903 New Hampshire Avenue

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(301) 796-2330

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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
02/11/2015

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Bcc: [Kwitkowski, Virginia](#)
Subject: NDA 205353 Proposed_Farydak draft label 06Feb15.doc - sent to sponsor 2-9-15 - Time sensitive -please respond by Thurs. 2/12/15.
Date: Monday, February 09, 2015 4:15:00 PM
Attachments: [Proposed_Farydak_draft_label_06Feb15- sent to sponsor.doc](#)
[Novartis draft rems 2- 9- 15 sent to sponsor.docx](#)

Hi Jeannie,

Please click on the attachment and view the DRAFT Farydak NDA 205353 label and the REMS document.

Please remember that any changes you make to these documents must be indicated in track changes.

Also, please respond by close of business on Thursday, February 12th .

The following REMS documents are not included at this time but will follow as soon as possible:

- *REMS Letter to Healthcare Providers (print and email versions)*
- *REMS Letter for Professional Societies (print and email versions)*
- *REMS Factsheet*
- *The Journal Information Piece*
- *FARYDAK REMS Website Landing Page*

Thank you.

Regards,

Diane

CAPT Diane Hanner

Senior Program Management Officer

FDA/CDER/OHOP/DHP

10903 New Hampshire Avenue

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/s/

DIANE C HANNER
02/09/2015



NDA 205353

PRE-APPROVAL REMS NOTIFICATION

Novartis Pharmaceuticals Corporation
Attention: Ms. Jeannie Shen
Sr. Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Shen:

Please refer to your March 22, 2014, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for FARYDAK[®] (panobinostat) 10 mg, 15 mg, and 20 mg capsules.

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for FARYDAK[®] (panobinostat) to ensure the benefits of the drug outweigh the risks of severe diarrhea and severe and fatal cardiac ischemic events, as well as arrhythmias and ECG changes in patients receiving FARYDAK[®] (panobinostat).

Your proposed REMS must include the following:

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe FARYDAK[®] (panobinostat) will support implementation of the elements of your REMS. The communication plan must provide for the dissemination of information about the risks of severe diarrhea and cardiac toxicities that have occurred in patients receiving FARYDAK[®] (panobinostat).

The communication plan must include, at minimum, the following:

- REMS Letter to Healthcare Providers
- REMS Letters to Professional Societies
- REMS Fact Sheet for Healthcare Providers
- REMS Website
- Make REMS materials available at professional scientific meetings or conferences where commercial FARYDAK[®] (panobinostat) product information is displayed
- Journal Information Piece

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven years after the REMS is initially approved. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information pertinent to FARYDAK[®] (panobinostat) (see Appendix A). Additionally, all relevant proposed REMS materials including educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS: and the plan for REMS assessments (see Appendix B).

Before we can continue our evaluation of this NDA, you will need to submit the revised proposed REMS.

For administrative purposes, designate all subsequent submissions related to the proposed REMS “**PROPOSED REMS for NDA 205353**” and all subsequent submissions related to the proposed REMS as “PROPOSED REMS for NDA 205353-AMENDMENT.” If you do not submit electronically, please send 5 copies of your REMS-related submissions.

We request that you submit the revised proposed REMS and other REMS-related materials in Word format. Provide a Word document with track changes and a clean Word version of all revised materials and documents. Submit the revised Proposed REMS with attached materials in one document and the REMS Supporting Document in a separate document in the same submission. Submission in Word format assists in the review of these materials. Word documents can efficiently be made compliant with Section 508 (29 U.S.C. Section 794d) to

ensure timely posting of the document on the website upon approval. If possible, submit the entire REMS document and attached materials in a single Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such.

If you have any questions, call Ms. Diane Leaman, Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Robert C. Kane, MD.
Deputy Director for Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:

REMS Appendices A and B

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/s/

ROBERT C KANE
02/04/2015

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: NDA 205353 (panobinostat)- Information Request 2-2-15
Date: Monday, February 02, 2015 4:33:00 PM
Importance: High

Hi Jeannie,

Please address the following label and labeling recommendations regarding Farydak (NDA 205353):

Carton Labeling (Trade Size and Sample)

We recommend the following:

- 1). While keeping the bolded advisory storage statement "Store blister pack in original carton to protect from light" on the principal display panel (PDP) to ensure sufficient prominence of this advisory storage statement, relocate the additional storage information, "Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F)." to the back panel as the PDP should be reserved only for the most important product information. The usual storage information regarding keeping the product at room temperature crowds the important advisory statement regarding keeping the blister pack in original carton; thus, decreasing prominence of the statement.
- 2). Relocate the "Each capsule contains 10 mg panobinostat" statement from the PDP to the back panel to increase readability of the important information on the principal display panel (PDP) and reduce duplicative information on the PDP.
- 3). Debold the statement "Rx Only" because it appears as prominent as other important information on the principal display panel.

Reference:

Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Draft Guidance [Internet].

FDA. April 2013 [cited 2015 February 2]. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

Please respond by c.o.b. Wednesday, February 4, 2015.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
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(301) 796-2330
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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
02/02/2015

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Bcc: [Kwitkowski, Virginia](#)
Subject: NDA 205353 panobinostat -DRAFT label, Med Guide, and REMs fact sheet - time sensitive: Please respond by 4:00 p.m. Mon., 2/2/15
Date: Friday, January 30, 2015 5:01:00 PM
Attachments: [Proposed Farydak draft label sent to sponsor 1-30-15.doc](#)
[Farydak REMS Factsheet v3.doc](#)
[Med Guide_NDA_205353_panobinostat -sent to sponsor 1-30-15 \(2\).doc](#)
Importance: High

Hi Jeannie,

Attached please find the panobinostat NDA 205353 – Draft Label (PI), Medication Guide and REMS fact sheet.

Please note that the Agency is requesting that these documents be returned by **4:00 p.m., Monday, February 2, 2015.**

Preamble:

We have received and reviewed your proposed revised panobinostat label (prescribing information). Many of the changes that you made are not acceptable to the Division, particularly in the safety descriptions. It is important to clearly communicate the risks associated with panobinostat without minimizing them. Time is of the essence in reaching agreement on the labeling for panobinostat since final labeling is a necessary prerequisite for other review processes. This is especially true because the REMS materials associated with FARYDAK cannot be reviewed and completed until there is final, agreed-upon prescribing information. The Division requests your urgent cooperation to assure timely completion of all activities on this application well before the PDUFA date. Additionally, it is imperative that any changes you make to the label be indicated in track changes.

REMS:

1. As stated in our previous comments sent to you via email on December 31, 2014 regarding the December 3, 2014 REMS submission, the proposed REMS materials submitted on January 13, 2015 are text heavy and include no graphics or color. Improve the visual interest and readability of these documents with color, graphics, bulleting, and font. In your January 13, 2015 cover letter you state “Novartis would like to gain agreement on the text of the REMS Factsheet, REMS Letters and Journal Information pieces, after which point the final layout can be rapidly provided”. However, the text and how it is presented (overall format and design) of each piece is an important aspect of assessing the readability. To assist you developing these materials, we have provided a draft version of the REMS Factsheet based on the label sent to you today. We expect Novartis can improve substantially upon the Factsheet and the other materials with the expertise and resources available to you.
2. Provide a MS Word document and PDF (with mock-up of graphics and color) of each revised material and/or documents. We will not provide additional revisions to the any of the other proposed REMS materials until you resubmit all the pieces with improved visual interest and readability as stated above.

3. We will provide a revised REMS Document under separate cover.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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/s/

DIANE C HANNER
01/30/2015

From: Hanner, Diane
To: "[Shen, Jeannie](#)"
Subject: Panobinostat, Farydak, LBH589/ NDA 205353 -information request
Date: Thursday, January 29, 2015 5:05:00 PM
Importance: High

Hi Jeannie,

Please address the following label and labeling recommendation regarding Farydak NDA 205353:

Carton Labeling (Trade Size and Sample)

We recommend relocating the advisory storage statement "Store blister pack in original carton to protect from light" to the principal display panel (PDP) to increase the prominence of this statement. We provide this recommendation because the product may degrade in the presence of light. Thus, to mitigate the risk to patients, it is important that patients can easily identify this statement without having to turn the carton around to see the storage information.

Please respond by Monday, February 2, 2015.

Thank you,

Regards,

Diane

CAPT Diane Hanner

Senior Program Management Officer

FDA/CDER/OHOP/DHP

10903 New Hampshire Avenue

Bldg. 22/Room 2119

Silver Spring, Maryland 20993

(301) 796-2330

FAX (301) 796-9845

E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
01/29/2015

Hanner, Diane

From: Hanner, Diane
Sent: Monday, January 26, 2015 3:12 PM
To: Shen, Jeannie (jeannie.shen@novartis.com)
Subject: FDA Response to Novartis Revision to PMRs - NDA 205353 (panobinostat)

Importance: High



FDA Response to
Novartis Rewi...

Hi Jeannie,

Please click on the attached document and view the latest NDA 205353 (panobinostat) PMRs revisions and please response by Wednesday at 12pm Eastern Time.

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

FDA Response to Novartis Revision to PMRs

Date: 01/26/15

In response to Novartis document titled “Response to FDA comments on PMRs” dated 1/23/15:

In this response, you stated that during our teleconference on January 21, 2015: “Novartis agreed to the FDA proposal for PMR-1 to expand the sample size and perform an interim analysis for the phase 2 study evaluating (b)(4) panobinostat which will now be a global study.”

The Agency does not agree, at this time, that the (b)(4) are the doses that should be studied in the PMR-1 trial. The PMR description that is agreed upon will not contain mention of (b)(4). When you submit your protocol for Agency review, you should provide clear justifications supporting the efficacy and safety for the doses that you propose to study.

We would also like to retain the language in the PMR -1 description that states “ ‘at least’ two doses” will be studied.

As written, the primary endpoint of PMR-2 seems to be (b)(4) which could be considered a landmark analysis, which we do not prefer. We have changed the text to state that the primary endpoint would be to compare the PFS between arms.

Below, is the current FDA recommended PMR trial descriptions that we seek your agreement on:

PMR-1: Conduct a randomized phase 2 clinical trial of panobinostat in combination with subcutaneous bortezomib and dexamethasone to characterize the safety and efficacy of at least two different doses of panobinostat. Eligible patients will include patients with relapsed multiple myeloma who have been previously exposed to immunomodulatory agents. The primary objective is to assess the overall response rate (ORR) in all treatment arms according to IMWG criteria by investigator assessment. The study would include one interim analysis. The results of this trial will be used to inform the dose selection for the confirmatory Phase 3 trial. Submit a final study report with full datasets.

Preliminary Protocol Submission to Include SAP:	April 2015
Final Protocol Submission:	September 2015
First Patient Enrolled:	December 2015
50% Trial Accrual:	November 2016
Trial Fully Accrued:	August 2017
Interim Analysis:	August 2017
Trial Completion:	August 2018

Final Report Submission:

August 2019

PMR-2: Conduct a multicenter, randomized, placebo-controlled phase 3 trial comparing panobinostat in combination with subcutaneous bortezomib and dexamethasone with subcutaneous bortezomib and dexamethasone in patients with relapsed multiple myeloma who have been previously exposed to immunomodulatory agents. The panobinostat dose selection will be based upon results from the trial described in PMR-1. Eligible patients will have previously treated multiple myeloma, 1-3 prior lines of therapy, prior immunomodulatory agent exposure (either thalidomide, lenalidomide, or pomalidomide), and measurable disease. The primary objective is to **compare the PFS in both treatment arms by investigator assessment.**

Preliminary Protocol Submission to Include SAP:

March 2017

**Final Protocol Submission:
PMR-1)**

September 2017 (driven by interim results of

First Patient Enrolled:

December 2017

50% Trial Accrual:

May 2019

Trial Fully Accrued:

December 2019

Trial Completion:

December 2020

Final Report Submission:

December 2021

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/s/

DIANE C HANNER
01/26/2015

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: Panobinostat, Farydak NDA 205353 Information Request
Date: Friday, January 23, 2015 4:38:00 PM
Importance: High

Hi Jeannie,

Please address the following label and labeling recommendations for Farydak NDA 205353 listed below:

Shell Pack Labeling and Carton Labeling (Trade Size and Sample)

Revise the advisory statement on the Farydak label and labeling items listed below from (b) (4) to “Store blister pack in original carton to protect from light”.

Please respond to the label by Monday, 12:00 p.m., and the additional packaging changes by Wednesday, January 28, 2015.

Thank you.

Regards,

Diane

CAPT Diane Hanner

Senior Program Management Officer

FDA/CDER/OHOP/DHP

10903 New Hampshire Avenue

Bldg. 22/Room 2119

Silver Spring, Maryland 20993

(301) 796-2330

FAX (301) 796-9845

E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
01/23/2015

From: Hanner, Diane
To: "[Shen, Jeannie](#)"
Subject: NDA 205353-Panobinostat: FDA Labeling and Medication Guide
Date: Wednesday, January 21, 2015 6:02:00 PM
Attachments: [1-21-15 Farydak Label sent to sponsor.doc](#)
[Med Guide sent to sponsor NDA 205353 panobinostat 21 JAN 2015.doc](#)
Importance: High

Hi Jeannie,

The FDA review team has provided the attached proposed labeling and Medication Guide changes regarding NDA 205353 (panobinostat). Please review and accept all changes that you agree with. For those changes that you do not accept, please make proposed edits in tracked changes and provide rationale/comment for the new text. Please do not reject any FDA proposed changes.

Please provide a response to the labeling changes via email by **January 26, 2015, 12 noon, EST.**

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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/s/

DIANE C HANNER
01/21/2015

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: NDA 205353 - panobinostat - DRAFT PMRs
Date: Tuesday, January 20, 2015 2:17:00 PM
Attachments: [1-20-15 DRAFT Revised PMRs with Preamble.doc](#)

Hi Jeannie,

Please click on the attachment and view the DRAFT NDA 205353 (panobinostat) PMRs that have been revised.

Please acknowledge receipt of the PMRs as this will be the focus of the teleconference scheduled for tomorrow at 11:30 a.m. (EST).

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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(301) 796-2330
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/s/

DIANE C HANNER
01/20/2015

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: NDA 205353 (panobinostat) - packaging labels
Date: Friday, January 16, 2015 3:36:00 PM

Hi Jeannie,

The information provided by Novartis is deemed acceptable (as written) as it pertains to the reading direction of the dosing schedule on the blister pack.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Thursday, January 15, 2015 2:40 AM
To: Hanner, Diane
Subject: RE: NDA 205353 (panobinostat) - packaging labels

Hi Diane,

In our discussion today, we briefly discussed the packaging components as provided in the FDA general advice letter, and Novartis' response sent on 27-Oct-2014 (copy attached). I believe you mentioned that the review team had provided comments on the Blister Label (as discussed in FDA comment #4, page 8 of the attached copy). When you have a chance, would you be able to email those FDA comments?

Also, we didn't have a chance to discuss earlier; however, have you received any updates on the REMs?

Thanks so much.

with best regards,
Jeannie

Jeannie Shen

Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7783343

Cell [REDACTED] (b) (6)

Fax +1 973 7813320

jeannie.shen@novartis.com

www.novartis.com

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/s/

DIANE C HANNER
01/16/2015

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Bcc: [Ryan, Qin \(Qin.Ryan@fda.hhs.gov\)](mailto:Qin.Ryan@fda.hhs.gov)
Subject: NDA 205353- panobinostat- information request
Date: Wednesday, January 14, 2015 3:47:00 PM

Hi Jeannie,

Please see our additional clarifying comments below regarding the previously sent information request:

To clarify our IR: The datasets in the original NDA has the following data cut-off dates: 10-Aug-2011 for B2207; 04-Dec-2012 for DUS71; and 10-Sept-2013 D2308. We are requesting the datasets your used for safety update, which have following cut off dates: 07-Oct-2013 for B2207; 26-Feb-2014 for DUS71; and 15-Mar-2014 for D2308. If these datasets have been submitted, please indicate the location. However, they definitely not in the NDA000, because your data cut-off for safety update was only 7 days before the NDA 000 submission. You datasets should be readily to submit and we expecting you submit them by COB today.

Thank you.
Regards,
Diane

CAPT Diane Hanner
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Silver Spring, Maryland 20993
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FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

-----Original Message-----

From: Hanner, Diane
Sent: Wednesday, January 14, 2015 12:50 PM
To: Shen, Jeannie
Subject: NDA 205353- panobinostat- information request

Hi Jeannie,

I need to request that you please respond to the information request within 24 hour. It would be preferable, if you could please send me the requested information tonight.

Thanks you.
Regards,
Diane

-----Original Message-----

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Wednesday, January 14, 2015 12:41 PM
To: Hanner, Diane
Subject: RE: NDA 205353- panobinostat- information request

Dear Diane,

Thank you for sending the email request. The Panobinostat team will be working on the response.

with best regards,

Jeannie

Jeannie Shen
Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7783343
Cell [REDACTED] (b) (6)
Fax +1 973 7813320
jeannie.shen@novartis.com
www.novartis.com

-----Original Message-----

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Wednesday, January 14, 2015 11:12 AM
To: Shen, Jeannie
Subject: NDA 205353- panobinostat- information request
Importance: High

Hi Jeannie,

Please address the following information request and please respond within two business days, (January 16, 2015):

"Please submit the datasets of AAEV.xpt, AECG.xpt, AECGINT.ept, ALBHCNAE.xpt, ALRS.xpt, AVSN.xpt, and LRSGRD.ept with a cut-off date for your NDA clinical safety update. If you already submitted these datasets, please indicate the date of the submission."

Thank you.
Regards,
Diane

CAPT Diane Hanner
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10903 New Hampshire Avenue
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/s/

DIANE C HANNER
01/15/2015

From: Hanner, Diane
To: "Shen, Jeannie"
Bcc: Ryan, Qin (Qin.Ryan@fda.hhs.gov)
Subject: NDA 205353- panobinostat- information request
Date: Wednesday, January 14, 2015 12:49:00 PM

Hi Jeannie,

I need to request that you please respond to the information request within 24 hour. It would be preferable, if you could please send me the requested information tonight.

Thanks you.

Regards,

Diane

-----Original Message-----

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Wednesday, January 14, 2015 12:41 PM
To: Hanner, Diane
Subject: RE: NDA 205353- panobinostat- information request

Dear Diane,

Thank you for sending the email request. The Panobinostat team will be working on the response.

with best regards,

Jeannie

Jeannie Shen
Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7783343
Cell [REDACTED] (b) (6)
Fax +1 973 7813320
jeannie.shen@novartis.com
www.novartis.com

-----Original Message-----

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Wednesday, January 14, 2015 11:12 AM
To: Shen, Jeannie
Subject: NDA 205353- panobinostat- information request
Importance: High

Hi Jeannie,

Please address the following information request and please respond within two business days, (January 16, 2015):

"Please submit the datasets of AAEV.xpt, AECG.xpt, AECGINT.ept, ALBHCNAE.xpt, ALRS.xpt, AVSN.xpt, and LRSGRD.ept with a cut-off date for your NDA clinical safety update. If you already submitted these datasets,

please indicate the date of the submission."

Thank you.
Regards,
Diane

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/s/

DIANE C HANNER
01/14/2015

From: Hanner, Diane
To: "[Shen, Jeannie](#)"
Subject: IR -NDA 205353 (panobinostat)- Please respond by Monday, January 12, 2015
Date: Wednesday, January 07, 2015 3:40:00 PM
Importance: High

Hi Jeannie,

We identified 193 patients on Trial 2308 who received prior treatment with both bortezomib and an immunomodulating agent (thalidomide or lenalidomide) compared to the (b) (4) patients included in the subgroup analyses presented in your Response to IR-43 to the Agency. There is discrepancy between our analyses for the 15 patients listed below. (We used field [PT_TXT] from the dataset PTM to identify this subgroup.)

We also note that in Table 5.1 of Appendix 1 from the same submission, the baseline characteristic of prior bortezomib is (b) (4). This number should be 100% considering the definition of the subgroup.

Please review the patient ID numbers below and provide justification for your numbers or concurrence with ours by noon Friday 1/9. If you do concur, please rerun the analyses done in Appendix 1 with the subgroup of 193 patients and submit by Monday 1/12.

Included by Applicant but not FDA:

0055_00002
0110_00001
0128_00005
0264_00001
0267_00002
0337_00006
0337_00012
0357_00001
0506_00001
0901_00002

Included by FDA but not Applicant:

0337_00009
0357_00005
0430_00003
0592_00002
0902_00002

Thank you,
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
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/s/

DIANE C HANNER
01/07/2015

From: Hanner, Diane
To: "[Shen, Jeannie](#)"; [Rana, Jiten](#)
Subject: Panobinostat - NDA 205353 - REMS Comments
Date: Wednesday, December 31, 2014 6:31:00 AM

Hi,

Please see the following (panobinostat) NDA 205353 REMS comments below:

1. At this time the need for a REMS is under review. However, we recommend focusing the proposed REMS on the risks addressed in the Boxed Warning (i.e., cardiac toxicities and diarrhea) along with appropriate patient selection consistent with approved indication.
2. Remove the Medication Guide from the REMS.
3. You proposed a REMS that consists of letters, an educational brochure, and webpage. In general, communication plans should be more comprehensive; similar to the REMS approved for Zydelig (idelalisib). The REMS materials should include: a REMS letter for healthcare providers, a REMS letter for professional societies, a REMS factsheet, and presentation of REMS materials (Factsheet, in addition to prescribing information and Medication Guide) at relevant scientific meetings.
4. The proposed pieces are text heavy and include no graphics or color. Improve the visual interest and readability of these documents with color, graphics, bulleting, and font for a consistent look and feel to the planned promotion and marketing campaign for panobinostat.
5. The proposed REMS Document, Materials, and REMS Supporting Document should be consistent with the revised labeling you plan to submit to the Agency on January 8, 2014.
6. Resubmission Requirements and Instructions: Provide a MS Word document and PDF (with final mock-up of graphics and color) of each revised material and/or documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
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/s/

DIANE C HANNER
12/31/2014

Jones, Jacquin

From: Jones, Jacquin
Sent: Friday, December 19, 2014 8:21 PM
To: 'Shen, Jeannie'
Cc: Hanner, Diane
Subject: NDA 205353-Panobinostat: FDA Labeling and PMRs Comments due by Jan 8
Attachments: NDA 205353_Panobinostat_FDAProposedLabeling_12-19-14.doc

Dear Ms. Shen,

Please refer to the NDA 205353 Farydak® (panobinostat, LBH589) received March 24, 2014.

The FDA review team has provided the attached proposed labeling changes. Please review and accept all changes that you agree with. For those changes that you do not accept, please make proposed edits in tracked changes and provide rationale/comment for the new text. Please do not reject any FDA proposed changes.

Please provide a response to the labeling changes via email (and follow-up with an official submission) by **January 8, 2015, 12noon, ET.**

In addition to the proposed labeling changes, this correspondence includes the following proposed Post-Marketing Requirements. As we continue our review of your NDA, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief summaries are intended to describe the main trial characteristics of interest. Please supplement and comment to clarify mutually acceptable descriptions of the key trial elements. We are available to discuss by TCON if needed.

Upon mutual agreement for the content and timing of all PMR/PMCs, submit to us, both by email and officially the full text and the timeline for each PMR and PMC study/trial you will perform with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Milestone times only need a month and year. For milestone calculations purposes only, assume that an approval occurs on the PDUFA date. Note that the "Final Protocol Submission" date is the date on (or before) which you submit a complete protocol that has already received full review and concurrence by FDA. We suggest that you consider realistic milestone times. Final PMR designation numbers will be assigned later. Please provide a response to the labeling changes via email (and follow-up with an official submission) by **January 8, 2015, 12noon, ET.**

#1

NDA # 205353
Product Name: Farydak® (panobinostat, LBH589)

PMR Description:

2181-1
Conduct a randomized clinical trial sufficient to characterize the safety and efficacy of at least two different doses of panobinostat in combination with once weekly subcutaneous bortezomib and dexamethasone. Eligible patients will include United States patients with relapsed multiple myeloma who have been previously exposed to

immunomodulatory agents. The primary objective is to assess the overall response rate (ORR) in both treatment arms according to IMWG criteria by investigator assessment. Secondary objectives will include Progression Free Survival; rate of Complete Response, stringent Complete Response, and Very Good Partial Response by IMWG criteria per investigator assessment; Overall Survival, Time to Progression, Safety, Duration of Response, Time to Response, and Pharmacokinetics. Submit a final study report with full datasets.

PMR Schedule Milestones: Preliminary Protocol Submission to Include SAP: _____
Final Protocol Submission: _____
First Patient Enrolled: _____
50% Trial Accrual: _____
Trial Fully Accrued: _____
Study/Trial Completion: _____
Final Report Submission: _____

#2

NDA # 205353
Product Name: Farydak® (panobinostat, LBH589)

PMR Description:

2181-2
Conduct a multicenter, randomized, three-arm, double-blind, placebo controlled phase 3 trial of two different doses of panobinostat in combination with weekly, subcutaneous bortezomib and dexamethasone in patients with relapsed multiple myeloma who have been previously exposed to immunomodulatory agents. Eligible patients will have previously treated multiple myeloma, 1-3 prior lines of therapy, prior immunomodulatory agent exposure (either thalidomide, lenalidomide, or pomalidomide), and measurable disease.

The primary objective will be progression-free survival. The key secondary objective is the rate of very good partial response, complete response, and stringent complete response by IMWG criteria between arms. Submit a final study report with full datasets.

PMR Schedule Milestones: Preliminary Protocol Submission to Include SAP: _____
Final Protocol Submission: _____
First Patient Enrolled: _____
50% Trial Accrual: _____
Trial Fully Accrued: _____
Study/Trial Completion: _____
Final Report Submission: _____

I am covering for Diane Hanner next week, so would request that you include both of us on any e-mail correspondence.

Please confirm receipt of this e-mail.

Regards,

Jacquie L. Jones, CDR, MS, RN, 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

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

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/s/

JACQUIN L JONES
12/19/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: Panobinostat (NDA 205353) IR- Please respond by 12/16/14
Date: Friday, December 12, 2014 1:08:00 PM
Importance: High

Hi Jeannie,

Please address the following NDA 205353 (panobinostat) information request:

Please conduct PK/PD simulations for single agent Panobinostat (PAN) to characterize the platelet count profiles of the following PAN regimens:

1. 20 mg three times per week (currently proposed dosing schedule)
2. 15 mg three times per week (currently proposed dosing schedule)
3. 10 mg three times per week (currently proposed dosing schedule)
4. 20 mg weekly
5. 15 mg weekly
6. 10 mg weekly

Using simulated PK and Platelet count profiles, please provide the following:

1. Estimated rates of Grade 3/4 thrombocytopenia for single Agent PAN and for PAN (regimens 1-6) + BTZ 1.3 mg/m².
2. Box plots showing the steady state AUC distribution of PAN for each regimen.

Provide the requested information by **COB Tuesday December 16, 2014**. Please provide the results in graphical and tabular form for simple comparison of regimens.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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Silver Spring, Maryland 20993
(301) 796-2330
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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
12/12/2014

From: Hanner, Diane
To: "Shen, Jeannie"
Subject: IR For NDA 205353 (Panobinostat)- Please respond by c.o.b. 12-11-14
Date: Thursday, December 04, 2014 2:47:00 PM

Hi Jeannie,

Please respond within a week (12-11-14) to the following information request regarding NDA 205353 (panobinostat).

For your phase 3 study, please provide a summary of dose distributions at the beginning of each cycle, providing the number and percentage of patients at each dose level. The % calculations should be based on the number of patients initially enrolled. For those patients who discontinued treatment, please assign a dose of zero. Please make the calculations for both Panobinostat and bortezomib. You may use the following format when sending the data. Please send the data as a sas transport file.

Cycle number	Total N	0 mg (n)	0 mg (%)	10 mg (n)	10 mg (%)	15 mg (n)	15 mg (%)	20 mg (n)	20 mg (%)
1	356	0	0	0	0	0	0	356	100%
2	356	20	6	0	0	30	8	306	86
3	N	x	x	x	x	x	x	x	x

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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(301) 796-2330
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/s/

DIANE C HANNER
12/04/2014

MEMORANDUM OF FACE TO FACE MEETING AND TELECONFERENCE

Meeting Date: November 19, 2014
Application Number: NDA 205353
Product Name: Panobinostat
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation
Subject: Face to Face and Teleconference between FDA and Novartis

FDA Participants

- Richard Pazdur, MD, Office Director, Office of Hematology and Oncology Products
- Ann Farrell, MD, Director, Division of Hematology Products, (DHP)
- Edvardas Kaminskas, MD, Deputy Director, DHP
- Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Leader, DHP
- Nicole Gormley, MD, Medical Officer, DHP
- Barry Miller, MS, CRNP, Clinical Reviewer, DHP
- John Jenkins, MD, Director, Office of New Drugs
- Robert Kane, MD, Deputy Director Safety, DHP
- Cynthia LaCivita, PhD, Team Leader, Division of Risk Management
- CAPT Diane Hanner, MPH, MSW, Senior Program Management Officer, DHP

Applicant Participants

Preliminary list of Novartis attendees:

- Alessandro Riva, MD, Executive Vice President, Global Head of Oncology Development
- Renaud Capdeville, MD, Vice President, Global Program Head
- David Lebwohl, MD, Sr. Vice President and Global Head, Oncology Clinical Development
- Kannan Natarajan, PhD, Sr. Vice President and Global Head of Oncology Biometrics & Data Management
- Sofia Paul, PhD, Director, Biostatistics
- Danny Howard, PhD, Vice President, Clinical Pharmacology
- Gabriela Gruia, MD, Sr. Vice President, Global Head, Drug Regulatory Affairs

- Shanthi Ganeshan, PhD, Vice President, North America Region Head, Drug Regulatory Affairs
- Jeannie Shen, RPh, Senior Associate Director, Drug Regulatory Affairs

1.0 BACKGROUND:

Novartis requested a meeting with the Agency immediately following the Oncology Drugs Advisory Committee (ODAC) which was convened on November 6, 2014.

On November 11, 2014, Novartis submitted the following Agenda (*via e-mail*):

Agenda:

- Introductions – 5 min
- Novartis presentation – 10 min
 - Unmet need and identified patient population
 - Dose / Confirmatory study
 - Safety
- Discussion - 40 min
- Wrap-up – 5 min

2.0 DISCUSSION:

The Agency informed Novartis that we would not be coming to a formal agreement with them during this meeting. However, the FDA stated that they were receptive to having a discussion regarding the following: proposed subgroup population, confirmatory trial design, and the safety management components of their trial. The Agency stated that they were deeming the Novartis submission of the revised IRC analysis of PFS (submitted before the late cycle meeting) as a Major Amendment to the NDA that would extend the review clock by 3 months.

Novartis proceeded to present numerous slides describing a pre-specified subgroup population from trial D2308 with limited treatment options, for which they believe that Accelerated Approval could be considered. This population includes patients with relapsed multiple myeloma who have received at least bortezomib and an IMiD who are bortezomib-sensitive. Novartis stated that this population appears to have a positive benefit to risk ratio and an unmet medical need. Novartis provided clarification that this population would be a 2nd and 3rd line population.

Novartis presented slide #5, which displayed the baseline characteristics of the patients in this population as being relatively well-balanced for all characteristics with the exception of the number of patients with “age ≥65” for which the placebo arm had 39% vs. 30% in the panobinostat arm. Slide #6 was reviewed and Novartis commented that the number of deaths were relatively well-balanced in this subpopulation (4 on the panobinostat arm and 7 on the placebo arm).

Slide #7 provided a summary of efficacy and safety for patients in this subgroup. The median PFS by INV for the panobinostat arm was 12.3 months as compared to 6.1 months in the placebo arm in this population. The Overall Response Rate was 59% in the panobinostat arm and 43% in the placebo arm. The incidences of grade 3-4 AEs were higher in the panobinostat arm for thrombocytopenia (20% difference), diarrhea (14% difference), fatigue (14% difference), infections (2% difference), and hemorrhage (1% difference).

The Subgroup analysis (patients with prior IMiDs) referred to in Slide #11 was discussed and the Agency expressed a concern regarding the incidence of thrombocytopenia (64% for panobinostat and 32% for placebo). Novartis stated that in the planned confirmatory trial they planned to use subcutaneous bortezomib which they hoped would reduce the incidence of thrombocytopenia and neuropathy while maintaining the same level of efficacy.

Slide #12 was reviewed which described the planned confirmatory Phase 3 trial. (b) (4)

[Redacted content]

Slide #13 which contained the planned Statistical Evaluation was also discussed. The Agency recommended that Novartis empanel a Safety Monitoring Board. Dr. Pazdur commented that the planned effect size might be too large to be achievable and that Novartis may want to revisit that. FDA requested clarification regarding how the primary endpoint would be measured and Novartis stated (b) (4)

[Redacted content]

The Agency also strongly encouraged Novartis to open the trial at sites that were more likely to have minority patients with the goal of enrolling a larger proportion of African American patients, who have a higher risk of Multiple Myeloma.

Novartis stated that they plan to submit a periodic listing of SAEs and deaths from the trial every 6 months to FDA, to have a Data Monitoring Committee review the safety data every 6 months, and to give reduced dose dexamethasone for all patients over 75 years of age.

A lengthy discussion ensued regarding the drug safety and need for a Risk Evaluation Mitigation Strategy (REMS) for panobinostat, should it receive approval

In order to enhance the information on the effect of panobinostat in combination with subcutaneous bortezomib plus dexamethasone in U.S. patients, Novartis plans to conduct a single-arm, Phase 2 trial in the US (only) in the same population as in PANORAMA-1 (1-3 lines, bortezomib sensitive). (b) (4)

(b) (4) if a primary endpoint of ORR by IMWG.

Slides 16, 17, and 18 were presented where Novartis detailed their plans for safety management. This includes a REMS (medication guide and communication plan), (b) (4)

updates to the Warnings and Precautions section of labeling, (b) (4)

The Agency recommended that Novartis take a close look at the previously approved drugs that currently have REMS. The Agency discouraged the plan (b) (4) and commented that this was not needed for a product like panobinostat with a broad scope of toxicities.

Novartis presented slides 19 and 20 where they described their planned “additional safety management components”. The FDA encouraged the company to consider the major safety issues when designing their confirmatory trial inclusion criteria.

Upon the completion of Novartis’ entire slide presentation, the Agency was amenable to receiving a proposed confirmatory trial protocol from Novartis.

3.0 ACTION ITEMS: Agency will send a letter confirming the Major Amendment review clock extension. Applicant will submit a proposed complete REMS. Applicant will submit proposed confirmatory trial protocol and Statistical Analysis Plan.

Attachments: Sponsor’s Slides (which were sent via e-mail on 11/18/14) are attached. Two additional handouts were presented during the meeting (please see attachment below.)

Table of Content for - ATTACHMENTS (BELOW)

*NOVARTIS PROPOSAL
RECEIVED *VIA* E-MAIL NOVEMBER 18, 2014

SLIDES RECEIVED FROM NOVARTIS *VIA* E-MAIL
*SLIDES 1-20
NOVEMBER 18, 2014

*TWO ADDITIONAL HANDOUTS attached Slides 21 & 22

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/s/

DIANE C HANNER
11/25/2014

From: Hanner, Diane
To: "[Shen, Jeannie](#)"
Subject: NDA 205353 (panobinostat) Information request for Novartis for Panobinostat- time sensitive
Date: Monday, November 24, 2014 3:28:00 PM

Hi Jeannie,

Please address the following NDA 205353 (panobinostat) information request and please respond within 2 weeks (by c.o.b. 12/8/14).

Please submit datasets as follows from trial D2308:

1. Efficacy dataset with listings for just the patients who you included in the "prior IMiD and bortezomib" subgroup
2. Safety dataset for the same patients.
3. Analyses of efficacy endpoints and safety analyses for just this population to be included in labeling.
4. Efficacy dataset with listings for just the patients who you included in the "prior IMiD and bortezomib with at least 2 prior regimens" subgroup.
5. Safety dataset for the same patients.
6. Analyses of efficacy endpoints and safety analyses of just this population to be included in labeling.

For the analyses of safety, please group the following terms:

Fatigue: Fatigue, Malaise, Asthenia, and Lethargy

Pneumonia: pneumonia, lower respiratory tract infection, lobar pneumonia, lung infection, pneumonia fungal, pneumonia influenzal, atypical pneumonia, bronchopneumonia, pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia haemophilus, pneumonia pneumococcal, and pneumonia respiratory syncytial viral

Sepsis: sepsis, septic shock, device related sepsis, neutropenic sepsis, streptococcal sepsis, haemophilus sepsis, staphylococcal sepsis, pneumococcal sepsis, candida sepsis

Thank you.

Regards,

Diane

CAPT Diane Hanner
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FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
11/24/2014



NDA 205353

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Novartis Pharmaceuticals Corporation
Attention: Ms. Jeannie Shen
Sr. Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Shen:

Please refer to your New Drug Application (NDA) dated March 22, 2014, received March 24, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for FARYDAK[®] (panobinostat) 10 mg, 15 mg, and 20 mg capsules.

We also refer to the amendment to your NDA received on October 07, 2014, wherein you provided the results of an additional sensitivity analysis of progression-free-survival (PFS) based on Independent Review Committee (IRC) assessment. This analysis was conducted after you realized that the IRC assessment of progression originally conducted and submitted with the NDA, did not take into account a confirmation assessment as required by modified EBMT criteria. To address this requirement, you performed an IRC PFS sensitivity analysis by considering progression, or relapse from CR, only when confirmed by a subsequent IRC assessment of progression, or relapse.

This submission constitutes a major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 24, 2015.

We have also determined that a Risk Evaluation and Mitigation Strategy (REMS) will be necessary to ensure that the benefits of FARYDAK outweigh the risks. In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 16, 2015.

If you have any questions, call CAPT Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

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

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/s/

ANN T FARRELL
11/21/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 3, 2014
Application Number: NDA 205353
Product Name: Panobinostat
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation
Subject: Teleconference between FDA and Novartis

FDA Participants

- Richard Pazdur, MD, Office Director, Office of Hematology and Oncology Products
- Ann Farrell, MD, Director, Division of Hematology Products, (DHP)
- Edvardas Kaminskas, MD, Deputy Director, DHP
- Virginia Kwitkowski, MS, RN, ACNP-BC, Lead Clinical Analyst, Clinical Team Leader, DHP
- Nicole Gormley, MD, Medical Officer, DHP
- Barry Miller, MS, CRNP, Clinical Reviewer, DHP
- Lori Ehrlich, MD, Medical Officer, DHP
- Rajeshwari Sridhara, PhD, Director, Division of Biometrics V (DB5)
- Thomas E. Gwise, PhD, Deputy Division Director, DB 5
- Chia-Wen Ko, PhD, Mathematical Statistician, DB 5
- Lei Nie, PhD, Statistical Team Leader, DB 5
- CAPT Diane Hanner, MPH, MSW, Senior Program Management Officer, DHP

Sponsor/Applicant Participants

Preliminary list of Novartis attendees:

- Alessandro Riva, MD, Executive Vice President and Global Head, Oncology Development & Medical Affairs
- Renaud Capdeville, MD, Vice President, Global Program Head
- David Lebwohl, MD, Sr Vice President and Global Head, Oncology Clinical Development
- Claudia Corrado, MD, Senior Global Clinical Leader, Oncology Clinical Development
- Kannan Natarajan, PhD, Sr Vice President and Global Head of Oncology Biometrics & Data Management
- Sofia Paul, PhD, Director, Biostatistics
- Gabriela Gruia, MD, Sr Vice President, Global Head, Drug Regulatory Affairs

- Jeannie Shen, RPh, Senior Associate Director, Drug Regulatory Affairs

1.0 BACKGROUND:

Novartis requested a teleconference with the Agency (*via e-mail*) to provide additional clarity on the information requested which was sent to Novartis on October 24, 2014, regarding their IRC analysis.

On October 30, 2014, Novartis submitted the following Agenda (*via e-mail*):

Agenda: Study D2308 Updated IRC (sensitivity) analysis (clarifies Novartis' response to FDA information request and answers any FDA questions)

Novartis position:

- Improvement of PFS in PAN+BTZ+Dex arm based on IRC with confirmed progressive disease (PD) is consistent with results of primary PFS analysis as assessed by investigator (3.7 vs 3.9 months)
- The IRC analysis with confirmed progressive disease (PD) is based on the mEBMT criteria as was applied for the primary analysis.
- Given the information provided by Novartis at the Late cycle meeting and the Responses to FDA Information Requests, Novartis no longer considers the original IRC analysis (without PD confirmation) provided in the NDA to be valid.

Novartis is seeking alignment with the FDA on the results and relevance of the IRC analysis based on the updated data. We would welcome any questions or comments prior to the meeting.

On November 3, 2014, the Division of Hematology Products conducted a teleconference with Novartis. The purpose of this teleconference was to discuss any questions that the Agency might have regarding the revised IRC analysis prior to the Oncology Drugs Advisory Committee (ODAC) which will be convened on November 6, 2014.

2.0 DISCUSSION:

The Sponsor inquired if the Agency had any questions regarding their updated IRC analysis and slides. They sought alignment with the Agency on the results of the IRC analysis based on their updated data analysis. Novartis stated that they were concerned that should the Agency present the original IRC analysis, they would not be presenting the correct analysis, because the progression events were not confirmed in that analysis.

Dr. Pazdur inquired of the Sponsor what they meant by having "alignment".

He further went on to state that the Agency is committed to being completely transparent.

All of the analyses may be presented by Novartis. Additional analysis may be presented either as exploratory analysis or sensitivity analysis. However, the fact that 1/4 of the data is missing contributes to the problem of determining the magnitude of the benefit derived from the drug. He also mentioned that no matter which analysis is utilized, they all appeared to have an issue

regarding clarity on the magnitude of the benefit. He reiterated that the missing data made the magnitude of the benefit of the drug very difficult to ascertain.

The Agency stated that they would be presenting the original analyses that were submitted in the NDA as well as several sensitivity analyses.

3.0 ACTION ITEMS: None

Attachments: Sponsor's Slides (which were sent via e-mail on 11/3/14) were never reviewed during the meeting.

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DIANE C HANNER
11/18/2014



NDA 205353

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Ms. Jeannie Shen
Sr. Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Shen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for panobinostat, LBH589.

We also refer to your late cycle slides that were submitted *via* e-mail, which were received on October 21, 2014, containing efficacy analyses information.

We are reviewing the statistical 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.

LIST COMMENTS AND INFORMATION REQUESTS

1. During the late cycle meeting, you explained that all assessments of progressive of disease (PD) and relapse recorded in the raw data res.dat are confirmed assessments. Please provide documents either to show the confirmation of the investigators' assessments is not needed or to demonstrate confirmation was applied to confirm PD/relapse for each subject listed in set 1 and 2, as examples. If a PD/relapse is confirmed in a follow up visit, clarify why the assessments of that follow up visit were not recorded in the dataset res.dat and where we can locate the data in your submission. Furthermore, clarify how unconfirmed PD/relapse are recorded in the raw datasets to indicate that they are PDs but not confirmed.

Set 1: 0003_00001, 0063_00001, 0080_00007, 0111_00009, 0118_00009, 0123_00005, 0127_00002, 0142_00001, 0156_00015, 0210_00012, 0252_00008, 0315_00002, 0415_00008 0527_00001, 0584_00001, 0290_0002, 0317_00008, 0174_00001

Set 2: 0039_00002 0055_00007 0075_00009 0097_00003 0118_00010 0145_00002 0156_00013 0170_00009 0172_00003 0175_00002 0176_00001 0232_00001

0232_00003 0232_00009 0253_00002 0285_00001 0285_00002 0373_00003
0374_00002 0415_00020 0561_00012 0025_00007 0170_00007 0174_00007
0178_00002 0232_00014 0262_00012 0262_00014 0262_00022 0263_00009
0263_00010 0265_00003 0266_00005 0290_00002 0314_00001 0325_00013
0337_00010 0356_00001 0386_00005 0386_00010 0416_00001 0503_00002
0573_00001 0586_00002

In addition, for subjects in set 1, both investigators and IRC (original submitted) classified them as PFS events with single PD/relapse. Clarify why you claim that these should not be PFS events per IRC although they are PFS events per investigator in your primary analysis.

2. Many subjects had PD/relapse per IRC right before they stopped treatment. Thus confirmation is not possible for them. IRC classified them as PFS events based on their knowledge. Ignoring the IRC classification lead to missing data and the missingness is likely informative, e.g. the visit is missing because they started new cancer therapy.
3. Some subjects appear to have confirmed PDs but you considered them non-confirmed. For example, subject 0087_00004 had IRC PD on day 112, had “no change” on the following visit on day 133 and day 164. Similar subject 0121_00009 , 0115_00003, 0129_00003, 0336_00013 for example.

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

DIANE C HANNER
10/24/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: Panobinostat NDA 205353: Novartis- Information request 10-14-14
Date: Tuesday, October 14, 2014 10:02:00 AM

Hi Jeannie,

Please provide within 2 business days the dataset used to generate the most recent interim overall survival analysis.

Thank you.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
10/14/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: 10-10-14 Panobinostat NDA 205353-information request
Date: Friday, October 10, 2014 9:56:00 AM

Hi Jeannie,

Please address the following NDA 205353 panobinostat information request.

We are unable to locate the CRFs of IRC Assessments of Disease Status. Please provide the location of these files within 1 business day.

Please provide a detailed explanation of how the IRC and INV assessment procedures were conducted. How would IRC handle missing assessments vs. non-PEP assessments?

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
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/s/

DIANE C HANNER
10/10/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:Shen,Jeannie.(jeannie.shen@novartis.com))
Subject: Panobinostat NDA 205353- Information request - Please respond by noon-Tuesday, October 14, 2014.
Date: Thursday, October 09, 2014 1:14:00 PM

Hi Jeannie,

Please address the following information request regarding the NDA 205353 (panobinostat) additional sensitivity analysis, and please respond by noon next Tuesday, (October 14, 2014).

Please provide the derived data used to perform the additional 'IRC with PD confirmation' sensitivity analysis. The to-be provided dataset should contain information on: patient id, treatment arm as randomized, investigator-determined PFS, IRC-PFS without PD confirmation, IRC-PFS with PD confirmation, and whether or not repeat assessments were available for a IRC-assessed PD confirmation. In addition, please clarify how you have dealt with no repeat assessments after the first report of progression/relapse in this additional sensitivity analysis.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Tuesday, October 07, 2014 5:58 PM
To: Hanner, Diane
Subject: Panobinostat NDA 205353, Follow-up to FDA IR received Aug 20, 2014

Dear Diane,

Reference is made to the FDA Information Request received on August 20, 2014 (IR-32) regarding concordance (or discordance) for Independent Review Committee (IRC) versus investigator assessed PFS events and to the Novartis response document submitted on August 26, 2014 (Seq no. 0038).

Novartis is presenting a follow-up to the previously submitted response document to include results of an additional sensitivity analysis of PFS based on IRC assessment considering progression, or relapse from complete response (CR), if confirmed by at least one repeat assessment based on M-protein. The Follow-up Response Document was sent through the FDA gateway today (please see enclosed for courtesy email copy).

This information is also planned to be provided in the Briefing Document to be submitted to the FDA in support of the November 6, 2014 Panobinostat ODAC. Please let me know if you have any questions or comments.

with best regards,
Jeannie

Jeannie Shen

Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

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jeannie.shen@novartis.com
www.novartis.com

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/s/

DIANE C HANNER
10/09/2014

From: Hanner, Diane
To: ["Shen, Jeannie"](#)
Subject: NDA 205353 panobinostat- ODAC Topics
Date: Monday, September 29, 2014 10:46:00 AM

Hi Jeannie,

As promised during the teleconference below please find the list of topics that we plan to focus our presentation on:

1. The benefit to risk ratio for panobinostat in combination with bortezomib and dexamethasone
2. The added toxicity (with increase in treatment-related deaths, Serious Adverse Events, severe adverse events, drug discontinuations, and dose-modifications) with the addition of panobinostat to bortezomib and dexamethasone.
3. Whether the dose that was selected for panobinostat for the Phase 3 trial was correct
4. The impact on the PFS improvement by the protocol violations regarding method of myeloma protein assessment.
5. The implications of the patient reported outcomes data collected in the trial.

Regards,

Diane

[CAPT Diane Hanner](#)
[Senior Program Management Officer](#)
[FDA/CDER/OHOP/DHP](#)
[10903 New Hampshire Avenue](#)
[Bldg. 22/Room 2119](#)
[Silver Spring, Maryland 20993](#)
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/s/

DIANE C HANNER
09/29/2014



NDA 205353

GENERAL ADVICE

Novartis Pharmaceuticals Corporation
Attention: Ms. Jeannie Shen
Sr. Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Shen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for panobinostat, 10 mg, 15 mg and 20 mg Capsules.

We also refer to your September 4, 2014, submission, containing the Novartis' mock-up samples of the packaging labels.

We have reviewed the referenced material and have the following comments/recommendations:

A. Trade Size Carton Labeling and Sample Carton Labeling

1. Add "with water" to swallow whole statement, so the entire statement will read "Swallow whole with water. Do not open, crush, or chew." And then relocate this statement to the principal display panel (PDP) under the dosage form to ensure the correct administration technique is readily visible to consumers.

B. Trade Size Shell Pack Front and Sample Shell Pack Front

1. See B.1 and revise the front of the shell pack labeling accordingly.
2. Consider addition of the statement "Take Farydak exactly as directed by your prescriber". We recommend an addition of this statement due to complicated dosing schedule related to this product, especially when dosing adjustments are needed.

C. Trade Size Shell Pack Back and Sample Shell Pack Back

1. Add the corresponding strength of the product to the shell pack back side to ensure the safe use of the product and that the user can easily identify the correct strength.

D. Trade Size Blister Card and Sample Blister Card

1. Consider revising the dosing schedule so that the user is able to read Week 1, Week 2, and Week 3 from left to right to help with comprehension of the information. Currently, this information should be read from right to left, which is not a common way to read in English language.

2. For Week 3, consider replacing reference to days where no medication should be taken with, “Rest Period. Do not take Farydak” (similarly to Shell Labeling Pack Back for Week 3).

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

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DIANE C HANNER
09/16/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:Shen, Jeannie (jeannie.shen@novartis.com))
Subject: Panobinostat NDA 205353 -information request (IR)
Date: Tuesday, September 16, 2014 10:10:00 AM

Hi Jeannie,

Please address the following IR regarding the Study D2308 protocol amendment for the additional OS analysis (submitted under IND 69862, SDN 638. Please response (within the next 2 days) by c.o.b. 9/18/14.

Please explain your consideration that the actual number of survival events may be $\geq 95\%$ of the total targeted events at the cut-off date for the proposed additional OS interim analysis. If this analysis is to occur as soon as the study reaches 90% of the targeted survival events, why would there be as many as 5% more events (equivalent to 21 more death events) at the data cut-off for this analysis?

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
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Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Tuesday, August 12, 2014 4:34 PM
To: Cox, Toni-Ann
Cc: Hanner, Diane
Subject: Panobinostat NDA 205353; Request for FDA comment

Dear Toni,

Reference is made to NDA 205353 for Farydak (panobinostat) Capsules. Reference is also made to a telephone conference on July 17, 2014, where the FDA informed Novartis of the need for an advisory committee meeting (ODAC to be held on November 5th or 6th) to discuss the Panobinostat NDA. At this same meeting, Novartis proposed to conduct an additional interim analysis (IA) for

Overall Survival (OS) for Study CLBH589D2308. The FDA was open to reviewing the OS data however, requested that Novartis submit a formal proposal in writing.

Please find enclosed the proposal for performing an additional IA for OS which was also submitted to the FDA via the gateway today. FDA's comments and response are appreciated by Tuesday, August 19, 2014 in order to provide results in a timely manner.

Thank you.

with best regards,
Jeannie

Jeannie Shen

Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

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jeannie.shen@novartis.com
www.novartis.com

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/s/

DIANE C HANNER
09/16/2014

From: Martin, Jewell
To: ["Ganser, Charlene"](#)
Cc: [Shen, Jeannie](#)
Subject: Information Request NDA 205353
Date: Thursday, September 11, 2014 4:58:00 PM

Charlene,

We have the following information request concerning NDA 205353. A written response is requested by September 18, 2014.

Your proposal (dated 8/29/14) to maintain the release and stability dissolution acceptance criteria of $Q = \frac{(b)}{(4)}\%$ in $\frac{(b)}{(4)}$ minutes and commitment to reassess the appropriateness of the acceptance criteria as a post-approval commitment is not acceptable.

Based on the provided dissolution data showing complete dissolution in $\frac{(b)}{(4)}$ minutes, we recommend that you implement the dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 15 minutes for your drug product. Please submit the revised drug product specifications table and stability protocol with the updated dissolution acceptance criterion.

Note that revisions to the dissolution acceptance criterion (if appropriate), can be requested post-approval via a prior approval supplement with complete dissolution data supporting such request.

In addition to formally submitting this information to your NDA, please provide a courtesy copy via email.

Please confirm receipt of this email.

Best,

Jewell

Jewell D. Martin, MA, MBA, PMP

Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment
Food and Drug Administration
White Oak Building 21, Rm 2625
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-2072
jewell.martin@fda.hhs.gov

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/s/

JEWELL D MARTIN
09/11/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:Shen_Jeannie_(jeannie.shen@novartis.com))
Subject: NDA 205353 -panobinostat - information request - datasets to assess hepatotoxicity
Date: Friday, August 29, 2014 3:51:00 PM

Hi,
Yes, the D2308 study
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Friday, August 29, 2014 3:32 PM
To: Hanner, Diane
Subject: RE: NDA 205353 -panobinostat - information request - datasets to assess hepatotoxicity

Dear Diane,

Thank you for your email. We received the FDA information request for datasets to assess hepatotoxicity. Would the FDA kindly specify for which study, Novartis needs to provide these datasets? We assume that the FDA is asking for the datasets for the pivotal, Phase III study, CLBH589D2308, however, would the FDA please confirm? Thank you.

with best regards,
Jeannie

Jeannie Shen
Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7783343
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From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Friday, August 29, 2014 2:10 PM
To: Shen, Jeannie
Subject: RE: NDA 205353 -panobinostat - information request

Hi Jeannie,

Please note that there are two data sets in the information request.
Regards,
Diane

From: Hanner, Diane
Sent: Friday, August 29, 2014 1:55 PM
To: 'Shen, Jeannie'
Subject: NDA 205353 -panobinostat - information request

Hi,

Please address the following information request regarding NDA 205353 panobinostat:

Please submit the datasets, described in the attached spreadsheet, in xpt format for our assessment of hepatotoxicity by 9/12/2014

Should you have questions regarding the data preparation, you may contact Dr Ted Guo at Ted.Guo@fda.hhs.gov. Please submit the eDISH data through the regular gateway to the FDA's Electronic Document Room (EDR) as you would for other data and put it in a folder named "eDISH". You **need not** mail the eDISH data on a CD or DVD as a desk copy as you may have done in the past.

Thank you
Regards,
Diane

eDishData Requirements:

Requirement	Standard variable	Variable means	Variable type
Required	STUDYID	Unique identifier for a study within the submission	Char
Required	USUBJID	Unique subject identifier within the submission	Char
Required	INVID	Investigator Identifier	Char

Optional	INVNAM	Investigator Name	Char
Optional	INVDISC	Investigator Description	Char
Required	BIRTHDT	Date of birth	Char (ISO 8601 YYYY-MM-DD)
Required	SEX	Sex (M/F)	Char
Optional	RACE	Race (WHITE, BLACK, OTHER)	Char
Optional	COUNTRY	Country	Char
Required	HEIGHT	Height in cm	Num
Required	WEIGHT	Weight in kg	Num
Optional	COMPLETE	Subject completing the study (Y/N)	Char
Optional	DROPDT	Date subject discontinued the study	Char (ISO 8601 YYYY-MM-DD)
Optional	DROPREAS	Reason for discontinuation	Char

Requirement	Standard variable	Variable means	Variable type
Required	STUDYID	Unique identifier for a study within the submission	Char
Required	USUBJID	Unique subject identifier within the submission	Char
Required	TRTCD	Treatment Code	Num
Required	TRTGRP	Treatment Group	Char
Required	EXSTDY	Start Date of Dose	Char (ISO 8601 YYYY-MM-DD)
Required	EXDT	Date of Exam	Char (ISO 8601 YYYY-MM-DD)
Required	EXENDT	End Date of Dose	Char (ISO 8601 YYYY-MM-DD)
Required	ALT	Serum alanine aminotransferase activity (U/L)	Num
Required	ALT_RHI	ALT High Normal Range (or Baseline*) (U/L)	Num
Required	BILI	Total serum bilirubin concentration (mg/dL)	Num
Required	BILI_RHI	BILI High Normal Range (or Baseline*) (mg/dL)	Num
Required	AST	Serum aspartate aminotransferase (U/L)	Num
Required	AST_RHI	AST High Normal Range (or Baseline*) (U/L)	Num
Required	ALP	Alkaline phosphatase (U/L)	Num
Required	ALP_RHI	ALP High Normal Range (or Baseline*) (U/L)	Num
	*SPECIAL	Baseline requires mean of two measures 2 to 4	
	NOTE FOR	weeks apart before the therapy starts, if the	
	BASELINE	measures not rise more than 30% If the higher	
	VARIABLE	value is > 30% of the lower value, repeat the	
		test in 2 weeks If the third < the higher value,	
		then take mean of the three measures However,if	
		rising, don't start study but investigate for the	
		cause of problems	

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/s/

DIANE C HANNER
08/29/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: Panobinostat 205353-Information Request- 8-29-14
Date: Friday, August 29, 2014 3:28:00 PM

Hi Jeannie,

We need more information about a “data unlock” that was reported at Dr. Bania Hungria’s site #262 in Brazil in trial CLBH589D2308.

Please provide responses to the following questions by 5pm EST on 09/05/14.

1. What were the dates of “unlock” and “relock” on the datasets?
2. What changes were made to the datasets at the data unlock?
3. Was this done to datasets for any other sites? If so, please provide the same information as in #1 and #2.

Also, please provide your written procedure that you followed for unblinding the data.

Thank you

Regards,

Diane

[CAPT Diane Hanner](#)
[Senior Program Management Officer](#)
[FDA/CDER/OHOP/DHP](#)
[10903 New Hampshire Avenue](#)
[Bldg. 22/Room 2119](#)
[Silver Spring, Maryland 20993](#)
[\(301\) 796-2330](#)
[FAX \(301\) 796-9845](#)
[E-mail: diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/

DIANE C HANNER
08/29/2014

From: Hanner, Diane
 To: "Shen, Jeannie"
 Subject: RE: NDA 205353 -panobinostat - information request
 Date: Friday, August 29, 2014 2:09:00 PM
 Attachments: eDISHDataRequirements.xls

Hi Jeannie,

Please note that there are two data sets in the information request.

Regards,
 Diane

From: Hanner, Diane
 Sent: Friday, August 29, 2014 1:55 PM
 To: 'Shen, Jeannie'
 Subject: NDA 205353 -panobinostat - information request

Hi,

Please address the following information request regarding NDA 205353 panobinostat:

Please submit the datasets, described in the attached spreadsheet, in xpt format for our assessment of hepatotoxicity by 9/12/2014

Should you have questions regarding the data preparation, you may contact Dr Ted Guo at Ted.Guo@fda.hhs.gov Please submit the eDISH data through the regular gateway to the FDA's Electronic Document Room (EDR) as you would for other data and put it in a folder named "eDISH" You **need not** mail the eDISH data on a CD or DVD as a desk copy as you may have done in the past

Thank you
 Regards,
 Diane

eDishData Requirements:

Requirement	Standard variable	Variable means	Variable type
Required	STUDYID	Unique identifier for a study within the submission	Char
Required	USUBJID	Unique subject identifier within the submission	Char
Required	INVID	Investigator Identifier	Char
Optional	INVNAM	Investigator Name	Char
Optional	INVDESC	Investigator Description	Char
Required	BIRTHDT	Date of birth	Char (ISO 8601 YYYY-MM-DD)
Required	SEX	Sex (M/F)	Char
Optional	RACE	Race (WHITE, BLACK, OTHER)	Char
Optional	COUNTRY	Country	Char
Required	HEIGHT	Height in cm	Num
Required	WEIGHT	Weight in kg	Num
Optional	COMPLETE	Subject completing the study (Y/N)	Char
Optional	DROPDT	Date subject discontinued the study	Char (ISO 8601 YYYY-MM-DD)
Optional	DROPREAS	Reason for discontinuation	Char

Requirement	Standard variable	Variable means	Variable type
Required	STUDYID	Unique identifier for a study within the submission	Char
Required	USUBJID	Unique subject identifier within the submission	Char
Required	TRTCD	Treatment Code	Num
Required	TRTGRP	Treatment Group	Char
Required	EXSTDY	Start Date of Dose	Char (ISO 8601 YYYY-MM-DD)
Required	EXDT	Date of Exam	Char (ISO 8601 YYYY-MM-DD)
Required	EXENDT	End Date of Dose	Char (ISO 8601 YYYY-MM-DD)
Required	ALT	Serum alanine aminotransferase activity (U/L)	Num
Required	ALT_RHI	ALT High Normal Range (or Baseline*) (U/L)	Num
Required	BILI	Total serum bilirubin concentration (mg/dL)	Num
Required	BILI_RHI	BILI High Normal Range (or Baseline*) (mg/dL)	Num
Required	AST	Serum aspartate aminotransferase (U/L)	Num
Required	AST_RHI	AST High Normal Range (or Baseline*) (U/L)	Num
Required	ALP	Alkaline phosphatase (U/L)	Num
Required	ALP_RHI	ALP High Normal Range (or Baseline*) (U/L)	Num
	*SPECIAL	Baseline requires mean of two measures 2 to 4	
	NOTE FOR	weeks apart before the therapy starts, if the	
	BASELINE	measures not rise more than 30% If the higher	
	VARIABLE	value is > 30% of the lower value, repeat the	
		test in 2 weeks If the third < the higher value,	
		then take mean of the three measures However,if	
		rising, don't start study but investigate for the	
		cause of problems	

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/s/

DIANE C HANNER
08/29/2014

From: Hanner, Diane
To: "Shen, Jeanie"
Subject: NDA 205353 - panobinostat - information request
Date: Friday, August 29, 2014 1:54:00 PM
Attachments: eDISHDataRequirements.xls

Hi,

Please address the following information request regarding NDA 205353 panobinostat:

Please submit the datasets, described in the attached spreadsheet, in xpt format for our assessment of hepatotoxicity by 9/12/2014

Should you have questions regarding the data preparation, you may contact Dr Ted Guo at Ted.Guo@fda.hhs.gov. Please submit the eDISH data through the regular gateway to the FDA's Electronic Document Room (EDR) as you would for other data and put it in a folder named "eDISH". You **need not** mail the eDISH data on a CD or DVD as a desk copy as you may have done in the past.

Thank you
Regards,
Diane

eDishData Requirements:

Requirement	Standard variable	Variable means	Variable type
Required	STUDYID	Unique identifier for a study within the submission	Char
Required	USUBJID	Unique subject identifier within the submission	Char
Required	INVID	Investigator Identifier	Char
Optional	INVNAM	Investigator Name	Char
Optional	INVDESC	Investigator Description	Char
Required	BIRTHDT	Date of birth	Char (ISO 8601 YYYY-MM-DD)
Required	SEX	Sex (M/F)	Char
Optional	RACE	Race (WHITE, BLACK, OTHER)	Char
Optional	COUNTRY	Country	Char
Required	HEIGHT	Height in cm	Num
Required	WEIGHT	Weight in kg	Num
Optional	COMPLETE	Subject completing the study (Y/N)	Char
Optional	DROPDT	Date subject discontinued the study	Char (ISO 8601 YYYY-MM-DD)
Optional	DROPREAS	Reason for discontinuation	Char

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/s/

DIANE C HANNER
08/29/2014

From: Agosto, Teicher
To: [Ganser, Charlene \(charlene.ganser@novartis.com\)](mailto:Charlene.ganser@novartis.com)
Subject: Information Request NDA 205353
Date: Tuesday, August 26, 2014 12:17:00 PM

Dear Ms. Ganser,

We are requesting the following information concerning your New Drug Application- NDA 205353. We request a prompt response to this IR request no later August 27, 2014 by 12 pm EST.

Please provide information for the following comment:

1. Please update the drug substance and the drug product specifications for the impurity (b) (4) as agreed in your response to the agency Information Request dated 23-Jun-2014, sequence 0017. Formally submit updated specifications to NDA 205 353.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

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/s/

TEICHER N AGOSTO
08/26/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: 8-26-14 Sample request for Farydak NDA 205353
Date: Tuesday, August 26, 2014 12:01:00 PM

Hi Jeannie,

The proposal in the e-mail below is acceptable.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Monday, August 25, 2014 4:00 PM
To: Hanner, Diane
Subject: RE: Sample request for Farydak NDA 205353

Dear Diane,

Reference is made to Farydak (panobinostat) NDA 205353 and to the FDA request for physical samples of the packaging components/labels. As Novartis does not have final FDA approval for the labels, the packaging components are not yet prepared for the Farydak (panobinostat) capsules. At this time, Novartis is willing to create a few mock-up samples for the purpose of FDA visualization and review of packaging labels; however, this process may take upwards of two weeks (manufacturing facility is in Barbera Spain). Therefore, we propose to provide physical samples of one representative strength (Farydak (panobinostat) 20mg capsules) packaging components to the FDA by Friday, September 5, 2014. Is this agreeable with the FDA?

with best regards,
Jeannie

Jeannie Shen
Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation

One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7783343
Cell [REDACTED] (b) (6)
Fax +1 973 7813320
jeannie.shen@novartis.com
www.novartis.com

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Monday, August 25, 2014 12:27 PM
To: Shen, Jeannie
Subject: Sample request for Farydak NDA 205353

Hi,
Please let me know the general timeframe of when you will be submitting the physical samples.
We were hoping for a 3D visual of the proposed label and labeling packaging to assist in our review.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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/s/

DIANE C HANNER
08/26/2014

From: Agosto, Teicher
To: [Ganser, Charlene \(charlene.ganser@novartis.com\)](mailto:Charlene.ganser@novartis.com)
Subject: Information Request NDA 205353
Date: Monday, August 25, 2014 2:45:00 PM

Dear Ms. Ganser,

We are requesting the following information concerning your New Drug Application- NDA 205353. We request a prompt response to this IR request no later COB August 26, 2014.

Please provide information for the following comment:

1. Base on the provided dissolution data in your response dated 8/18/14, showing complete dissolution in (b) (4) minutes, we recommend that you implement a dissolution acceptance criterion of Q= (b) (4) % at 15 minutes for your product. Please submit a revised drug product specification table and stability protocol with the updated dissolution acceptance criterion by Aug 26 , 2014.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

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/s/

TEICHER N AGOSTO
08/25/2014

From: Hanner, Diane
To: "[Shen, Jeannie](#)"
Subject: Sample request for Farydak NDA 205353
Date: Monday, August 25, 2014 12:27:00 PM

Hi,

Please let me know the general timeframe of when you will be submitting the physical samples.

We were hoping for a 3D visual of the proposed label and labeling packaging to assist in our review.

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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/s/

DIANE C HANNER
08/25/2014

From: Martin, Jewell
To: ["Ganser, Charlene"](#)
Cc: [Shen, Jeannie](#)
Subject: CMC Information Request NDA 205353
Date: Sunday, August 24, 2014 10:23:00 PM

Charlene,

We have the following information request concerning NDA 205353.

- Please update the drug substance and the drug product specifications for the impurity (b) (4) as agreed in your response to the agency Information Request dated 23-Jun-2014, sequence 0017. Formally submit updated specifications to NDA 205353.

Please confirm receipt of this email.

Best,

Jewell

Jewell D. Martin, MA, MBA, PMP

Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment
Food and Drug Administration
White Oak Building 21, Rm 2625
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-2072

jewell.martin@fda.hhs.gov



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/s/

JEWELL D MARTIN
08/24/2014

From: [Martin, Jewell](#)
To: [Shen, Jeannie](#)
Cc: [Ganser, Charlene](#)
Subject: CMC Information Request NDA 205353
Date: Sunday, August 17, 2014 10:09:00 PM

Hello Ms. Shen,

We have the following information request concerning NDA 205353. A written response is requested by COB Monday, August 18, 2014.

- As a follow w up to your response to Question no. 3 dated 07-Aug-2014, provide the UV spectra for the impurities (b) (4) and (b) (4) to allow complete evaluation of adequacy of the peak purity determination.

In addition to formally submitting this information to your NDA, please send me a courtesy copy via email.

Please confirm receipt of this email.

Best,

Jewell

Jewell D. Martin, MA, MBA, PMP

Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment
Food and Drug Administration
White Oak Building 21, Rm 2625
10903 New Hampshire Avenue
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/s/

JEWELL D MARTIN
08/24/2014

From: Hanner, Diane
To: ["Shen, Jeannie"](#)
Bcc: [Ko, Chia-Wen](#)
Subject: Information request for inconsistency in prior-line MM therapy percentages- NDA 205353 (panobinostat)
Date: Friday, August 22, 2014 9:56:00 AM

Hi,

Please address the following information request regarding NDA 205353 and please respond as soon as possible. "For Study D2308, the reported percentages for prior lines of anti-MM therapy appear to be inconsistent. Table 11-4 describes 51% of study patients had only one prior line of therapy, but the percentage is shown to be 46% in Table 14.1-1.3. Please clarify this discrepancy."

Thank you.

Regards,

Diane

[CAPT Diane Hanner](#)
[Senior Program Management Officer](#)
[FDA/CDER/OHOP/DHP](#)
[10903 New Hampshire Avenue](#)
[Bldg. 22/Room 2119](#)
[Silver Spring, Maryland 20993](#)
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[E-mail: diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/

DIANE C HANNER
08/22/2014

From: Hanner, Diane
To: ["Shen, Jeannie"](#)
Subject: NDA 205353 (panobinostat) IRC-PFS versus INV-PFS- information request
Date: Wednesday, August 20, 2014 12:45:00 PM
Importance: High

Hi Jeannie,

Please address the following information request regarding NDA 205353 (panobinostat) and please respond by COB of next Monday, August 25, 2014.

For Study D2308, please provide:

- (1) Percentages of concordance (or discordance) for IRC versus investigator assessed PFS events by treatment arm including the percentages of events identified as PD by the IRC assessments earlier than the investigator's assessment (or vice versa).
- (2) An assessment for possible reason(s) that could have explained discordance between the IRC and investigator assessment.

Thank you.

Regards,

Diane

[CAPT Diane Hanner](#)
[Senior Program Management Officer](#)
[FDA/CDER/OHOP/DHP](#)
[10903 New Hampshire Avenue](#)
[Bldg. 22/Room 2119](#)
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[E-mail: diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/

DIANE C HANNER
08/20/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:Shen_Jeannie_(jeannie.shen@novartis.com))
Subject: Sample request for Farydak NDA 205353
Date: Tuesday, August 19, 2014 2:09:00 PM

Hi Jeannie,

FYI- We are asking for the physical sample of the container closure system.

Thank you.

Regards,
Diane

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Monday, August 18, 2014 5:22 PM
To: Hanner, Diane
Subject: RE: Sample request for Farydak NDA 205353

Dear Diane,

Reference is made to NDA 205353 for Farydak (panobinostat) Capsules. Reference is also made to Trade packaging labels submitted to the original NDA application on March 24, 2014 (Seq no. 0000) and to revised Trade packaging labels and new Physician Sample packaging labels submitted in an Amendment to the NDA on July 11, 2014 (Seq no. 0025). Reference is additionally made to the FDA information request received via email on August 24, 2014:

Please submit a sample of both the proposed Trade Size and Sample label and labeling for Farydak NDA 205353.

This will allow us to visualize the Carton, Shell Pack Front label, Shell Pack Back label, and Blistercard. Please submit the samples by C.O.B., Monday, August 18, 2014.

As requested by the FDA, packaging labels (previously submitted to the NDA, as indicated above) are provided for the 10mg Trade and Physician Sample capsules (the shell pack back for the Physician Samples and Trade versions are common and thus the identical information will be displayed on the Physician Sample Shell Pack Back and the Trade Shell Pack Back and therefore are not duplicated here). In addition, for the purpose of FDA visualization of the packaging only, pictures are provided for orientation purposes however, should not be used for content review.

Please confirm that the packaging labels and pictures submitted via email are acceptable and will not need to be submitted to the NDA via the gateway, as the packaging labels were previously submitted to the NDA. If necessary, Mock-ups of the proposed container labels can be printed to actual size and sent to the FDA by UPS.

If you have any additional questions or comments, please let us know.

Thank you.

with best regards,
Jeannie

Jeannie Shen

Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7783343
Cell [REDACTED] (b) (6)
Fax +1 973 7813320
jeannie.shen@novartis.com
www.novartis.com

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Thursday, August 14, 2014 3:29 PM
To: Shen, Jeannie
Subject: Sample request for Farydak NDA 205353

Hi Jeannie,

Please submit a sample of both the proposed Trade Size and Sample label and labeling for Farydak NDA 205353.

This will allow us to visualize the Carton, Shell Pack Front label, Shell Pack Back label, and Blistercard.

Please submit the samples by C.O.B., Monday, August 18, 2014.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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/s/

DIANE C HANNER
08/19/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:Shen, Jeannie (jeannie.shen@novartis.com))
Subject: Panobinostat NDA 205353; FDA Response 8-18-14
Date: Monday, August 18, 2014 3:59:00 PM

Hi Jeannie,

Please find the FDA response to inquiry below regarding NDA 205353 (panobinostat):

“Your proposal is agreeable based on your anticipation for the amount of information at the time of analysis. Please also clarify in the protocol amendment about your intention with alpha spending if the number of events is between 90% and 95% of the final target OS events at the data cut-off.”

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Tuesday, August 12, 2014 4:34 PM
To: Cox, Toni-Ann
Cc: Hanner, Diane
Subject: Panobinostat NDA 205353; Request for FDA comment

Dear Toni,

Reference is made to NDA 205353 for Farydak (panobinostat) Capsules. Reference is also made to a telephone conference on July 17, 2014, where the FDA informed Novartis of the need for an advisory committee meeting (ODAC to be held on November 5th or 6th) to discuss the Panobinostat NDA. At this same meeting, Novartis proposed to conduct an additional interim analysis (IA) for Overall Survival (OS) for Study CLBH589D2308. The FDA was open to reviewing the OS data however, requested that Novartis submit a formal proposal in writing.

Please find enclosed the proposal for performing an additional IA for OS which was also submitted to the FDA via the gateway today. FDA's comments and response are appreciated by Tuesday,

August 19, 2014 in order to provide results in a timely manner.

Thank you.

with best regards,
Jeannie

Jeannie Shen

Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7783343

Cell [REDACTED] (b) (6)

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jeannie.shen@novartis.com

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/s/

DIANE C HANNER
08/18/2014

From: Hanner, Diane
To: "[Shen, Jeannie](#)"
Subject: Information request for NDA205353 Panobinostat
Date: Monday, August 18, 2014 12:35:00 PM

Hi Jeannie,

Please address the following information request regarding NDA205353, panobinostat and please respond by C.O.B.

August 20, 2014:

Osseous metaplasia in the lung was reported in the 39 week repeat dose toxicity study in dogs (Study # 0680133). Please describe this finding.

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
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/s/

DIANE C HANNER
08/18/2014

From: Hanner, Diane
To: ["Shen, Jeannie"](#)
Bcc: [Ko, Chia-Wen](#)
Subject: NDA 205353 panobinostat - information request
Date: Friday, August 15, 2014 11:57:00 AM

Hi Jeannie,

Please address the following information request regarding NDA 205353 (panobinostat), and please respond by the C.O.B. Wednesday, 8/20/14:

“For all the patients treated in Trial D2308, please provide a derived dataset containing 3 variables: subject id, treatment cycle number, and whether or not the individual had a dose modification/interruption per cycle. Please provide along a documentation explaining how the variables are derived from the raw dataset(s).”

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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/s/

DIANE C HANNER
08/15/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: Sample request for Farydak NDA 205353
Date: Thursday, August 14, 2014 3:29:00 PM

Hi Jeannie,

Please submit a sample of both the proposed Trade Size and Sample label and labeling for Farydak NDA 205353.

This will allow us to visualize the Carton, Shell Pack Front label, Shell Pack Back label, and Blistercard.

Please submit the samples by C.O.B., Monday, August 18, 2014.

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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/s/

DIANE C HANNER
08/14/2014

From: Martin, Jewell
To: ["Shen, Jeannie"](#)
Cc: [Ganser, Charlene](#)
Subject: CMC Information Request NDA 205353
Date: Wednesday, August 13, 2014 5:25:00 PM

Hello Ms. Shen,

We have the following information request concerning NDA 205353. A written response is requested by August 21, 2014.

- Provide the dissolution profile data for the registration stability batches (and clinical batch if available) at the current stability time point, measuring dissolution at 10, 15, 20, and 30 minutes, using the proposed dissolution method. For each batch, provide information such as age of batch, packaging, strength, batch number, storage conditions etc.

In addition to formally submitting this information to your NDA, please send me a courtesy copy via email.

Please confirm receipt of this email.

Best,

Jewell

Jewell D. Martin, MA, MBA, PMP

Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment
Food and Drug Administration
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/s/

JEWELL D MARTIN
08/13/2014

Cox, Toni-Ann

From: Cox, Toni-Ann
Sent: Monday, August 11, 2014 2:28 PM
To: 'jeannie.shen@novartis.com'
Cc: Hanner, Diane
Subject: Information Request regarding NDA 205353, Panobinostat

Importance: High

Good afternoon, Jeannie.

I am covering for Diane Hanner today and tomorrow August 12th.

The following information request was issued for NDA 205353, Panobinostat. Please provide a response by email no later than **noon EST, Tuesday August 12, 2014**.

- 1) Did you conduct any comprehension studies or risk benefit analysis regarding inclusion of dosing schedule on the labels and labeling? If so, include the reduced or omitted dosing scheduling in your study or analysis?

Please confirm receipt of this message.

Best Regards,
Toni

Toni-Ann Cox

Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | U.S. Food and Drug Administration
P: 240-402-4775 | F: 301-796-9849 | [✉toni-ann.cox@fda.hhs.gov](mailto:toni-ann.cox@fda.hhs.gov)

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/s/

TONI-ANN S COX
08/11/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Cc: [Cox, Toni-Ann](#)
Bcc: [Grillo, Joseph](#)
Subject: 8-8-14 Information request for panobinostat NDA 205353
Date: Friday, August 08, 2014 2:47:00 PM

Hi Jeannie,

Please address the following information request:

Please reconstruct Table 14.2-1.1.1c from your final study report for the drug interaction study LBH589B2110 to include an analysis of AUC(0-48). Please submit these revised tables within 2 business days.

Please send an unofficial response via email within 2 business days and an official response via the gateway with 5 business days.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
08/08/2014

From: Hanner, Diane
To: ["Rana, Jiten"](#)
Cc: [Shen, Jeannie](#)
Subject: Panobinostat NDA 205353- information request regarding the Carton/Container Shell Pack Back
Date: Monday, August 04, 2014 11:00:00 AM

Hi,
Correct, we are not asking for anything else to be sent in.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Rana, Jiten [<mailto:jiten.rana@novartis.com>]
Sent: Friday, August 01, 2014 2:43 PM
To: Hanner, Diane
Cc: Shen, Jeannie
Subject: RE: Panobinostat NDA 205353- information request regarding the Carton/Container Shell Pack Back

Thank you Diane for the response.

I would like to clarify if Novartis should still proceed with gateway submission of the draft sample blister foils or if the email provided yesterday suffices. Thank you and I will proceed according to your feedback.

Best regards,
Jiten Rana, Pharm.D.
Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza East Hanover, NJ 07936
Bldg. 337/B03.3B
Phone +1 862 7785662
Cell + (b) (6)

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Friday, August 01, 2014 11:47 AM
To: Rana, Jiten
Subject: Panobinostat NDA 205353- information request regarding the Carton/Container Shell Pack

Back

Hi,

Your response is deemed appropriate, and no additional information needs to be sent in at this time.

Thank you.

Regards,

Diane

From: Rana, Jiten [<mailto:jiten.rana@novartis.com>]

Sent: Thursday, July 31, 2014 5:03 PM

To: Hanner, Diane

Cc: Shen, Jeannie

Subject: RE: Panobinostat NDA 205353- information request regarding the Carton/Container Shell Pack Back

Hello Diane,

Please find the responses to the information request here:

FDA Question:

1. Do you intend to leave the Shell Pack Back and Blister Card the same?

If so then, just merely respond by indicating that this is the case.

If the Shell Pack Back and Blister Card are different then please submit both items immediately.

2. Please submit the Shell Pack Back for the Physician Samples, and please indicated whether you intend to leave this information left blank.

Novartis Response:

1. Can you please clarify that this is in reference to the physician samples submitted with SN0025 to NDA 205-353? If so, please note that the Shell Pack Back is common between the Physician Sample and Trade versions. The Blister Cards are different for the Physician Sample vs. Trade packs and are attached here. The attached files will be officially submitted via the Gateway.
2. The shell pack back for the Physician Samples and Trade versions are common and thus the identical information will be displayed on the Physician Sample Shell Pack Back and the Trade Shell Pack Back.

Please confirm if this response answers FDA's questions and please contact me if additional information or clarification is required. Thank you.

Best regards,

Jiten Rana, Pharm.D.

Oncology Regulatory Affairs

Novartis Pharmaceuticals Corporation

One Health Plaza East Hanover, NJ 07936

Bldg. 337/B03.3B

Phone +1 862 7785662

Cell + (b) (6)

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]

Sent: Thursday, July 31, 2014 12:10 PM

To: Rana, Jiten

Cc: Shen, Jeannie

Subject: Panobinostat NDA 205353- information request regarding the Carton/Container Shell Pack Back

Hi,

Please address the following information requests below regarding NDA 205353 (panobinostat):

A. Do you intend to leave the Shell Pack Back and Blister Card the same?
If so then, just merely respond by indicating that this is the case.

A.1 If the Shell Pack Back and Blister Card are different then please submit both items immediately.

B. Please submit the Shell Pack Back for the Physician Samples, and please indicated whether you intend to leave this information left blank.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
08/04/2014

From: Hanner, Diane
To: [Rana, Jiten \(jiten.rana@novartis.com\)](mailto:jiten.rana@novartis.com)
Subject: Panobinostat NDA 205353- information request regarding the Carton/Container Shell Pack Back
Date: Friday, August 01, 2014 11:46:00 AM

Hi,
Your response is deemed appropriate, and no additional information needs to be sent in at this time.
Thank you.
Regards,
Diane

From: Rana, Jiten [<mailto:jiten.rana@novartis.com>]
Sent: Thursday, July 31, 2014 5:03 PM
To: Hanner, Diane
Cc: Shen, Jeannie
Subject: RE: Panobinostat NDA 205353- information request regarding the Carton/Container Shell Pack Back

Hello Diane,

Please find the responses to the information request here:

FDA Question:

1. Do you intend to leave the Shell Pack Back and Blister Card the same?
If so then, just merely respond by indicating that this is the case.

If the Shell Pack Back and Blister Card are different then please submit both items immediately.

2. Please submit the Shell Pack Back for the Physician Samples, and please indicated whether you intend to leave this information left blank.

Novartis Response:

1. Can you please clarify that this is in reference to the physician samples submitted with SN0025 to NDA 205-353? If so, please note that the Shell Pack Back is common between the Physician Sample and Trade versions. The Blister Cards are different for the Physician Sample vs. Trade packs and are attached here. The attached files will be officially submitted via the Gateway.
2. The shell pack back for the Physician Samples and Trade versions are common and thus the identical information will be displayed on the Physician Sample Shell Pack Back and the Trade Shell Pack Back.

Please confirm if this response answers FDA's questions and please contact me if additional information or clarification is required. Thank you.

Best regards,
Jiten Rana, Pharm.D.
Oncology Regulatory Affairs

Novartis Pharmaceuticals Corporation
One Health Plaza East Hanover, NJ 07936
Bldg. 337/B03.3B
Phone +1 862 7785662
Cell + (b) (6)

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Thursday, July 31, 2014 12:10 PM
To: Rana, Jiten
Cc: Shen, Jeannie
Subject: Panobinostat NDA 205353- information request regarding the Carton/Container Shell Pack Back

Hi,

Please address the following information requests below regarding NDA 205353 (panobinostat):

- A. Do you intend to leave the Shell Pack Back and Blister Card the same?
If so then, just merely respond by indicating that this is the case.

A.1 If the Shell Pack Back and Blister Card are different then please submit both items immediately.

- B. Please submit the Shell Pack Back for the Physician Samples, and please indicated whether you intend to leave this information left blank.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
08/01/2014

From: Hanner, Diane
To: [Rana, Jiten \(jiten.rana@novartis.com\)](mailto:jiten.rana@novartis.com)
Cc: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: IR for panobinostat NDA 205353- 7-31-14
Date: Thursday, July 31, 2014 3:06:00 PM

Hi,

Please address the following information request regarding NDA 205353 (panobinostat).
Please respond by COB Friday,

August 8th.

Please recreate the exposure analysis presented in table 12-1 of the clinical study report for trial D2308. For this analysis please use the modified safety set 2 population which assigns patients 0292_00002, 0087_00001, 0170_00002, 0319_00005 and 0909_00001 to the panobinostat arm.

Thank you.

Regards,

Diane

[CAPT Diane Hanner](#)
[Senior Program Management Officer](#)
[FDA/CDER/OHOP/DHP](#)
[10903 New Hampshire Avenue](#)
[Bldg. 22/Room 2119](#)
[Silver Spring, Maryland 20993](#)
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[E-mail: diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/

DIANE C HANNER
07/31/2014



NDA 205353

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Ms. Jeannie Shen
Sr. Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Shen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Panobinostat (LBH589) 10 mg, 15 mg and 20 mg capsules.

We also refer to your Original NDA submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response by August 7, 2014, order to continue our evaluation of your NDA.

1. Set points and normal operating ranges (NORs) must be provided in the description of the manufacturing process for the drug substance (S.2.2) and the drug product (P.3.3).

Drug substance:

- Provide the set point and NORs for all process variables including solvents and reagents in the description of the manufacturing process.
- The lower limit of PAR for the (b) (4) is not supported by experimental data. Similarly, the experimental data do not support the lower limit of PAR for the (b) (4).
Revise PARs for the (b) (4) based on the manufacturing experience or experimental data. If PAR is equals to NOR, identify the edge of failure.

Drug Product:

- Provide supporting data for the proposed set point for (b) (4) of NMT (b) (4)
- The proposed PAR for (b) (4) appears to be close to the edge of failure and tighter range must be provided as NOR (<PAR) in the description of the manufacturing process.

- Both upper and lower limits for the proposed PAR for [REDACTED] (b) (4) appear to be close to the edge of failure. Provide tighter range as NOR (<PAR) in the description of the manufacturing process.

Any change of the NORs must be reported to the Agency as a Post Approval Supplement (PAS). PARs are not acceptable as regulatory process. However, the PARs can be referenced for knowledge management purposes but not for implementing any change of process.

2. [REDACTED] (b) (4)

3. There is a [REDACTED] (b) (4) observed [REDACTED] (b) (4) of the HPLC chromatograms. Demonstrate that the [REDACTED] (b) (4) impurity is not exceeding the identification threshold as per ICH Q3B. Additionally, describe in more details the way of calculating the peak purity for LBH589.

If you have any questions, please contact Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
07/31/2014



NDA 205353

DEFICIENCIES PRECLUDE DISCUSSION

Novartis Pharmaceuticals Corporation
Attention: Ms. Jeannie Shen
Sr. Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Shen:

Please refer to your March 24, 2014, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for panobinostat, 10 mg, 15 mg and 20 mg Capsules.

We also refer to our May 22, 2014, letter in which we notified you of our target date of August 29, 2014, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2008 Through 2012."

As part of our ongoing review of your application, we have identified safety issues that warrant further discussion and your application will be the subject of an Oncology Drug Advisory Committee (ODAC) meeting. Therefore, the need for an FDA advisory committee meeting precludes a discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

If you have any questions, call CAPT Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Virginia 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

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/s/

VIRGINIA E KWITKOWSKI
07/29/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Bcc: [Grillo, Joseph](#)
Subject: 7-22-14 Information request for panobinostat NDA 205353
Date: Tuesday, July 22, 2014 5:38:00 PM

Hi Jeannie,

Please address the following information request regarding NDA 205353 (panobinostat):

To facilitate our review of your PBPK simulation report: "Study 1400363 - ACAT absorption model for LBH589 in humans and the assessment of varying stomach pH on LBH589 absorption in humans" submitted on May 5, 2014, you should submit executable Gastroplus model files being used to simulate final results in this study report. The model files should include, but are not limited to model compound file(.mdb), solubility vs pH (.spd), particle size distribution(.psd), Tissue/Plasma Conc. vs. Time Data: Other Dosage Forms (.opd), and User-Defined ACAT Model (.cat).

Please submit this information by close of business July 25, 2014.

Thank you,
Regards,
Diane

[CAPT Diane Hanner](#)
[Senior Program Management Officer](#)
[FDA/CDER/OHOP/DHP](#)
[10903 New Hampshire Avenue](#)
[Bldg. 22/Room 2119](#)
[Silver Spring, Maryland 20993](#)
[\(301\) 796-2330](#)
[FAX \(301\) 796-9845](#)
[E-mail: diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/

DIANE C HANNER
07/22/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: July 17, 2014

Application Number: NDA 205353

Product Name: Panobinostat

Sponsor Name: Novartis Pharmaceuticals Corporation

Subject: Teleconference between FDA and Novartis

FDA Participants

- Richard Pazdur, MD, Office Director, Office of Hematology and Oncology Products
- Paul G. Kluetz, MD, Acting Deputy Office Director, Office of Hematology and Oncology Products
- Ann Farrell, MD, Director, Division of Hematology Products, (DHP)
- Virginia Kwitkowski, MS, RN, ACNP-BC, Lead Clinical Analyst, Clinical Team Leader, DHP
- Barry Miller, MS, CRNP, Clinical Reviewer, DHP
- Adam George, PharmD, Clinical Analyst, DHP
- Lei Nie, PhD, Statistical Team Leader, DB 5
- CAPT Diane Hanner, MPH, MSW, Senior Program Management Officer, DHP

Novartis Participants

- Renaud Capdeville, MD, Vice President, Global Program Head
- Gabriela Gruia, MD, SVP & Global Head DRA Oncology
- Shanthi Ganeshan, PhD, Vice President, North America Region Head, DRA
- Laura Grazioli, PhD, Global Program Regulatory Director
- Jeannie Shen, RPh, Senior Associate Director, Drug Regulatory Affairs
- David Lebwohl, MD, SVP & Global Head Oncology Clinical Development
- Florence Binlich, MD, Executive Director, Global Clinical Program Head
- Kannan Natarajan PhD, SVP & Global Head Oncology Biometrics & Data Management
- Antonella Maniero, PhD US Site Head Clinical Development Biostatistics
- Sofia Paul, PhD, Director, Biostatistics

1.0 BACKGROUND:

On July 17, 2014, the Division of Hematology Products conducted a teleconference with Novartis. The purpose of this teleconference was to notify them of our intention to take the panobinostat application to the Oncology Drugs Advisory Committee (ODAC) on either November 5 or 6, 2014.

2.0 DISCUSSION:

Dr. Pazdur explained the rationale for the public discussion is to receive feedback from the committee on the benefit/risk assessment of panobinostat with the observed increment in progression-free survival and the differential toxicity. Our primary safety concerns at this time are imbalance in deaths and SAEs.

The current status of the overall survival curve was discussed as immature. The applicant asked whether they should conduct an interim analysis (before the final analysis) of Overall Survival. The Agency responded that we would certainly consider this, but that the Applicant should formally propose such an analysis taking into consideration the alpha penalty needed to add the analysis. The Applicant agreed to approach the Agency about this formally.

3.0 ACTION ITEMS:

FDA will notify Novartis of the exact date of the planned meeting

FDA will schedule ODAC planning meeting with Novartis

FDA will provide timelines to Novartis for items due with regards to the ODAC (slides, briefing packages, etc.)

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/s/

DIANE C HANNER
07/22/2014

Hanner, Diane

From: Hanner, Diane
Sent: Monday, July 14, 2014 10:56 AM
To: Shen, Jeannie (jeannie.shen@novartis.com)
Subject: 7-14-14- Information request for panobinostat NDA 205353

Hi Jeannie,

Please address the following IR regarding NDA 205353 (panobinostat):

Please submit the electronic case report form for patient CLBH589B2108_0001_00001 in study B2108 within 48 hours.

Thank you.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
07/14/2014

From: Hanner, Diane
To: ["Shen, Jeannie"](#)
Bcc: [Grillo, Joseph](#)
Subject: 7-7-14 Information request for panobinostat NDA 205353
Date: Monday, July 07, 2014 2:08:00 PM

Hi Jeannie,

Please address the following information request regarding NDA 205353 (panobinostat):

We note in your clinical pharmacology summary that you state that the “Oxidative metabolism by CYP P450 accounts for approximately 40% of panobinostat metabolism [study B2110],...” We reviewed your final report for trial B2110 and the basis for this statement is not obvious. Provide additional context regarding how the 40% estimate was derived, and please respond within 3 business days (July 10, 2014).

Thank you.
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
07/07/2014

From: Agosto, Teicher
To: [Ganser, Charlene \(charlene.ganser@novartis.com\)](mailto:Charlene.ganser@novartis.com)
Subject: Information Request NDA 205353
Date: Thursday, June 26, 2014 2:46:00 PM

Dear Ms. Ganser,

We are requesting additional information concerning your New Drug Application- NDA 205353. We request a prompt response to this IR request no later than Thursday COB July 10, 2014.

Please provide information for the following comments:

1. Provide detailed information regarding [REDACTED] (b) (4) [REDACTED] that fail to meet specifications.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

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/s/

TEICHER N AGOSTO
06/26/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: 6-25-14 Information Request for NDA 205353 Panobinostat - Please respond by 7-2-14.
Date: Wednesday, June 25, 2014 4:15:00 PM

Hi Jeannie,

Please address the information request below regarding NDA 205353 panobinostat, and please respond by c.o.b., Wednesday, July 2, 2014.

For trial D2308 please recreate the analysis for Dose Intensity, Relative Dose Intensity and Relative Dose Intensity "Categories" as presented in Table 12-2, page 218 of the clinical study report for trial D2308 as followed:

1. Use the same definition for Dose Intensity, Relative Dose Intensity and Relative Dose Intensity "Categories" used to generate Table 12-2 of the D2308 clinical study report.
2. For this analysis population patients 0292-00002 and 0087-00001 should be included in the panobinostat arm as both of these patients were exposed to panobinostat.

Thank you.

Regards,

Diane

[CAPT Diane Hanner](#)
[Senior Program Management Officer](#)
[FDA/CDER/OHOP/DHP](#)
[10903 New Hampshire Avenue](#)
[Bldg. 22/Room 2119](#)
[Silver Spring, Maryland 20993](#)
[\(301\) 796-2330](#)
[FAX \(301\) 796-9845](#)
[E-mail: diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/

DIANE C HANNER
06/25/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: IR Panobinostat- NDA 205353 dated 6-25-14- Please respond by c.o.b. June 27, 2014.
Date: Wednesday, June 25, 2014 2:43:00 PM

Hi Jeannie,

Please see the additional NDA 205353 (panobinostat) information request below, we need clarification regarding the updated DI-response analysis and conducting case-control analysis for PFS and ORR:

1. In your updated dose intensity (DI) -response analysis submitted on June-23-2014, DI is defined as the cumulative dose take taken within actual treatment duration, which is different from the definition in your previous submitted analysis (cumulative dose divide by the duration of the interval). In addition, we notice that DI is not treated as a time-dependent variable in the updated analysis. Please clarify for this inconsistency. For consistency of results, please update the analysis to use dose intensity as the time-dependent variable.
2. Please conduct additional case-control analysis for PFS and ORR with post-treatment events included.

Please submit your response by c.o.b., June 27, 2014.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
06/25/2014

From: Hanner, Diane
To: ["Shen, Jeannie"](#)
Cc: [Rana, Jiten](#)
Subject: Novartis comments to FDA IR Panobinostat- NDA 205353 received June 16, 2014
Date: Thursday, June 19, 2014 1:58:00 PM

Hi Jeannie,

The Friday, June 27th date is acceptable.

Regards,
Diane

From: Shen, Jeannie [mailto:jeannie.shen@novartis.com]
Sent: Thursday, June 19, 2014 1:32 PM
To: Hanner, Diane
Cc: Rana, Jiten
Subject: Novartis comments to FDA IR Panobinostat- NDA 205353 received June 16, 2014

Dear Diane,

Hope all is well with you. Reference is made to FDA Information Request received on Monday, June 16, 2014.

FDA IR Part 1: In your previously submitted dose intensity-response analysis, you only considered the events and responses up to the date of the last PAN dose. However, events and responses that occur after treatment could also be associated with dose intensity and therefore be included to allow a relevant comparison of the effect of dose intensity. Please update the dose intensity-response analysis with post-treatment events included, following same the derivation and censoring rules of the primary analysis of study D2308. Please submit the analysis results by COB June 23rd, 2014.

-
Novartis comment: Novartis confirms that we are planning to submit the response to FDA by June 23, 2014, as requested.

FDA IR Part 2: Develop a dose intensity-platelet count model using data from both arms in study D2308 to link the dose-intensity and time profile of platelet count. Based on the developed model, conduct simulation to predict the incidence of thrombocytopenia over time throughout the treatment period (48 weeks). Predict the “all grades (Grade 1-4)” and “grade 3-4” thrombocytopenia from your model and compare with the rate of thrombocytopenia observed in the study. Please submit the analysis results by COB June 23rd, 2014.

-
Novartis comment: The Novartis panobinostat team is working diligently on identifying the best model using a mixed effect (repeated measures) model, but as the data are somewhat complex, Novartis is requesting additional time until next Friday, June 27th to provide a response. **Is this acceptable to the FDA?**

Additional Novartis comments: Reference is made to FDA IR received Thursday, June 12, 2014.

Please address the following information request regarding NDA 205353 Panobinostat. Please respond within 3 weeks, by the c.o.b. July 3, 2014.

Patient numbers 0292-00002 and 0087-0001 received treatment to which they were not randomized. Both of these patients were exposed to panobinostat. For the purposes of FDA analyses these patients will be included in the panobinostat as the definition for the safety analysis set in protocol D2308 was "as treated". Therefore, please resubmit the following tables for trial D2308 including these 2 patients in the panobinostat group: Adverse events, Serious adverse events, Deaths, Adverse events leading to discontinuation, Adverse events leading to treatment interruption/modification.

Novartis comment: Novartis confirms that we are planning to submit the response to FDA by July 3, 2014, as requested.

As I may be out of the office for a couple of hours this afternoon, would it be possible to also copy my colleague, Jiten Rana, on comments from FDA? thanks.

with best regards,
Jeannie

Jeannie Shen

Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7783343
Cell [REDACTED] (b) (6)
Fax +1 973 7813320
jeannie.shen@novartis.com
www.novartis.com

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Monday, June 16, 2014 1:50 PM
To: Shen, Jeannie
Subject: IR Panobinostat- NDA 205353- Time Sensitive- Please respond by c.o.b. 6/23/14
Importance: High

Hi Jeannie,

Please address the following (Panobinostat) NDA 205353 information request regarding the additional dose-response analysis on your pivotal trial.

1. In your previously submitted dose intensity-response analysis, you only considered the events and responses up to the date of the last PAN dose. However, events and responses that occur after treatment could also be associated with dose intensity and therefore be included to allow a relevant comparison of the effect of dose intensity. Please update the dose intensity-response analysis with post-treatment events included, following same the

derivation and censoring rules of the primary analysis of study D2308.

2. Develop a dose intensity-platelet count model using data from both arms in study D2308 to link the dose-intensity and time profile of platelet count. Based on the developed model, conduct simulation to predict the incidence of thrombocytopenia over time throughout the treatment period (48 weeks). Predict the “all grades (Grade 1-4)” and “grade 3-4” thrombocytopenia from your model and compare with the rate of thrombocytopenia observed in the study.

Please submit the analysis results by COB June 23rd, 2014.

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
06/19/2014



NDA 205353

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Novartis Pharmaceuticals Corp.
Attention: Jeannie Shen
Senior Associate Director
One Health Plaza
East Hanover, NJ 07936-1080
FAX: (973) 781-5217

Dear Jeannie Shen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Farydak (panobinostat) Capsules, 10 mg, 15 mg and 20 mg.

We will be performing methods validation studies on Farydak (panobinostat) Capsules, 10 mg, 15 mg and 20 mg, as described in NDA 205353.

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

Method, current version

- 20501.01 Identity by IR (b) (4)
- 20901.01 Identity by XRPD
- 54001.01 Impurities by HPLC
- 54501.01 Assay by HPLC
- 50111.01 Dissolution by UV
- 54501.01 Degradation products by HPLC
- 38011.01 Accompanying substance by HPLC - (b) (4)

Samples and Reference Standards

- 3 x 500 mg LBH589 Lactate (panobinostat) drug substance
- 3 x 300 mg LBH589 Lactate (panobinostat) reference standard
- 50 mg of (b) (4) impurity standard if available
- 50 mg of (b) (4) impurity standard if available
- 50 mg of (b) (4) impurity standard if available
- 50 mg of (b) (4) impurity standard if available
- 50 mg of (b) (4) impurity standard if available
- 50 mg of (b) (4) impurity standard if available
- 50 mg of (b) (4) impurity standard if available
- 100 mg of (b) (4)
- 80 LBH589 (Panobinostat) 10 mg hard gelatin capsules
- 80 LBH589 (Panobinostat) 15 mg hard gelatin capsules
- 80 LBH589 (Panobinostat) 20 mg hard gelatin capsules

Equipment

- 1 (b) (4)
- 1 (b) (4)
- 1 (b) (4)
- 1 (b) (4)
- 30 (b) (4)
- 10 (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 (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
06/18/2014



NDA 205353

MID-CYCLE COMMUNICATION

Novartis Pharmaceuticals Corporation
Attention: Ms. Jeannie Shen
Sr. Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Shen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for panobinostat, 10 mg, 15 mg and 20 mg Capsules.

We also refer to the teleconference between representatives of your firm and the FDA on June 11, 2014. 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, call CAPT Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Virginia 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:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: June 11, 2014 @ 9:00 a.m.

Application Number: NDA 205353

Product Name: Panobinostat

Indication: Multiple Myeloma

Applicant Name: NDA 205353

Meeting Chair: Virginia Kwitkowski

Meeting Recorder: Diane Hanner

FDA ATTENDEES

- Edvardas Kaminskas, MD, Deputy Director, DHP
- Virginia Kwitkowski, MS, RN, ACNP-B.C., Lead Clinical Analyst, Clinical Team Leader
- Adam George, PharmD, Clinical Analyst, DHP
- Nitin Mehtrotra, PhD, Team Leader, Division of Pharmacometrics
- Bahru Habtemariam, PharmD, Acting Team Leader, DCP5
- Emily Place PhD, MPH, Pharmacologist, DHOT
- Elsbeth Chikhale, PhD, Biopharmaceutics Reviewer, ONDQA
- Danuta Gromek-Woods, PhD, Chemistry Reviewer, ONDQA
- Vipul Dholakia, PhD, Consumer Safety Officer, Office of Compliance
- Janice Brown, PhD, CMC Lead, ONDQA
- Wana Manitpisitkul, PharmD, BCPS. Safety Evaluator, DPV II
- Michelle K. Rutledge, PharmD, Safety Evaluator, DMEPA
- Lei Nie, PhD, Statistical Team Leader, DB 5

- Suzanne Robottom, PharmD, Senior Risk Management Analyst, DRISK (by phone)
- Joseph A. Grillo, PharmD, Clinical Pharmacology Reviewer, DCP5 (by phone)
- CAPT Diane Hanner, MPH, MSW, Senior Program Management Officer, DHP

APPLICANT ATTENDEES

- Renaud Capdeville, MD, Vice President, Global Program Head
- Florence Binlich, MD, Executive Director, Global Clinical Program Head
- Carol Paley, MD, Executive Director, Clinical Research Physician
- Rong Lin, MD, Executive Director, Lead Brand Safety Leader
- Antonella Maniero, PhD, Executive Director, Global Biostatistics
- Sofia Paul, PhD, Director, Biostatistics
- Bourras-Rezki Bengoudifa, PhD, Expert Statistician
- Song Mu, PhD, Director, Principle Fellow, Oncology Clinical Pharmacology
- Diane Zezza, PhD, Global Head Regulatory CMC
- Thomas Gengenbacher, PhD, Franchise Head – Regulatory CMC
- Charlene Ganser, Associate Director, Global Regulatory Affairs, CMC
- Vijay Raju, MS, MBA, Principal Fellow, Technical Research and Development
- Amy Lambert, PhD, Senior Investigator, Preclinical Safety, NIBR
- Shanthi Ganeshan, PhD, Vice President, North America Region Head, Drug Regulatory Affairs
- Laura Grazioli, PhD, Global Program Regulatory Director
- Jeannie Shen, RPh, Senior Associate Director, Drug Regulatory Affairs
- Jiten Rana, PharmD, Associate Director, Drug Regulatory Affairs

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

CLINICAL

Gastrointestinal toxicity, severe myelosuppression, hemorrhage, and severe infections are the main safety issues with panobinostat. It may be possible to mitigate the risk of these toxicities with appropriate labeling. No significant review issues at this time.

CLINICAL PHARMACOLOGY

- IR to sponsor on May 23, 2014 to conduct multivariate logistic regression and time-to-event analysis (e.g., cox proportional hazard model) to explore relationship between dose intensity and efficacy (E) or safety (S) endpoints:
- Dose intensity (different measures of dose intensity): as a measure of drug exposure related to response
- Efficacy: Progression-free survival (PFS) and overall response rate (ORR)
- Safety: Most frequent treatment-emergent AEs including thrombocytopenia, diarrhea, anemia, fatigue, neutropenia and hypokalemia
- Identify potential factors (baseline characteristics) related to efficacy and safety; Case-control analysis
- IR response received June 2, 2014

CMC

No significant review issues at this time.

The following issues and comments were sent to the applicant in form of Information Request on June 10, 2014.

Drug Substance:

1. As per regulatory requirements, you must report any changes in the specifications of the starting materials using the appropriate regulatory route.
2. Provide DOE data in support of the proposed Proven Acceptable Ranges (PARs) outlined in section 3.2.S.2.4, Control of Critical Steps. Alternatively, you may provide Normal Operating Ranges (NOR) with a statement that any change of NORs will be reported to the Agency as a PAS.
3. Provide data to show that your (b) (4) method is capable to measure the amount of (b) (4)

4. Provide justification for not testing the drug substance batches manufactured *via* the (b) (4) in toxicology studies.
5. Specification:
 - a. In addition to X90, include X50 and X10 in your particle size distribution specification.
 - b. Tighten the limit for the degradation product “(b) (4)” as the acceptance criterion of NMT (b) (4) % is not supported by stability results.
6. Demonstrate mass balance for the assay and degradation products analytical method

Drug Product:

1. Provide DOE data in support of the proposed Proven Acceptable Ranges (PARs) outlined in section 3.2.P.3.4, Control of Critical Steps. Alternatively, you may provide Normal Operating Ranges (NOR) with a statement that any change of NORs will be reported to the Agency as a PAS.
2. Specification:
 - a. Your proposed acceptance criterion for the degradation product (b) (4) (NMT (b) (4) %) is not supported by results from stability studies (highest amount is (b) (4) %). Therefore, tighten specification accordingly.
 - b. Acceptance criterion of NMT (b) (4) % for Impurity (b) (4) (specified, unidentified) is above the ID Threshold of (b) (4) %. Therefore, either identify this impurity or revise its specification according to ICH Q3B.
 - c. As per ICH Q3B, acceptance criteria for any unspecified impurity should be NMT 0.1%. Revise your specifications accordingly.
 - d. Demonstrate physical stability of the desired polymorphic form in drug product during the manufacturing process and on stability.
3. Provide FAR citation (CFR 172.1520) for all packaging configurations used for all strengths of panobinostat capsules.

BIOPHARMACEUTICS:

- An information response (dissolution method development) received May 22, 2014.
- No significant review issues identified at this time

STATISTICS

- No significant review issues identified at this time

PHARMACOLOGY AND TOXICOLOGY

- No significant review issues identified at this time

3.0 INFORMATION REQUESTS

Several information requests have already been conveyed to the Applicant.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

The need for a Risk Evaluation and Mitigation Strategy (REMS) has not been identified at this time.

5.0 ADVISORY COMMITTEE MEETING

At the time of the Midcycle meeting, we have determined that there will not be a need to discuss this application at an advisory committee meeting.

6.0 LATE-CYCLE MEETING (LCM)/OTHER PROJECTED MILESTONES

The LCM should be face-to-face, unless the applicant requests a teleconference and the division agrees.

The proposed date for the LCM is currently scheduled for September 11, 2014 at 1:00 p. m. in the White Oak building 22, room 1309, at which time we will discuss the other projected milestones for the remainder of the review cycle.

The PDUFA action goal date is November 24, 2014.

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/s/

VIRGINIA E KWITKOWSKI
06/18/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205353

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

ATTENTION: Jeannie Shen
Senior Associate Director, Drug Regulatory Affairs

Dear Ms. Shen:

Please refer to your New Drug Application (NDA) dated and received March 24, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Panobinostat Capsules, 10 mg, 15 mg, and 20 mg.

We also refer to your March 24, 2014, correspondence, received March 24, 2014, requesting review of your proposed proprietary name, Farydak.

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

If any of the proposed product characteristics as stated in your March 24, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Diane Hanner, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
06/18/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Bcc: [Ma, Lian](#)
Subject: IR Panobinostat- NDA 205353- Time Sensitive- Please respond by c.o.b. 6/23/14
Date: Monday, June 16, 2014 1:49:00 PM
Importance: High

Hi Jeannie,

Please address the following (Panobinostat) NDA 205353 information request regarding the additional dose-response analysis on your pivotal trial.

1. In your previously submitted dose intensity-response analysis, you only considered the events and responses up to the date of the last PAN dose. However, events and responses that occur after treatment could also be associated with dose intensity and therefore be included to allow a relevant comparison of the effect of dose intensity. Please update the dose intensity-response analysis with post-treatment events included, following same the derivation and censoring rules of the primary analysis of study D2308.
2. Develop a dose intensity-platelet count model using data from both arms in study D2308 to link the dose-intensity and time profile of platelet count. Based on the developed model, conduct simulation to predict the incidence of thrombocytopenia over time throughout the treatment period (48 weeks). Predict the “all grades (Grade 1-4)” and “grade 3-4” thrombocytopenia from your model and compare with the rate of thrombocytopenia observed in the study.

Please submit the analysis results by COB June 23rd, 2014.

Thank you.

Regards,

Diane

[CAPT Diane Hanner](#)
[Senior Program Management Officer](#)
[FDA/CDER/OHOP/DHP](#)
[10903 New Hampshire Avenue](#)
[Bldg. 22/Room 2119](#)
[Silver Spring, Maryland 20993](#)
[\(301\) 796-2330](#)
[FAX \(301\) 796-9845](#)
[E-mail: diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/

DIANE C HANNER
06/16/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: IR for NDA 205353 (panobinostat)
Date: Thursday, June 12, 2014 10:20:00 AM

Hi Jeannie,

Please address the following information request regarding NDA 205353 Panobinostat. Please respond within 3 weeks, by the c.o.b. July 3, 2014.

Patient numbers 0292-00002 and 0087-0001 received treatment to which they were not randomized. Both of these patients were exposed to panobinostat. For the purposes of FDA analyses these patients will be included in the panobinostat as the definition for the safety analysis set in protocol D2308 was "as treated". Therefore, please resubmit the following tables for trial D2308 including these 2 patients in the panobinostat group:

- Adverse events
- Serious adverse events
- Deaths
- Adverse events leading to discontinuation
- Adverse events leading to treatment interruption/modification

Thank you.

Regards,

Diane

[CAPT Diane Hanner](#)
[Senior Program Management Officer](#)
[FDA/CDER/OHOP/DHP](#)
[10903 New Hampshire Avenue](#)
[Bldg. 22/Room 2119](#)
[Silver Spring, Maryland 20993](#)
[\(301\) 796-2330](#)
[FAX \(301\) 796-9845](#)
[E-mail: diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/

DIANE C HANNER
06/12/2014

From: Agosto, Teicher
To: [Ganser, Charlene \(charlene.ganser@novartis.com\)](mailto:Charlene.ganser@novartis.com)
Subject: Information Request NDA 205353
Date: Tuesday, June 10, 2014 10:55:00 AM

Dear Ms. Ganser,

We are requesting the following information concerning New Drug Application- NDA 205353, submitted March 24, 2014. We request a prompt response to this IR request no later than COB Monday, June 23, 2014. Please provide information for the following comments:

Drug Substance:

1. As per regulatory requirements, you must report any changes in the specifications of the starting materials using the appropriate regulatory route.
2. Provide DOE data in support of the proposed Proven Acceptable Ranges (PARs) outlined in section 3.2.S.2.4, Control of Critical Steps. Alternatively, you may provide Normal Operating Ranges (NOR) with a statement that any change of NORs will be reported to the Agency as a PAS.
3. Provide data to show that your (b) (4) method is capable to measure the amount of (b) (4).
4. Provide justification for not testing the drug substance batches manufactured *via* the (b) (4) in toxicology studies.
5. Specification:
 - a. In addition to X90, include X50 and X10 in your particle size distribution specification.
 - b. Tighten the limit for the degradation product “(b) (4)” as the acceptance criterion of NMT (b) (4)% is not supported by stability results.
6. Demonstrate mass balance for the assay and degradation products analytical method

Drug Product:

1. Provide DOE data in support of the proposed Proven Acceptable Ranges (PARs) outlined in section 3.2.P.3.4, Control of Critical Steps. Alternatively, you may provide Normal Operating Ranges (NOR) with a statement that any change of NORs will be reported to the Agency as a PAS.
2. Specification:
 - a. Your proposed acceptance criterion for the degradation product (b) (4) (NMT (b) (4)%) is not supported by results from stability studies (highest amount is (b) (4)%). Therefore, tighten specification accordingly.
 - b. Acceptance criterion of NMT (b) (4)% for Impurity (b) (4) (specified, unidentified) is above the ID Threshold of (b) (4)%. Therefore, either identify this

- impurity or revise its specification according to ICH Q3B.
- c. As per ICH Q3B, acceptance criteria for any unspecified impurity should be NMT 0.1%. Revise your specifications accordingly.
 - d. Demonstrate physical stability of the desired polymorphic form in drug product during the manufacturing process and on stability.
3. Provide FAR citation (CFR 172.1520) for all packaging configurations used for all strengths of panobinostat capsules.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

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/s/

TEICHER N AGOSTO
06/10/2014

From: Agosto, Teicher
To: [Ganser, Charlene \(charlene.ganser@novartis.com\)](mailto:Charlene.ganser@novartis.com)
Subject: RE: Information Request NDA 205353
Date: Tuesday, May 27, 2014 7:45:00 AM

Dear Ms. Ganser,

We are requesting the following information concerning New Drug Application- NDA 205353, submitted March 24, 2014. We request a prompt response to this IR request no later than COB Thursday, May 29, 2014.

1. Provide raw stability data in Excel or SAS formats for (b) (4) including all storage conditions (25oC/60% RH, 30oC/75%RH, and 40oC/75%RH) in the proposed packaging systems. In addition, provide the statistical analysis for (b) (4) related to the stability data.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,
Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

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/s/

TEICHER N AGOSTO
05/27/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: 5-23-14- IR Panobinostat- NDA 205353 -Time sensitive
Date: Friday, May 23, 2014 9:55:00 AM
Attachments: [IR_panobinostat.doc](#)

Hi Jeannie,

Please address the following Clinical Pharmacology Information Request (which is also attached) regarding NDA 205353 (panobinostat):

Given exposure data is not available for the pivotal phase 3 study D2308, submit a report with dose intensity-response analysis based on efficacy and safety data from this study. The primary objective of the analysis requested below is to explore the impact of dose intensity and prognostic factors on efficacy and safety endpoints (especially thrombocytopenia events).

The corresponding datasets (raw/tabulation, intermediate, and final analysis), SAS programs (data processing and analysis) and corresponding define file(s) should be provided. For general expectations of submitting pharmacometric data and models, please refer to <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>

Dose intensity-response (DI-R) analysis for efficacy endpoints and safety events for the Phase 3 study D2308

Conduct multivariate logistic regression and time-to-event analysis (e.g., cox proportional hazard model) to assess the association between various dose-intensity metrics and each of the clinical endpoints of interest. These endpoints are described below.

Efficacy endpoints: Progression-free survival (PFS) and overall response rate (ORR)

Safety endpoints: Most frequent treatment-emergent AEs including: thrombocytopenia, diarrhea, anemia, fatigue, neutropenia and hypokalemia. Separate analysis should be conducted for “all grades (Grade 1-4)” and “grade 3-4” AE events.

Prognostic factors (baseline characteristics): The clinical measures and dose adjustments may be associated with prognostic factors. Therefore, we recommend that in addition to univariate analysis, you also conduct multivariate analysis to examine the effect of prognostic factors that are considered to be related to efficacy or safety (e.g., such as age, race, body surface area, baseline platelet counts, time since diagnosis, etc.) In addition, case-control analysis should be performed to rule out potential unbalanced risk factors. Refer to published paper by Jun Yang et al. 2012. “The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making,” J. Clin. Pharmacol., 53(2): 160–166.

Dose intensity metrics: Applicant should make every effort to identify most relevant dose intensity metrics for each of aforementioned clinical endpoints using multivariate logistic regression or time-to-event analysis. Given that all patients start with a 20 mg TIW dose and are allowed to receive dose adjustments based on tolerability, the relevant dose intensity metrics leading to the event should be explored as time-dependent variables.

If a patient has an event, dose intensity should be calculated as follows: 1) from beginning of treatment up to the time of the event; 2) within 4 weeks, 8 weeks, 12 weeks and 16 weeks prior to the event, respectively. If a patient has no event, dose intensity should be calculated up to the actual day of last dose (note: this may not be same day of discontinuation adjudicated by investigating physicians) and within 4 weeks, 8 weeks, 12 weeks and 16 weeks prior to the actual day of last dose. Similarly, applicant should make every effort to identify other relevant dose-intensity metrics to conduct the logistic regression or time-to-event analysis.

Since the doses for bortezomib and dexamethasone are also allowed to be titrated over time based on the drug specific toxicity, the time-dependant contribution of these two agents should be adjusted in the analysis. One of the ways to do so is by including them as categorical covariates in the analysis model.

Please submit the Dose Intensity-Response analysis results by COB May 30th, 2014.

Please submit the case-control analysis results by COB June 5th, 2014.

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
05/23/2014

From: Hanner, Diane
To: ["Shen, Jeannie"](#)
Subject: Information request regarding NDA 205353 (panobinostat) - Novartis request for clarification
Date: Tuesday, May 20, 2014 2:23:00 PM

Hi Jeannie,

Your proposal is acceptable.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Tuesday, May 20, 2014 1:51 PM
To: Hanner, Diane
Subject: RE: Information request regarding NDA 205353 (panobinostat) - Novartis request for clarification

Dear Diane,

Thank you for contacting us yesterday (19-May-2014) regarding FDA requests for information. Novartis would like to seek clarification/agreement with the Agency on the following:

FDA Information Request- Part 1:

"We are unable to clearly identify the dose and regimen (i.e., MWF qw, MWF qow, or Mth q.w.) for the PK related datasets for the dose escalation trial B2101. Within 2 business day please submit revised "PKparm" and "pkconc" datasets for the following trials or affirm that this information is readily available within in these data sets: B1101, B2101, B2102, A2101, and a 2102.

Novartis Position:

The pooled SCP database including TRT dataset provided in the submission contains the variables TRTDDOS and SCHEDULE, which store the dose and regimen information for all of the studies referenced above. The format of these variables is shown in Table 1 (attached). For the datasets requested for individual studies, Novartis plans to create variables SCHDSC and TDOSDSC to store a character version of variables SCHEDULE and TRTDDOS. These four variables will be added to PKCONC and PKPARM and the corresponding revised datasets for studies B1101, B2101, B2102, A2101, and A2102 will be submitted to the NDA within 2 business day, i.e. by EOB Wednesday, 21-

May-2014, as requested by the FDA.

For studies A2101 and A2102, the datasets containing PK concentration and PK parameter data were not named PKCONC or PKPARAM respectively. These datasets will be renamed to be consistent with the other studies. Does the Agency agree that this adequately addresses FDA's request in Part 1?

FDA Information Request- Part 2:

“In addition revise other datasets related to safety, efficacy, PD, and laboratory in these trials so that both the dose and regimen is readily identifiable within 5 business days”

Novartis Position:

Novartis proposes to add the same variables (TRTDDOS, SCHEDULE, TDOSDSC, SCHDSC) to all raw datasets for studies B1101, B2101, B2102, A2101, and A2102 and submit the corresponding revised raw datasets to the NDA within 5 business days, i.e., by EOB Tuesday, 27-May-2014 (as Monday 26-May-2014 is a Federal Holiday) as requested by the FDA. Does the Agency agree that this adequately addresses Part 2 of the Agency's request?

with best regards,
Jeannie

Jeannie Shen

Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7783343
Cell (b) (6)
Fax +1 973 7813320
jeannie.shen@novartis.com
www.novartis.com

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Monday, May 19, 2014 3:56 PM
To: Shen, Jeannie
Subject: Information request regarding NDA 205353 (panobinostat)
Importance: High

Hi Jeannie,

We are unable to clearly identify the dose and regimen (i.e., MWF qw, MWF qow, or Mth q.w.) for the PK related datasets for the dose escalation trial B2101. Within 2 business day please submit revised “PKparm” and “pkconc” datasets for the following trials or affirm that this information is readily available within in these data sets: B1101, B2101, B2102, A2101, and a 2102. In addition revise other datasets related to safety, efficacy , PD, and laboratory in these trials so that both the dose and regimen is readily identifiable within 5 business days.

Thank you.
Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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/s/

DIANE C HANNER
05/20/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: Information request regarding NDA 205353 (panobinostat)
Date: Monday, May 19, 2014 3:56:00 PM
Importance: High

Hi Jeannie,

We are unable to clearly identify the dose and regimen (i.e., MWF qw, MWF qow, or Mth q.w.) for the PK related datasets for the dose escalation trial B2101. Within 2 business day please submit revised “PKparm” and “pkconc” datasets for the following trials or affirm that this information is readily available within in these data sets: B1101, B2101, B2102, A2101, and a 2102. In addition revise other datasets related to safety, efficacy , PD, and laboratory in these trials so that both the dose and regimen is readily identifiable within 5 business days.

Thank you.
Regards,
Diane

[CAPT Diane Hanner](#)
[Senior Program Management Officer](#)
[FDA/CDER/OHOP/DHP](#)
[10903 New Hampshire Avenue](#)
[Bldg. 22/Room 2119](#)
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/s/

DIANE C HANNER
05/19/2014

From: Agosto, Teicher
To: [Ganser, Charlene \(charlene.ganser@novartis.com\)](mailto:Charlene.ganser@novartis.com)
Subject: Information Request NDA 205353
Date: Wednesday, May 14, 2014 11:00:00 AM

Dear Ms. Ganser,

We are requesting the following information concerning New Drug Application- NDA 205353, submitted March 24, 2014. We request a prompt response to this IR request no later than COB Wednesday, May 21, 2014.

Provide the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

- a.** Solubility data for the drug substance covering the pH range.
- b.** Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (*i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*). If a surfactant was used, the data supporting the selection of the type and amount of surfactant should be included. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (*i.e., 15, 20, 30, 45, & 60 minutes*) and cover at least 85% of drug release of the label amount or whenever a plateau (*i.e., no increase over 3 consecutive time-points*) is reached. We recommend that at least twelve samples be used per testing variable.
- c.** Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for the proposed drug product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).
- d.** Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (*i.e., method robustness, etc.*) and analytical method (*precision, accuracy, linearity, stability, etc.*). In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (*i.e. aberrant formulations and manufacturing conditions*) for the most relevant manufacturing variables (*e.g. drug substance particle size, solid state, etc.*). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards

Teicher Agosto, Pharm D, RPh

Regulatory Health Project Manager

FDA\CDER\OPS

Office of New Drug Quality Assessment

10903 New Hampshire Ave W021,Rm 2615

Silver Spring, MD 20993

Teicher.agosto@fda.hhs.gov

P: (240) 402-3777

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/s/

TEICHER N AGOSTO
05/14/2014

From: Agosto, Teicher
To: [Ganser, Charlene \(charlene.ganser@novartis.com\)](mailto:Charlene.ganser@novartis.com)
Subject: Information Request NDA 205353
Date: Monday, May 12, 2014 10:24:00 AM

Dear Ms. Ganser,

We are requesting the following information concerning New Drug Application- NDA 205353, submitted March 24, 2014. We request a prompt response to this IR request no later than COB Monday, May 26, 2014.

(b) (4)

If a drug product release specification includes tests and acceptance criteria for a given attribute, (b) (4). However, microbial limits testing may be omitted from the product release specification provided adequate upstream microbiological controls are established and documented. If you wish to omit the microbial limits specification, more information on your process is needed. Address the following points:

1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product. At a minimum, you should define the maximum processing time for the (b) (4).
2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
3. Describe activities taken when microbiological acceptance criteria are not met at control points.

In addition to these points, you should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.

If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced.

Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the

review cycle. If you have any questions or comments feel free to contact me.

Best Regards,
Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
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/s/

TEICHER N AGOSTO
05/12/2014

From: Agosto, Teicher
To: [Ganser, Charlene \(charlene.ganser@novartis.com\)](mailto:Charlene.ganser@novartis.com)
Subject: Information Request NDA 205353
Date: Friday, May 09, 2014 2:28:00 PM

Dear Ms. Ganser,

We are requesting additional information concerning your New Drug Application- NDA 205353, submitted March 24, 2014. We request a prompt response to this IR request no later than COB Wednesday, May 14, 2014.

Please provide information for the following comments:

1. To better review the stability profiles for the product, please provide the raw stability data at 30°C/75% condition and 40°C/75% accelerated condition.
2. At 30°C/75% condition, please explain the rationales and adjustments of the exclusion of "strength" factor in statistics model..

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
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/s/

TEICHER N AGOSTO
05/09/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: NDA 205353- Panobinostat IR - Time sensitive- please respond by c.o.b. tomorrow - May 6, 2014.
Date: Monday, May 05, 2014 3:12:00 PM

Hi Jeannie,

Please address the following IR to regarding NDA 205353- Panobinostat and please respond by c.o.b. tomorrow, May 6, 2014.

It is unclear as to why the derived AAEE and ATEEBMT datasets contain data for 769 patients when the ITT for the trial is 768.

Please provide a response to clarify that issue.

Also, when you submit the requested dataset, please be sure to only include the ITT population (n=768).

Thank you.

Regards,

Diane

CAPT Diane Hanner
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/s/

DIANE C HANNER
05/05/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: IR- NDA 205353 panobinostat- time sensitive -Please respond by c.o.b. Tuesday, 5/6/14.
Date: Friday, May 02, 2014 3:25:00 PM

Hi Jeannie,

Please address the following information request regarding NDA 205353 panobinostat:

We have evaluated the DAR dataset and we have the following issues:

1. We are unable to decipher whether patients received placebo or panobinostat because variable DARTYP1C has only three codes: 37 (Dexamethasone); 503 (bortezomib); and 745 (panobinostat/placebo). There are no other values in this column in this dataset. We need to know the exact drug that the patients with code 745 actually received (was it placebo OR panobinostat)? Please do not assume that the randomized treatment assignment is the actual treatment received.
2. We are unable to determine the study day on which treatments were received. Please inform us which variable in which dataset this information is available.
3. Please submit a single dataset that provides (at a minimum) a variable that identifies the Subject Identifier (SID1A), Randomization Treatment Group (text and code), and the actual treatment received (text and code).

Please respond to this request by close of business on Tuesday, May 6, 2014.

Thank you.
Regards,
Diane

CAPT Diane Hanner
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/s/

DIANE C HANNER
05/02/2014

From: Agosto, Teicher
To: ["Jeannie.shen@novartis.com"](mailto:Jeannie.shen@novartis.com)
Subject: Information Request NDA 205353
Date: Thursday, May 01, 2014 12:35:00 PM

Dear Ms. Shen,

We are requesting the following information concerning your New Drug Application- NDA 205353, submitted March 24, 2014. We request a prompt response to this IR request no later than COB Wednesday, May 7, 2014.

Please provide information for the following comments:

1. Please submit the raw stability data in Excel or SAS file along with the data definitions.
2. From the stability report "RSR6139.1 Data-1B", there are 2 different strengths (10mg, 20mg) products included in the stability data. But in the provided statistical evaluation (Page 41-Page 71), the "strength" is not included as a "factor" in the statistic modeling for shelf life extrapolation. Please explain the rationales and adjustments of the exclusion of "strength" factor in statistics model.

In general, "Strength" is an important factor in statistics modeling for stability analyses because products with different strengths may have different degradation profiles.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
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/s/

TEICHER N AGOSTO
05/02/2014

From: Hanner, Diane
To: "[Shen, Jeannie](#)"
Subject: Panobinostat IR - NDA 205353- Follow up regarding the teleconference
Date: Friday, May 02, 2014 1:29:00 PM

Hi Jeannie,
Based upon our teleconference discussion no additional information or data sets need to be submitted at this time.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
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FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Friday, May 02, 2014 11:53 AM
To: Hanner, Diane
Subject: RE: Panobinostat IR - NDA 205353- TC this afternoon

Dear Diane,

Thanks again for setting up the TC for this afternoon. From Novartis, besides myself, the following people will be included on the call:

Sofia Paul, Director Biostatistics
Xiaohui Wang, Senior Principal Programmer
Hong Yan, Senior Principal Programmer

Would you kindly indicate whom from the FDA will be join the call?

Thanks. Talk to you at 1pm.

with best regards,
Jeannie

Jeannie Shen

Oncology Regulatory Affairs
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USA

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jeannie.shen@novartis.com
www.novartis.com

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Thursday, May 01, 2014 6:39 PM
To: Shen, Jeannie
Subject: RE: Panobinostat IR - NDA 205353

Hi,
I have it scheduled.
Thanks.
Diane

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Thursday, May 01, 2014 6:30 PM
To: Hanner, Diane
Subject: RE: Panobinostat IR - NDA 205353

Dear Diane,

Tomorrow from 1pm to 2pm for a TC would work well with us. Besides myself, there will be two people from the Stats function joining the meeting. Please see the dial in number provided below.

Thank you and look forward to talking with you tomorrow.

Dial in numbers

USA [REDACTED] (b) (4)

Participant Passcode: [REDACTED] (b) (4)

with best regards,
Jeannie

Jeannie Shen
Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7783343
Cell [REDACTED] (b) (6)
Fax +1 973 7813320
jeannie.shen@novartis.com
www.novartis.com

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Thursday, May 01, 2014 5:53 PM
To: Shen, Jeannie
Subject: RE: Panobinostat IR - NDA 205353

Hi,
Yes, we can have a teleconference on tomorrow.
Will you be availability tomorrow between 830-10a or 1p-2p?
Please provide me with the dial in numbers.
Thank you.
Regards,
Diane

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Thursday, May 01, 2014 5:22 PM
To: Hanner, Diane
Subject: RE: Panobinostat IR - NDA 205353

Dear Diane,

Regarding the FDA information request received earlier today (please see below email), the Novartis team would like to request clarification on the request. Would it be possible to speak to the reviewer by phone tomorrow at the FDA's convenience?

Thanks,

with best regards,
Jeannie

Jeannie Shen
Oncology Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7783343
Cell [REDACTED] (b) (6)
Fax +1 973 7813320
jeannie.shen@novartis.com
www.novartis.com

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Thursday, May 01, 2014 1:38 PM
To: Shen, Jeannie
Subject: Panobinostat IR - NDA 205353
Importance: High

Hi Jeannie,

Please respond to the following information request regarding NDA 205353 (panobinostat) by COB, Monday, May 5, 2014.

We do not use derived datasets to conduct our analyses. Please send a single raw demographic dataset that contains Universal subject ID and randomization arm (in text not code). The dataset can contain other variables, but must contain these two.

Thank you.
Regards,
Diane

CAPT Diane Hanner
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/s/

DIANE C HANNER
05/02/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Subject: Panobinostat IR - NDA 205353
Date: Thursday, May 01, 2014 1:37:00 PM
Importance: High

Hi Jeannie,

Please respond to the following information request regarding NDA 205353 (panobinostat) by COB, Monday, May 5, 2014.

We do not use derived datasets to conduct our analyses. Please send a single raw demographic dataset that contains Universal subject ID and randomization arm (in text not code). The dataset can contain other variables, but must contain these two.

Thank you.
Regards,
Diane

CAPT Diane Hanner
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/s/

DIANE C HANNER
05/01/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:Shen,Jeannie(jeannie.shen@novartis.com))
Subject: Information request regarding NDA 205353 (panobinostat)
Date: Friday, April 25, 2014 11:15:00 AM

Hi Jeannie,
That is correct 101 and 102.
Regards,
Diane

From: Shen, Jeannie [<mailto:jeannie.shen@novartis.com>]
Sent: Friday, April 25, 2014 10:07 AM
To: Hanner, Diane
Subject: RE: Information request regarding NDA 205353 (panobinostat)

Dear Diane,

Hope your day is going well. Regarding the FDA clinical pharmacology information request received on April 22nd (attached), we would like to request clarification on comment no. 6, as follows:

***Comment 6:** Please provide electronic data sets for the following trials: A2101, A2101, B2101, B2102, B1101, E2214, B1201, B2201, B2202, B2203, and B2211 as a SAS transport files (*.xpt). Datasets for these clinical pharmacology and biopharmaceutics related trials should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. While we note some of these trials utilized sparse PK sampling, all of these data are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes. CDISK format is not required to satisfy this request. Provided your response within ten business days.*

Novartis would like to request clarification on comment #6:

Would the FDA please confirm:

- Study No. A2101 is listed twice. Novartis assumes that the request is for studies A2101 and **A2102** and therefore proposed to include electronic data from both studies A2101 and **A2102**.
- The .xpt files for each study will be sent as CRT package.

We hope to have clarification from the FDA as soon as possible so that we can provide the response as requested.

Thanks very much and have a nice weekend.

with best regards,
Jeannie

Jeannie Shen
Oncology Regulatory Affairs

Novartis Pharmaceuticals Corporation
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USA

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Cell [REDACTED] (b) (6)
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jeannie.shen@novartis.com
www.novartis.com

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Tuesday, April 22, 2014 5:40 PM
To: Shen, Jeannie
Subject: Information request regarding NDA 205353 (panobinostat)

Hi Jeannie,

Please click on the attachment and view the information request regarding NDA 205353 (panobinostat).

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
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/s/

DIANE C HANNER
04/25/2014



NDA 205353

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Ms. Jeannie Shen
Sr. Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Shen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for panobinostat, LBH589.

We also refer to your March 24, 2014, submission containing your New NDA submission.

We are reviewing the clinical pharmacology 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. Justify your labeling proposal [REDACTED] (b)(4) with concurrent use of FARYDAK and strong CYP3A inhibitors as opposed to recommending a dose modification or avoidance. Your justification should be based on the dedicated trial information in the context of your exposure-response and exposure-safety analysis as well as other information you deem appropriate. In addition, [REDACTED] (b)(4) include actionable information. Provided your justification within ten business days.
2. Justify your labeling proposal [REDACTED] (b)(4) with concurrent use of FARYDAK and sensitive CYP2D6 substrates with a narrow therapeutic index as opposed to recommending avoidance. Your justification should be based on the dedicated trial information in the context of exposure-response and exposure-safety analysis that may be publically available for these agents as well as other information you deem appropriate. In addition, [REDACTED] (b)(4) include actionable information. Provided your justification within ten business days.
3. Justify your labeling proposal [REDACTED] (b)(4) with the use of FARYDAK in patients with hepatic impairment as opposed to recommending a dose modification or avoidance. Your justification should be based on the dedicated trial information and possibly in silico simulation of unstudied populations in the context of your exposure-response and exposure-

safety analysis as well as other information you deem appropriate. In addition, (b) (4) include actionable information. Provided your justification within ten business days.

4. Define the BCS classification of panobinostat. Provided your response within ten business days.
5. Please justify not conducting a study to assess the effect of pH-elevating agents (e.g., proton pump inhibitors, H² antagonists and antacids) on the absorption of the panobinostat given you state that its aqueous solubility is strongly pH dependent. Provided your response within ten business days.
6. Please provide electronic data sets for the following trials: A2101, A2101, B2101, B2102, B1101, E2214, B1201, B2201, B2202, B2203, and B2211 as a SAS transport files (*.xpt). Datasets for these clinical pharmacology and biopharmaceutics related trials should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. While we note some of these trials utilized sparse PK sampling, all of these data are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes. CDISK format is not required to satisfy this request. Provided your response within ten business days.
7. Your report DMPK R1200672 (Ex vivo protein binding of LBH589 in clinical plasma samples from CLBH589X2105 trial) states that analysis of the data was based on hepatic impairment status; however, trial CLBH589X2105 is your dedicated renal impairment trial. Clarify this discrepancy. Provided your response within ten business days.
8. Your submission includes PBPK modeling and simulations to predict the effect of strong inducer (rifampin, Study R0600943-01) on the exposure of panobinostat, and to predict the effect of panobinostat as a time-dependent inhibitor of CYP3A in vivo (Study R0800469-01). Based on our preliminary review of your study reports, you should address the following within ten business days:
 - a. Regarding report R0600943-01, your PBPK model appears to significantly over predict the exposure of panobinostat by nearly 10-fold. Optimize your drug model using available human PK data. The optimization should consider potential nonlinearity of the pharmacokinetics of panobinostat, when (if?) applicable. The updated model should be independently verified using drug interaction study results from Study CLBH589B2110 (ketoconazole inhibition study), before it can be used to predict the effect of rifampin and its inhibition of CYP3A. If the simulated exposure change of panobinostat by ketoconazole model does not describe the observed data, modify panobinostat model (e.g., by adjusting the relative contribution of CYP3A). Further, conduct simulations using the newer version of the PBPK software so that you can use the updated ketoconazole model.
 - b. Regarding report R0800469-01, conduct necessary sensitivity analysis (e.g. time-dependent CYP3A inhibition parameters) to justify your position for panobinostat as an inhibitor of CYP3A in vivo.

- c. Submit the PBPK model files used to generate the results in the reports DMPK R0600943-01 and DMPK R0800469-01, and the final results requested above. The model files should be executable using SimCYP software Version 13 (such as .cmp, .lbr, and .wks). MS Excel files with the initial and revised simulation outputs should also be submitted. These files may be submitted via CD.

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

DIANE C HANNER
04/22/2014

From: Hanner, Diane
To: [Shen, Jeannie \(jeannie.shen@novartis.com\)](mailto:jeannie.shen@novartis.com)
Cc: "[Ganeshan, Shanthi](#)"
Subject: Please plan on presenting the Novartis Safety presentation during LBH589 AOM
Date: Friday, March 28, 2014 10:27:00 AM

Hi Jeannie,

It appears that FDA would like to have a presentation regarding the safety reporting process presented at the up-coming panobinostat (LBH589) applicant orientation meeting. Please note that this meeting is now scheduled for **1:30 p.m. to 3:00 p.m.**, on Friday, April 4, 2014, in Bldg 22, room 2205.

Please send me any additional foreign visitor forms that may need to be cleared.

I will also need a complete list of your attendees, so that I can issue you a lobby guard notice.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Ganeshan, Shanthi [<mailto:shanthi.ganeshan@novartis.com>]
Sent: Wednesday, March 26, 2014 1:19 PM
To: Jarow, Jonathan
Cc: Hanner, Diane
Subject: Confirmation - Novartis Safety presentation during LBH589 AOM

Dear Dr. Jarow,

I am reaching out to you since during the LBH589 preNDA meeting that Novartis had with DHP on February 5, 2014, you had mentioned that Novartis will be requested to present

the safety reporting process at the applicant orientation meeting for the compound. Subsequently, we had a call with Dr. Keegan and she mentioned that you were spearheading these efforts on behalf of the Oncology Office.

The AOM for LBH589 has been scheduled for Friday, April 5 and I am writing to confirm if you would like Novartis to present our process. Novartis is also working on an alternate proposal for safety reporting which we intend to send to you for review by March 31.

I would very much appreciate your feedback on the need for the safety presentation on April 5, so we can plan accordingly.

Thank you,
Shanthi

Shanthi Ganeshan, Ph.D.

North America Region Head, DRA

Oncology Global Development

Novartis Pharmaceuticals Corporation

Phone: +1 862 7782673

Cell: +1 (b) (6)

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/s/

DIANE C HANNER
03/28/2014



NDA 205353

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
Attention: Ms. Jeannie Shen
Sr. Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Shen:

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: (panobinostat, LBH589) 10 mg, 15 mg and 20 mg capsules

Date of Application: March 24, 2014

Date of Receipt: March 24, 2014

Our Reference Number: NDA 205353

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 May 23, 2014, 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

DIANE C HANNER
03/28/2014

From: Hanner, Diane
To: ["Shen, Jeannie"](#)
Bcc: [Orencia, Anthony](#)
Subject: Information Request for panobinostat NDA 205353- Please respond by c.o.b. April 3, 2014.
Date: Thursday, March 27, 2014 2:37:00 PM
Importance: High

Hi Jeannie,

Please respond to the following information request regarding NDA 205353 (panobinostat) by c.o.b. April 3, 2014.

We seek clarification for the DISCONT variable below in Study CLBH589D2308.

In the clinsite.xpt dataset, values by site, by treatment arm, for "ENROLL" and "DISCONT" are identical; thus it appears all subjects, at every site, were discontinued from study. In the clinsitedefine.pdf, "DISCONT" is noted to be populated from "cmp.dcnrsn1c". When reviewing variables dcnrsn1a and dcnrsn1c in cmp.xpt, it is not clear that 100% of subjects discontinued prematurely from study. Please confirm that all subjects enrolled in the study discontinued prematurely or provide a corrected clinsite.xpt dataset.

Thank you.

Regards,

Diane

[CAPT Diane Hanner](#)
[Senior Program Management Officer](#)
[FDA/CDER/OHOP/DHP](#)
[10903 New Hampshire Avenue](#)
[Bldg. 22/Room 2119](#)
[Silver Spring, Maryland 20993](#)
[\(301\) 796-2330](#)
[FAX \(301\) 796-9845](#)
[E-mail: diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/

DIANE C HANNER
03/27/2014



Pre-NDA/IND 069862

MEETING MINUTES

Novartis Pharmaceutical Corp
Attention: Jeannie Shen
Associate Director
1 Health Plaza
East Hanover, New Jersey 07936

Dear Ms. Shen:

Please refer to your Investigational New Drug Application (IND) file for LBH589 (panobinostat) capsules.

We also refer to the meeting between representatives of your firm and the FDA on February 5, 2014. The purpose of the meeting was to discuss: the content of the NDA, seek feedback on proposed data presentation for the NDA, ensure that the risk management approach is acceptable, and achieve an agreement on Novartis' outstanding questions.

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 me at (240) 402-0992.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, M.S., 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

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: February 5, 2014 at 10:00 AM – 11:00 AM (ET)
Meeting Location: White Oak, Building 22, Conference Room: 1419

Application Number: Pre-NDA/IND 069862
Product Name: LBH589 (panobinostat) capsules
Indication: Panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy

Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Virginia Kwitkowski, M.S., RN, ACNP-BC
Meeting Recorder: Amy Chi, M.S.N.

FDA ATTENDEES

Division of Hematology Products

Edvardas Kaminskas, M.D., Deputy Division Director
Virginia Kwitkowski, M.S., RN, ACNP-BC, Lead Clinical Analyst, Clinical Team Leader
Adam George, Pharm.D., Clinical Reviewer
Diane Leaman, B.S., Safety Regulatory Project Manager
Jessica Boehmer, M.S., Regulatory Project Manager
Amy Chi, M.S.N., Regulatory Project Manager
Tinya Sensie, M.H.A., Regulatory Project Manager
Alycia Anderson, B.S., Regulatory Project Manager

Office of New Drug Quality Assessment

Janice Brown, M.S, CMC Lead
Angelica Dorantes, Ph.D., Team Leader
Li Shan Hsieh, Ph.D., Product Quality Reviewer

Office of Biostatistics

Lei Nie, Ph.D., Team Leader
Yun Wang, Ph.D., Reviewer

Office of Medication Error Prevention and Risk Management

Yelena Maslov, Ph.D., Safety Evaluator
Michelle Rutledge, Pharm.D., Safety Evaluator
Tracy M. Salaam, Pharm.D., Safety Evaluator
Sonny Saini, Pharm.D., Safety Project Manager

Office of Business Informatics/Division of Data Management Services & Solutions

Lisa Lin, Project Manager Officer, eData Team Project Manager

Program Evaluation and Implementation Staff

Kimberly Taylor, Operations Research Analyst

Division of Risk Management

Joyce Weaver, Pharm.D., Reviewer

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES

Renaud Capdeville, M.D., Global Program Head, Novartis Oncology

Florence Binlich, M.D., Global Clinical Program Head, Executive Director, Novartis Oncology

Sofia Paul, Ph.D., Director, Oncology Biostatistics, Novartis Oncology

Rong Lin, M.D., Executive Director/Lead Brand Safety Leader, Novartis Oncology

Shanthi Ganeshan, Ph.D., VP, North America Region Head, DRA, Novartis Oncology

Jeannie Shen, R.Ph., Senior Associate Director, DRA Novartis Oncology

1.0 BACKGROUND

Panobinostat (LBH589, PAN), a DAC inhibitor belonging to a structurally novel cinnamic hydroxamic acid class of compounds, is being investigated for the treatment of multiple myeloma, an orphan disease. Through its effects on histone acetylation and gene expression, as well as on the oncogenic function of non-histone proteins such as Hsp90, PAN offers a multifaceted approach for the inhibition of cancer cell proliferation and survival. The planned new drug application (NDA) of panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy is the topic for the pre-NDA meeting. The NDA will contain quality, safety, and efficacy information of panobinostat with dosage regimen at 20 mg three times a week, two weeks on and one week off. Panobinostat is formulated as a hard gelatin capsule with dosage strengths of 10, 15 and 20 mg intended for commercialization. Multiple myeloma (MM) is a rare condition (incidence ranges from 0.4 to 5 per 100,000 per year) and all treated patients ultimately progress with no evidence of a cure despite marked improvements in available therapies. Orphan designation was granted on August 21, 2012 for PAN in MM. The panobinostat clinical development program in MM focuses on panobinostat in combination with BTZ and DEX, and includes one randomized, double-blind, placebo controlled design Phase III study, one supportive Phase II study, and data from the dose expansion phase of a Phase Ib study ([Table 1-1](#)):

Table 1-1 Overview of key studies included in the panobinostat submission

Study No.	Phase	Population	Recruitment	
			status	(n)
Study LBH589B2207	Ib	Relapsed or relapsed and refractory Including BTZ refractory patients	completed	62
Study LBH589DUS71	II	Relapsed and refractory Selectively BTZ refractory patients	completed	55
Study LBH589D2308	III	Relapsed or relapsed/refractory Excluding BTZ refractory patients	completed	768

The timing for the NDA will be dependent upon the outcome of the pre-NDA meeting and could occur as early as March 2014. In the meeting, the Sponsor stated a plan to submit at the end of March 2014.

2.0 DISCUSSION

2.1. Clinical

Question 1: Registration trial

Novartis considers that the data, based on the placebo-controlled randomized pivotal Phase III study CLBH589D2308 supported by the phase II study CLBH589DUS71, are sufficient and adequately support the filing and review for the proposed indication “treatment of patients with multiple myeloma, who received at least one prior therapy”.

Does the Agency agree?

FDA Response to Question 1:

Yes, the results provided appear to support a new drug application for the proposed indication. Whether the application is filed, is a review issue. You should plan to submit a complete application.

Discussion:

No discussion occurred.

Question 2: Completeness of clinical data in the electronic Common Technical Document (eCTD):

a) Does the Agency agree that the clinical studies to be included in the eCTD supports the submission of the NDA for the proposed indication?

FDA Response to Question 2:

Yes.

Discussion:

No discussion occurred.

Question 3: Efficacy and safety summaries

Does the Agency agree to the proposed content and format of the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) and to waive the requirement for providing an Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS)?

FDA Response to Question 3:

Yes.

Discussion:

No discussion occurred.

Question 4: Clinically significant/notable adverse events

Does the Agency agree that the clinically significant / notable adverse events identified by Novartis and the MedDRA search criteria, to be used for analyses in the SCS, are appropriate?

FDA Response to Question 4:

No, we recommend that diarrhea be included in these notable adverse events, as it occurred commonly in single-agent trials of panobinostat.

Discussion:

The Sponsor agrees to include diarrhea under clinically significant adverse events.

Question 5: Patient narratives

Does the Agency agree with the proposed categories for patient narratives?

FDA Response to Question 5:

Yes.

Discussion:

No discussion occurred.

Question 6: Safety update

Does the Agency agree to the content of the safety update?

FDA Response to Question 6:

Yes.

Discussion:

No discussion occurred.

Question 7: Risk management

Novartis believes that the risks associated with treatment with panobinostat can be managed adequately with appropriate labeling and routine pharmacovigilance activities. Does the Agency agree?

FDA Response to Question 7:

Whether a REMS will be needed to provide for the safe use of panobinostat in combination with bortezomib and dexamethasone will be a review issue.

Discussion:

The Agency stated that review of the safety data will be conducted to determine whether a REMS is needed for the safe use of panobinostat. This information will be shared with the applicant as soon as it is available.

Question 8: Electronic datasets

- a) The format of the datasets and programs for this submission?
- b) The documentation to support FDA inspections of clinical sites

FDA Response to Question 8:

Yes. For the datasets with large size, they should be resized to the maximum length used for each character variable prior to splitting. Please also note them in the define.pdf file so that these split datasets can be easily identified.

Discussion:

No discussion occurred.

2.2. Clinical Pharmacology

Question 9: Clinical pharmacology package for submission

Does the Agency agree that the clinical pharmacology properties of panobinostat have been adequately characterized in support of registration in Multiple Myeloma??

FDA Response to Question 9:

Yes.

Discussion:

No discussion occurred.

2.3 Quality

Question 10: Request for Biowaiver

Novartis proposes to submit a bio-waiver request in the NDA for the 15 mg panobinostat hard gelatin capsule and intends to apply the FDA recommendations provided to fulfill the 10 mg panobinostat hard gelatin capsule bio-waiver request as previously discussed with the Agency.

Does the Agency concur with Novartis' approach to submit a bio-waiver request for the 15 mg panobinostat hard gelatin capsule in the NDA?

FDA Response to Question 10:

We agree with your proposal to submit in your NDA a bio-waiver request for the 15 mg strength of your proposed product. The granting of the biowaiver will be based on the acceptability of the overall information/data supporting this request.

Discussion:

No discussion occurred.

2.4 Regulatory/Administrative

Question 11: Overall Content of the NDA

Does the Agency agree that the (eCTD) Table of Contents provided in this briefing document is acceptable to support a complete NDA?

FDA Response to Question 11:

From a technical standpoint (not content related) yes, the draft TOC for the planned NDA is acceptable. However, please see additional comments below

- **Notes to Reviewers should be a separate document from the cover letter (not an attachment to the cover letter)**
 - **Orphan designation letter should reside under m1.2 (cover letter section) with a clear leaf title.**
 - **The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be linked to the referenced studies in m5.**
 - **1.6.3 Correspondence regarding meetings – a single pdf file can be provided (instead of separate pdf files for each document) with proper bookmarks of all correspondence, table of contents and hyperlinks.**
 - **Providing Table of Contents in m3.1 is not necessary in the eCTD structure.**
 - **Sponsors options of cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.**
1. **To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section m1.4.4 of the eCTD, detailing previously submitted information that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), and (5) the submission identification (e.g., submission serial number, volume number, electronic folder, and file name) of the referenced document. Hyperlinks to those documents are optional, but could be of help to reviewers, if provided.**
 2. **To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server. The applications need to include the appropriate prefix in the href links (e.g. nda, ind.). Also, when cross application links are used, it's strongly recommended that a cross reference document be placed**

in m1.4.4, in case any of the links don't work and in the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference" and application number (e.g. Cross Ref to nda123456). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application and the application that is being referenced.

Prior to using cross application linking in an application, it is recommended that sponsor submit an "eCTD cross application links" sample to ensure successful use of cross application links.

- **To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. Please refer to the Sample Process web page which is located at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>**

Discussion:

The Sponsor confirms that they will submit the content as listed in the table of contents which will be a complete application.

Question 12: Priority Review

Novartis believes that that the combined results of Study D2308 and Study DUS71 in a relapsed/refractory patient population are clinically meaningful addressing a population with an unmet need and qualifies for priority review.

Does the Agency agree?

FDA Response to Question 12:

Preliminary review of the data provided appears to demonstrate that panobinostat has provided an improvement in PFS over available therapy (bortezomib/dexamethasone). However, the determination of the review priority is determined at the time of NDA filing.

Discussion:

The Sponsor enumerated the reasons why the panobinostat application should be considered for priority review, as it is a new class of agents for treatment of multiple myeloma, in addition to the usual reasons why priority review is granted. The Agency cannot commit itself at this time. The decision will be reached at filing.

Question 13: User fee waiver

Novartis believes that this application is exempt from a user fee as panobinostat has been granted an orphan drug designation for the treatment of multiple myeloma. Does the Agency agree that a user fee waiver will be accepted?

FDA Response to Question 13:

Yes, products and indications with orphan drug designation are exempt from user fees.

Discussion:

No discussion occurred.

Question 14: Waiver for pediatric study requirement

Does the Agency agree to grant a waiver for pediatric studies in this application?

FDA Response to Question 14:

A pediatric waiver is not necessary for drugs/indications with orphan drug designation.

Discussion:

No discussion occurred.

Additional Comments related to ODAC:

Preliminary review of the top line information does not indicate a current need for AC discussions. Should this change during the review the Applicant will be notified as soon as it is considered.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor confirms that they will submit the content as listed in the table of contents which will be a complete application.

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 review of the safety data will be conducted to determine whether a REMS is needed for the safe use of panobinostat. This information will be shared with the applicant as soon as it is available.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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 of 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, 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. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

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.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

None.

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/s/

VIRGINIA E KWITKOWSKI
02/06/2014

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 205353

LATE-CYCLE MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Ms. Jeannie Shen
Sr. Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Shen:

Please refer to your New Drug Application (NDA) dated March 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for panobinostat, 10 mg, 15 mg and 20 mg Capsules.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 23, 2014.

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, call CAPT Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Virginia 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:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: October 23, 2014, @ 1:00 p.m.

Meeting Location: White Oak Campus in Building 22, room 2205

Application Number: NDA 205353

Product Name: Panobinostat

Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Virginia Kwitkowski, MS, RN, ACNP-BC

Meeting Recorder: CAPT Diane Hanner, MPH, MSW

FDA ATTENDEES

- Ann T. Farrell, MD, Division Director, DHP
- Edvardas Kaminskas, MD, Deputy Director, DHP
- Virginia Kwitkowski, MS, RN, A.C.N.P.-BC, Clinical Team Leader, DHP
- Barry Miller, MS, CRNP, Clinical Reviewer, DHP
- Nicole Gormley, MD, Medical Officer, DHP
- Lori Ehrlich, MD, Medical Officer, DHP
- Emily Place, PhD, Pharmacology/Toxicology Reviewer, DHOT
- Christopher Sheth, PhD, (acting) Pharmacology/Toxicology Supervisor, DHOT
- Robert Kane, MD, Deputy Director Safety, DHP
- Theresa Carioti, MPH., Chief Project Manager (CPMS), DHP
- Paul Kluetz, MD, Medical Officer, OHOP
- Tamy Kim, Pharm D, Associate Director of Regulatory Affairs, OHOP
- Diane Leaman, BS, Safety Regulatory Project Manager
- Janice Brown, PhD, CMC Lead, ONDQA, Division 3, Branch 5
- Joseph A. Grillo, Pharm D, Clinical Pharmacology Reviewer, DCP5

Late-Cycle Meeting Minutes

- Bahru Habtemariam, PharmD, Clinical Pharmacology Reviewer, DCP5
- Nam Atiqur Rahman, PhD, Director, Office of Clinical Pharmacology, DCP5
- Chia-Wen Ko, PhD, Mathematical Statistician, DB 5
- Lei Nie, PhD, Statistical Team Leader, DB 5
- Lain Ma, PhD, Pharmacometrics Reviewer, DCP5
- Zhon Li, PhD, Interdisciplinary Scientist, Office of Compliance
- Wana Manitpisitkul, Pharm D, BCPS, Safety Evaluator, Division of Pharmacovigilance II
- Thomas E. Gwise, PhD, Deputy Division Director, DBV
- Vikram Sinha, PhD, Division Director Pharmacometrics, Office of Clinical Pharmacology
- Tracy Salaam, Pharm D, Safety Evaluator Team Leader, Division of Pharmacovigilance II
- Naomi Redd, Pharm D, (acting) Team Leader, Division of Risk Management
- Justin C. Earp, PhD, (acting) Pharmacometrics Team Leader, Office of Clinical Pharmacology
- Elsbeth Chikhale, PhD, Biopharmaceutics Reviewer, (by phone)
- CAPT Diane Hanner, MPH, MSW, Senior Program Management Officer

EASTERN RESEARCH GROUP ATTENDEES

- Patrick J. Zhou, Independent Assessor

APPLICANT ATTENDEES

- Alessandro Riva, MD, President, Novartis Oncology
- Renaud Capdeville, MD, Vice President, Global Program Head
- David Lebwohl, MD, Sr Vice President and Global Head, Oncology Clinical Development
- Carol Paley, MD, Executive Director, Clinical Research Physician
- Kannan Natarajan, PhD, Sr Vice President and Global Head of Oncology Biometrics & Data Management
- Sofia Paul, PhD, Director, Biostatistics
- Danny Howard, PhD, Vice President, Clinical Pharmacology
- Song Mu, PhD, Director, Principle Fellow, Oncology Clinical Pharmacology
- Gabriela Gruia, MD, , Sr Vice President, Global Head, Drug Regulatory Affairs

- Shanthi Ganeshan, PhD, Vice President, North America Region Head, Drug Regulatory Affairs
- Jeannie Shen, RPh, Senior Associate Director, Drug Regulatory Affairs (joining by phone)
- Jiten Rana, PharmD, Associate Director, Drug Regulatory Affairs
- Charlene Ganser, Associate Director, Global Regulatory Affairs, CMC

- **External consultant (joining by phone):**

-

(b) (4)

1.0 BACKGROUND

NDA 205353 was submitted on March 22, 2014, for FARYDAK[®] (panobinostat, LBH589) 10 mg, 15 mg and 20 mg capsules.

Proposed indication: FARYDAK[®] (panobinostat), 10 mg, 15 mg and 20 mg capsules, in combination with bortezomib (BTZ) and dexamethasone (Dex), for the treatment of patients with multiple myeloma (MM), who have received at least 1 prior therapy.

PDUFA goal date: November 24, 2014

FDA issued a Background Package in preparation for this meeting on October 10, 2014.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

- **Clinical and Biostatistics**

The benefit: risk assessment for panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior therapy does not appear favorable. The increased rate of grade ≥ 3 toxicities and serious adverse events along with an imbalance of deaths due to treatment emergent events is not outweighed by a 3.9 month improvement in investigator assessed median progression free survival. Further, the IRC sensitivity analysis demonstrated a 2.2 months difference in PFS (favoring the panobinostat arm). The amount of missing efficacy assessments and censoring was excessive and leads us to question the reliability of the trial results.

Discussion:

Novartis submitted slides via e-mail on October 21, 2014, (please see the attachment below) and started a dialogue regarding the results of their new IRC Analyses. Numerous slides were referenced including slides #5, 6, 9, 10, and 11. Novartis stated that they had discovered after the NDA submission that the IRC PFS analysis program had been incorrectly programmed to NOT require confirmation of myeloma protein progression events. Novartis referred to an updated IRC analysis where myeloma protein progression events were only counted if they were confirmed, and censored if they were not confirmed. Novartis requested that the FDA revise their advisory committee briefing package to include the 'updated IRC analysis'. Novartis further requested that the Agency add a footnote to FDA slides that present the initial IRC analysis indicating that there is an updated version. The Agency stated that they only revised the briefing book to correct factual errors. The Agency did not consider the original IRC analysis as a factual error as it was submitted in the NDA. The Agency responded that they would have to meet internally to discuss whether they would footnote the original IRC analysis in the Agency ODAC slide deck.

There was discussion with regards to how the Investigator analysis would have handled one progression as an event but censor it in the IRC analysis.

Novartis conveyed a willingness to send all of the raw datasets pertaining to each patient to the Agency. It was agreed upon that the Agency would send an information request to Novartis regarding the raw datasets so that a proper assessment could be made of the updated PFS analyses.

• **Clinical Pharmacology**

The data obtained from phase 1b dose escalation trial CLBH589B2207 (hereinafter referred to as Trial 2207), single agent phase 2 trial CLBH589B2203 (hereinafter referred to as Trial 2203) and registration Trial 2308 results show the absence of acceptable therapeutic window for the overall clinical benefit at the proposed dosing regimen of panobinostat in combination with bortezomib and dexamethasone:

- Trial 2207 showed that following treatment with the proposed treatment regimen, 87% of patients experienced Grade 3/4 adverse events (AEs), 73% of patients had dose interruptions or modifications, and 33% of patients were hospitalized due to adverse events.

In Trial 2203, panobinostat at 20 mg dose was not shown to be efficacious because the planned threshold of response was not achieved at the end of stage 1 of this study.

- Increased rate of serious adverse events and deaths were observed in the treatment arm compared to the active control group in Trial 2308.

- Since all the patients in the Trial 2308 started with a 20 mg panobinostat dose, it is not possible to determine if a lower starting dose would offer a better benefit-risk profile.

Discussion:

There was discussion regarding the safety profile of panobinostat in patients with relapsed/refractory multiple myeloma. Novartis referenced slides #14, 15, 16, 17, 18, and 19. Novartis identified thrombocytopenia and diarrhea as toxicities of concern for panobinostat.

The Agency expressed concerns regarding the tolerability of the proposed dose and conveyed concerns that the dose may be too excessive.

Novartis also presented the Agency with an Overview of Deaths handout during the meeting (see attachment below).

3. Discussion of Upcoming Advisory Committee Meeting – 15 minutes

- **Date of AC meeting:** November 6, 2014
- **Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management:** October 17, 2014.

Potential questions and discussion topics for AC Meeting are as follows:

- Risk-Benefit of Farydak in combination with bortezomib and dexamethasone for patients with relapsed multiple myeloma.
- We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:
<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

Discussion:

This question was mentioned and appropriately noted.

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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
11/12/2014



NDA 205353

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Novartis Pharmaceuticals Corporation
Attention: Ms. Jeannie Shen
Sr. Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Shen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FARYDAK[®] (panobinostat, LBH589) 10 mg, 15 mg and 20 mg capsules.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 23, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call CAPT Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C.
Lead Clinical Analyst, 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 23, 2014, @ 1:00 p.m.

Meeting Location: White Oak Campus in Building 22, room 1311

Application Number: NDA 205353

Product Name: FARYDAK[®] (panobinostat, LBH589) 10 mg, 15 mg and 20 mg capsules.

Indication: FARYDAK[®] (panobinostat), 10 mg, 15 mg and 20 mg capsules, in combination with bortezomib (BTZ) and dexamethasone (Dex), for the treatment of patients with multiple myeloma (MM), who have received at least 1 prior therapy.

Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

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 for NDA 205353.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

- **Clinical and Biostatistics**

The benefit:risk assessment for panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior therapy does not appear favorable. The increased rate of grade ≥ 3 toxicities and serious adverse events along with an imbalance of deaths due to treatment emergent events is not outweighed by a 3.9 month improvement in investigator assessed median progression free survival. Further, the IRC sensitivity analysis demonstrated a 2.2 months difference in PFS (favoring the panobinostat arm. The amount of missing efficacy assessments and censoring was excessive and leads us to question of the reliability of the trial results.

- **Clinical Pharmacology**

The data obtained from phase 1b dose escalation trial CLBH589B2207 (hereinafter referred to as Trial 2207), single agent phase 2 trial CLBH589B2203 (hereinafter referred to as Trial 2203) and registration Trial 2308 results show the absence of acceptable therapeutic window for the overall clinical benefit at the proposed dosing regimen of panobinostat in combination with bortezomib and dexamethasone:

- Trial 2207 showed that following treatment with the proposed treatment regimen, 87% of patients experienced Grade 3/4 adverse events (AEs), 73% of patients had dose interruptions or modifications, and 33% of patients were hospitalized due to adverse events.

In Trial 2203, panobinostat at 20 mg dose was not shown to be efficacious because the planned threshold of response was not achieved at the end of stage 1 of this study.

- Increased rate of serious adverse events and deaths were observed in the treatment arm compared to the active control group in Trial 2308.
- Since all the patients in the Trial 2308 started with a 20 mg panobinostat dose, it is not possible to determine if a lower starting dose would offer a better benefit-risk profile.

We defer discussion on PMRs and PMCs until after the ODAC meeting.

ADVISORY COMMITTEE MEETING

Date of AC meeting: November 6, 2014

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: October 17, 2014.

Potential questions and discussion topics for AC Meeting are as follows:

- 1.) Risk-Benefit of Farydak in combination with bortezomib and dexamethasone for patients with relapsed multiple myeloma.

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

REMS OR OTHER RISK MANAGEMENT ACTIONS

At this time, we do not see the need for a REMS.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 20 minutes

Each issue (noted above) will be introduced by FDA and followed by a discussion.

3. Discussion of Upcoming Advisory Committee Meeting – 15 minutes

4. REMS or Other Risk Management Actions – 1 minute

5. Postmarketing Requirements/Postmarketing Commitments – 1 minute

6. Major labeling issues – 5 minutes

- No major labeling issues have been identified to date. Minor revisions were identified and will be sent to the Applicant directly following the ODAC meeting.

7. Review Plans – 5 minutes

The primary and secondary reviews are complete. Tertiary review are ongoing and pending the ODAC meeting.

8. Wrap-up and Action Items – 5 minutes

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/s/

VIRGINIA E KWITKOWSKI
10/10/2014