CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205353Orig1s000

OTHER REVIEW(S)

Safety Team Review for NDA 205353

Re:	NDA safety analyses on diarrhea, electrolyte abnormality and cardiac events
NDA/SDN/PMR/IND	205353
Submission Date	3/22/2014, 6/2/2014, 6/20/2014
EDR	http://darrts.fda.gov:9602/darrts/viewEDR.do?suppDocId=9178170
Proposed Product Name	Farydak (panobinostat)
Proposed Indication and Dosage	Given 20 mg oral t.i.w. for 2/3 weeks in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least 1 prior therapy
Sponsor	Novartis
Office/Division	OND/OHOP/DHP
Safety RPM	Diane Leaman
Medical Officer for Safety	Qin Ryan, MD, PhD
Deputy Director for Safety	Robert Kane, MD
Date Review Completed	2/18/2015

1. Summary

This review summarizes the safety team's assessment on the specific safety question arisen during the review of the panobinostat NDA, labeling and REMS regarding the characteristics of diarrhea, cardiac events and electrolyte abnormality in the panobinostat treated group. More important, whether there is any relationship between these three events.

The conclusions and recommendations of the DHP safety assessment based on the adjudicated safety population of study D2308 are as follows (see section 3.2 for details):

a. All grade diarrheas occurred in 70% patients who received panobinostat treatment. Patients with Grade 3 or 4 diarrheas were 26%. Grades 1 and 2 diarrheas were 23% and 20% respectively. The safety team agrees with the clinical team's recommendation on the labeling regarding diarrhea.

b. There were 97 cardiac events occurred in 68 patients (18%), of which, 24 Grade 3/4 events occurred in 20 patient (5%). QTc prolongations reported as adverse events were 2% in both panobinostat and placebo groups. No Grade 3 QT prolongation adverse event was reported from the panobinostat group. The survey on the abnormal ECG description revealed 3% QTc prolongations post panobinostat dosing compare to 2% after placebo. It is noteworthy that per protocol design, patients had ECG test at baseline and pre-dosing of each cycle. Panobinostat was withheld if pre-dosing QTc was >480 mscs (CTCAE Grade 2), which may have prevented any Grade 3 QTc-prolongation occuring during the trial. Therefore, the sponsor proposed labeling statement, "(b) (4) is promotional and should be removed from the labeling. In addition, the dose withholding strategy based on QTc reading should be included in the labeling.

c. The overall electrolyte abnormalities that reported as adverse events, including Na, Cl, Ca, Mg, P and glucose, occurred in 7% of panobinostat treated patients (n=25). Nine patients (2%) who received panobinostat treatment found to have Grade 3 laboratory electrolyte abnormalities that were reported as adverse events. However, few were clinically meaningful.

d. There is a trend of more patients with more than one adverse events of our interest in the panobinostat group. In the panobinostat group, 18% patients experience both diarrhea with a cardiac event or an abnormal ECG description compared to 6% in the placebo group. However, the frequency of all 3 AES, diarrhea, electrolyte abnormality and cardiac events occurred simultaneously in the same patient was less than 1%. Small sample size and limited case description created made it difficult to identify a clear sequential timing of the events in the same patient. Furthermore, the factors clearly confound the causality determination existed in majority of these cases, such as the end organ abnormality from underlying multiple myeloma. Although it is difficult to establish a causal relationship, in theory and with clinical experience, severe diarrhea could cause electrolyte abnormalities, which could further exacerbate the cardiac toxicity. Therefore, the safety team suggests including the possible relationship between the diarrhea, electrolyte abnormality and cardiac event in the labeling.

2. Background

Panobinostat, a histone deaccetylase inhibitor, has been test in several clinical trials, including a randomized trial in patients with multiple myeloma (MM) and submitted for NDA review as a new molecular entity (NME).

Proposed Indications: In the original New Drug Application (NDA No. 205353), for oral panobinostat (PAN, LBH589), in combination with bortezomib (BTZ) and dexamethasone (Dex) for the treatment of adult patients with multiple myeloma (MM), having received at least one prior therapy, clinical safety was primarily based on safety data generated from the randomized trial LBH589D2308.

Proposed Regiment: Farydak is administered orally at 20 mg once every other day for three doses per week (on days 1, 3, 5, 8, 10 and 12) of weeks 1 and 2 of each 21 day cycle. Treatment may continue until toxicity or progression.

The safety signals from panobinostat randomized study indicated increase diarrhea and cardiac events in the panobinostat treatment group comparing the to the placebo group. The question of this review is the characteristics of diarrhea, cardiac events and electrolyte abnormality in panobinostat treated group. More important, whether there is any relationship between these three events.

3. Review

This review summarized specific safety analyses focusing on the incidence and potential relations among adverse events of diarrhea, electrolytes abnormality and cardiac events.

3.1 The material reviewed and analyzed

The safety analyses are based on the submissions and datasets listed in the Table 1.

Table 1: Submissions, including datasets, reviewed and analyzed

Submission	Date submitted	Notes

NDA	3/22/2014	Data cut-off dates see Table 3 for original NDA
IR response	6/2/2014	Data cut-off dates is as safety update
Safety Update	6/20/2014	Data cut-off dates see Table 3 for safety update
IR response	1/15/2015	Data cut-off dates see Table 3 for safety update

Source: NDA 205353

The analyses were primarily focus on the study D2308, which is outlined in Table 2. Additional safety data was noted from the pooling of three combination studies in MM patients (Studies B2207, DUS71, and D2308).

Table 2: MM trials using proposed combination regimen included for this safety evaluation

Trial ID	**Study design and endpoints**	**Patients enrolled (N)**	**Treatment duration**	**Treatment/dose[1]**
D2308	Multi-center, international, randomized, double-blind, placebo- controlled. *Primary*: PFS *Secondary*: OS (key secondary), ORR, nCR, MRR, TTR, TTP, DOR, safety, QoL, PK in a subset of JPN pts.	768 patients with relapsed or relapsed and refractory MM, excluding BTZ refractory and primary refractory	Total of 48 weeks (12 cycles) of PAN (eight 21-day cycles, and four 42-day cycles)	20 mg PAN three times a week, 2 weeks on /1 week off
DUS71	Multi-center, single-arm, open-label *Primary*: ORR *Secondary*: MR, TTR, DOR, PFS, TTP, OS, safety and tolerability:	55 patients with relapsed and BTZ refractory MM who had received at least 2 prior lines of therapy. Including immunomodulatory drug	Total of 48 weeks (12 cycles) of PAN (eight 21-day cycles, and four 42-day cycles)	20 mg PAN three times a week, 2 weeks on /1 week off
B2207	Multi-center, open-label, dose-escalation *Primary*: Determination of MTD of PAN *Secondary*: Safety and tolerability, PK and PD of biomarkers, preliminary efficacy	15 relapsed or relapsed and refractory, including BTZ refractory	Until progression	20 mg PAN three times a week, 2 weeks on / 1 week off (for expansion phase) Different doses of PAN in the dose escalation phase

BTZ: bortezomib; Dex: dexamethasone; DOR: duration of response; MR: minimal response; MRR: minimal response rate; MTD: maximum tolerated dose; nCR: near complete response; ORR: overall response rate; OS: overall survival; PAN: panobinostat; PD: pharmacodynamics; PFS: progression free survival; PK: pharmacokinetics; QoL: quality of life; TTP: time to progression; TTR: time to response

1. In addition to panobinostat, patients received 1.3 mg/m^2 BTZ and 20 mg Dex

Source: NDA 205353

As noted in the Table 1, there are different cut-off dates of datasets, as indicated in the Table 3. This safety analyses are primarily using the data from cut-off date for safety update.

Table 3 Data cut-off dates for the Studies included in the safety update

Trail ID	Cut-off date For NDA submission	Number of patients in treatment at the NDA cut-off date	Cut-off date for safety update
B2207	Aug 10, 2011	8[1]	Oct 7, 2013[2]
DUS71	Dec 4, 2012	2	Feb 26, 2014[2]
D2308	Sep 10, 2013	0	Mar 15, 2014

1. Four patients were still on-treatment in the dose expansion phase (part of MM combination pool) and four patients in the dose escalation phase (not part of the MM combination pool).
2. Final database lock; the trial completed

Source: NDA 205353

Reviewer notes: All datasets submitted in this NDA cycle were derived. The sponsor did not provide any raw datasets related to this NDA for FDA assessment. Therefore, the reliability of the derived datasets in relation to the raw datasets could not be verified.

The efficacy and safety population of study D2308 are identical at both data cut-off dates. However, the adjudicated efficacy and safety population were different. The analyses included in this review used adjudicated safety population (ASP) at the cut-off date for safety update.

It is noteworthy that the safety profile for study D2308 between the cut-off dates of the original NDA and the safer safety update are not significantly different. The safety data collected after the cut-off date of Sep 10, 2013 for Study D2308 were limited to a few deaths and severe adverse events.

Table 4: Patient Population in various datasets of trial D2308:

BTZ+Dex+	Sep 10, 2013 cut-off		Mar 15, 2014 cut-off[1]		Adjudicated[2]	
	Randomized	Treated	Randomized	Treated	Randomized	Treated
PAN	382	380	382	380	382	381
PBO	378	376	378	376	376	377
Registered	9	13	9	13	n/a	n/a

1. Although the patient number did not change at the safety update cut-off, 8 more adverse events were added to the datasets of AAEV.xpt.
2. The sponsor adudicated datasets with specific adverse events, such as diarrhea, ischemic heart disease, and hypokalemia with adjudicated numbers of randomized and treated patients per clinical pharmacology team request.

Source: NDA 205353

3.2 The specific safety profile of study D2308

Using adjudicated safety population, the Table 5 summarized the event frequency of and number of patients with diarrhea, cardiac, and electrolytes adverse events. In patients received panobinostat treatment, adverse events of specific interest were noted as following:

- Nine hundreds forty-five diarrhea events, of which 166 were Grade 3/4, occurred in a sum of 264 (70%) patients;
- Ninety-seven cardiac events occurred in 68 patients (18%) and of which, 24 Grade 3/4 events occurred in 20 patient (5%)
- Forty-one electrolytes (Na, Cl, Ca, Mg, P and glucose) occurred in 25 (7%) patients.

Table 5: Summary of specific adverse events (diarrhea, cardiac and electrolytes) of study D2308 (ASP, 3/15/2014 cut-off)

Specific adverse events (Mar 15, 2014 cut-off)	**Any Events**				**Number of Patients with Events**			
Treatment groups: BTZ+Dex+	**PAN**		**PBO**		**PAN N=381(%)**		**PBO N=377 (%)**	
Grade	**All**	**3/4**	**All**	**3/4**	**All**	**3/4**	**All**	**3/4**
Any AEs	11202	2745	7430	1359	381 (100)	367 (96.3)	372 (98.6)	*307 (81.4)*
Diarrhea[1]	945	166	400	42	264 (69.5)	*98 (25.7)*	153 (40.7)	*29 (7.7)*
Cardiac events[2]	97	24	51	14	68 (17.8)	*20 (5.2)*	39 (10.3)	*13(3.4)*
Abnormal cardiac test reported as AEs	20	0	18	1	16 (4.2)	*0*	14 (3.7)	*1 (0.3)*[3]
Abnormal ECG reported as AEs	12	0	11	1	11 (2.9)	*0*	9 (2.4)	*1 (0.3)*[3]
QT prolongation	8	0	9	1[3]	7 (1.8)	*0*	7 (1.9)	*1 (0.3)*
Recorded abnormal ECGs readings not present on baseline and pre 1st dose[4]								
Incidences of abnormal ECG	186	n/a	96	n/a	33 (8.7)	*n/a*	23 (6.1)	*n/a*
Types of abnormal ECG	41	n/a	14	n/a				
QT prolongation	51	n/a	41	n/a	12 (3.1)	*n/a*	7 (1.9)	*n/a*
Electrolytes abnormalities by AEs[5]	41	10	22	16	25 (6.6)	*9 (2.3)*	14 (3.7)	*10 (2.7)*
Hypomagnesemia	1	0	0	0	2 (0.5)	*0*	0	*0*
Hyperkalemia	1	0	0	0	1 (0.3)	*0*	0	*0*
Hypokalemia	10	2	4	2	5 (1.3)	*1 (<0.3)*	2 (0.5)	*1(0.3)*
Recorded lab Electrolytes testing results	n/a	n/a	n/a	n/a	n/a	*n/a*	n/a	*n/a*

1. MedDRA preferred term. It is noteworthy that Grade 2 diarrhea events were 261 for PAN and 95 for PBO arms. The number of patients who had at least one Grade 2 diarrhea event were 213 (55.9%) for PAN and 123 (32.6%) for PBO.
2. Any preferred term recorded under SOC for Cardiac disorders. Grade 2 cardiac events were 5.2%
3. This is the only Grade 3 QT prolongation reported.
4. ECG: dataset used Sep 10, 2013 cut-off, because no additional ECG data added to the safety update cut-off datasets. Total number of ECG were 23,852, including baseline, pre-dosing and 3 hours after dosing of each panobinostat cycle, and unscheduled. The post panobinostat ECG tests account for approximately 20, 542, of which, 1245 (6%) were unscheduled and 1,283 (6%) were uninterpretable due to technical problems or inadequate results, 284 ECG of 57 patients were abnormal. Because the frequent ECG monitoring, no QTc > 500 were observed, however, any QTc>480 triggered hold off panobinostat at any time of the treatment course, therefore, more and longer QTc prolongations may occurred post marketing. Recommend remove the sentence of (b) (4) from the labeling.
5. Electrolyte abnormality include Na, Cl, Ca, Mg, P and glucose recorded as Grade 1-4 adverse events. The actual data of abnormal laboratory testing results, although available, did not list sufficient reference information for safety analyses of this review.

Source: NDA 205353

The following subsections pertain to further details of specific interested adverse events.

3.2.1 Diarrhea

The diarrhea analyses used MedDRA preferred term for searching in the adjudicated safety population with the cut of date of March 15, 2014. The broader term search only involved an increase of a few number of event in less than 1% of patients. The events of and number of patients with diarrhea are summarized in Table 6 by toxicity grades. It is noteworthy that Grade 2 diarrhea events were 261 for PAN and 95 for PBO arms. The number of patients who had at least one Grade 2 diarrhea event were 213 (55.9%) for PAN and 123 (32.6%) for PBO.

Table 6: Diarrhea events and patients with diarrhea events by grade (ASP, 3/15/2014 cut-off)

Grades	Total	PAN+BTZ+Dex N = 381 (%)	PBO+BTZ+Dex N = 377 (%)
Number of diarrhea events, any grade			
1	781	518	263
2	356	261	95
3	201	161	40
4	7	5	2
Number of patients with at least one diarrhea events, any grade			
1	164	89 (23.4)	75 (19.9)
2	126	77 (20.2)	49 (13.0)
3	120	93 (24.4)	27 (7.2)
4	7	5 (1.3)	2 (0.5)

Source: NDA 205353

Of the 70% patients with diarrhea, Grade 1, 2 and 3 were about third each. Therefore, 2/3 of patients with diarrhea in the panobinostat treatment group were Grade 1 or Grade 2. The sponsor proposed label described diarrhea as 68%, which was based non-adjudicated safety population at the Sep 10, 2013 cut-off resulting a <2% lower incidence in all grades and <1% incidence in Grade 3/4. This does not significantly change the safety profile regarding diarrhea.

3.2.2. Electrolyte abnormality

The overall electrolyte abnormalities, including Na, Cl, Ca, Mg, P and glucose, are summarized in Table 7 by toxicity grades. The overall reported frequency of electrolyte abnormalities from study D2308 are only 7%. The electrolyte abnormalities by each grade are less than 3 %. The electrolyte imbalances that most likely related to a cardiac event are even lower, such as 0.5% for hypomagnesemia, 0.3% for hyperkalemia and 1.3% for hypokalemia in the panobinostat treated group (Table 5). Each treatment group, panobinostat and placebo, reported one patient with Grade 3 hypokalemia. It is unexpected that hypomagnesemia, which is the toxicity of the class of histone

deaccetylase, were only 2 cases reported in the panobinostat group. No Grade 3 or higher hypomagnesemia reported in either treatment group.

Table 7: Electrolyte abnormal events and patients with events by grades (ASP, 3/15/2014 cut-off)

Grades	Total	PAN+BTZ+Dex N = 381 (%)	PBO+BTZ+Dex N = 377 (%)
Number of cardiac events, any grade			
1	27	23	4
2	10	8	2
3	25	10	15
4	1	0	1
Number of patients with cardiac events, any grade			
1	13	11 (2.9)	2 (0.5)
2	7	5 (1.3)	2 (0.5)
3	18	9 (2.4)	9 (2.4)
4	1	0	1 (0.2)

Source: NDA 205353

In addition to reported adverse events of electrolytes, there is a laboratory dataset (alrs.xpt) available. The dataset alrs.xpt included all the baseline laboratory data and changes above or below normal limits. However, this dataset did not include patient identification number and, therefore, it cannot be used for our analyses.

3.2.3 Cardiac events

In patients in the panobinostat treated group, the cardiac events were 7 % for Grade 1, 5% for Grade 2, 3% for Grade 3 and 2% for Grade 4, as described in Table 8. Total 46 cardiac events occurred in 28 patients who received panobinostat. Among these events, QTc prolongations reported as adverse events were 2% for both panobinostat and placebo groups (Table 5). The only one Grade 3 adverse event of QTc prolongation reported was from the placebo group (Table 5). Per protocol design, patients had ECG test at baseline and pre-dosing of each cycle. Panobinostat was withheld if pre-dosing QTc was >480 mscs (CTCAE Grade 2), which might prevent any Grade 3 QTc-prolongation occur during the trial. Therefore, the sponsor-proposed labeling statement, "(b) (4) is promotional and should be removed. The dose withholding strategy should be included in the labeling.

Table 8: Numbers of cardiac events and patients with events (ASP, 3/15/2014 cut-off)

Grades	Total	PAN+BTZ+Dex N = 381 (%)	PBO+BTZ+Dex N = 377 (%)
Number of cardiac events, any grade			
1	69	46	23
2	41	27	14
3	21	13	8
4	17	11	6

Number of patients with cardiac events, any grade			
1	41	28 (7.3)	13 (3.4)
2	33	20 (5.2)	13 (3.4)
3	20	12 (3.1)	8 (2.1)
4	13	8 (2.1)	5 (1.3)

Source: NDA 205353

A dataset, aecg.xpt, collected ECG abnormality descriptions, which might or might not report as AEs. Although our analyses on ECG abnormal description used the dataset, aecg.xpt, with March 15, 2014 cut-off date, no additional ECG data was added to the safety update cut-off datasets since the Sep 10, 2013 cut-off date.

Total number of ECG collected were 23,852, including baseline, pre-dosing and 3 hours after dosing of each panobinostat cycle, and unscheduled. The ECG tests at post panobinostat dosing account for approximately 86% (20, 542), of which, 1245 (6%) were unscheduled and 1,283 (6%) were uninterpretable due to technical problems or inadequate results. Among the post dosing ECGs, 282 ECGs from 55 patients were abnormal.

There was 9% abnormal post-dosing ECGs in the panobinostat group compared to 6% in the placebo group (Table 5). For QTc prolongation, there were 3% described in the panobinostat group compared to 2% described in the placebo group. It is not clear whether the QT prolongation in the panobinostat group were accurately reported as adverse events.

In addition, it is worth reiterating that because the frequent ECG monitoring, any QTc >480 mscs triggered interuption of panobinostat use at any time of the treatment course, therefore, only one Grade 3 QTc prolongation recorded in the trial. However, more and longer QTc prolongations may occurred post marketing. Recommend remove the sentence of "(b) (4)" from the labeling and implement withholding panobinostat for QTc>480 mscs.

3.2.4 Analyzing the relationship between the diarrhea, electrolyte abnormality and cardiac events

As shown in Table 9, there is a trend of more patients with more than one adverse events of our interest in the panobinostat group. In the panobinostat group, the frequency of patients having combination of two events were 18% for diarrhea with either a cardiac event or an abnormal ECG description, 13% for diarrhea with a cardiac event, 7% for diarrhea with an abnormal ECG description, 9% for abnormal electrolytes with an abnormal ECG description, 1% for abnormal electrolytes with a cardiac event, and 2% for diarrhea with both cardiac event and abnormal ECG description. However, the frequency of all 3 AES, diarrhea, electrolyte abnormality and cardiac events occurred simultaneously in the same patient was less than 1% (total 4 cases, 3 in PAN arm and 1 in PBO arm).

Table 9: Coincidence of diarrhea, electrolyte abnormality, cardiac event, and/or ECG abnormality in the same patient (ASP, 3/15/2014 cut-off)

Events that a patient having	PAN+BTZ+Dex N = 381 (%)	PBO+BTZ+Dex N = 377 (%)
Diarrhea with both electrolyte abnormality and cardiac events	3 (0.8)	1 (0.3)
Diarrhea with either cardiac event or abnormal ECG description	70 (18.4)	23 (6.1)
Diarrhea with cardiac event	51 (13.4)	15 (4.0)
Diarrhea with abnormal ECG description	26 (6.8)	10 (2.7)
Any electrolyte abnormality[1] with abnormal ECG description	33 (8.7)	23 (6.1)
Any electrolyte abnormality[1] with cardiac event	5 (1.3)	2 (0.5)
Diarrhea with both cardiac event and abnormal ECG description	7 (1.8)	2 (0.5)

1. Electrolyte abnormality include Na, Cl, Ca, Mg, P and glucose recorded as Grade 1-4 adverse events.
Source: NDA 205353

Further review on the available CRFs and patient adverse event listing, we are not able to identify a clear sequential timing of the events in the same patient. Furthermore, the factors clearly confound the causality determination existed in majority of these cases, such as the end organ abnormality from underlying multiple myeloma. Although it is difficult to establish a causal relationship, in theory and with clinical experience, severe diarrhea could cause electrolyte abnormalities, which could further exacerbate the cardiac toxicity. Therefore, the safety team suggests this information to be included in the labeling.

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/s/

QIN C RYAN
02/19/2015

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

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

Memorandum

Date: January 23, 2015

To: Diane Hanner
Regulatory Project Manager
Division of Hematology Products (DHP)

From: Adam George, PharmD. Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Acting Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for NDA #205353
Farydak® (panobinostat) capsules, for oral use

In response to your consult dated March 27, 2014, we have reviewed the draft PI for Farydak (panobinostat) capsules, for oral use and offer the following comments. OPDP has made these comments based on review of the January 21, 2015 version of the substantially complete labeling. Please note that OPDP's comments pertaining to the Information for Patients and Caregivers (also known as patient prescribing information) were communicated in the joint consult response with the patient labeling group dated October 10, 2014.

Section	Statement from draft	Comment
12.2 Pharmacodynamics	(b) (4)	
		In addition, OPDP recommends deleting this sentence from section 12.2 as it is not supported by adequate evidence.

Section	Statement from draft	Comment
		According to section 2.2.2 of Dr. Joseph Grillo's Clinical Pharmacology Review: "In PK trials the primary pharmacodynamic biomarker was the level of histone acetylation in a surrogate tissue (i.e., peripheral blood mononuclear cells [PBMC]). PBMC was used because the applicant found collecting serial biopsies from patients for PD assessments challenging compared to the preclinical studies in animal models. Unfortunately, a robust pharmacokinetic/pharmacodynamic (PK/PD) analysis could not be performed due to limitations in the sample matrix (i.e., quality PBMC isolation), and that lack of a well characterized and qualitative assay. Consequently, the investigation of the PD of PAN relies mainly upon the clinical safety and efficacy endpoints in this application."

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/s/

ADAM N GEORGE
01/23/2015

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

PATIENT LABELING REVIEW

Date:	October 9, 2014
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)** Robert Kane, MD Deputy Director for Safety **Division of Hematology Products (DHP)**
Through:	Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nathan Caulk, MS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adam George, PharmD. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	FARYDAK (panobinostat)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 205-353
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On March 24, 2014, Novartis Pharmaceuticals Corporation submitted for the Agency's review an original New Drug Application (NDA) 205-353 for FARYDAK (panobinostat) capsules. The proposed indication for FARYDAK (panobinostat) capsules is for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy, in combination with bortezomib and dexamethasone.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on September 25, 2014, and March 27, 2014 respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for FARYDAK (panobinostat) capsules.

2 MATERIAL REVIEWED

- Draft FARYDAK (panobinostat) capsules PPI received on March 24, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 25, 2014.
- Draft FARYDAK (panobinostat) capsules Prescribing Information (PI) received on March 24, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 25, 2014.
- Approved BELEODAQ (belinostat) comparator labeling dated July 3, 2014.
- Approved ISTODAX (romidepsin) comparator labeling dated June 13, 2014.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

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

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
10/09/2014

ADAM N GEORGE
10/10/2014

BARBARA A FULLER
10/10/2014

LABEL AND LABELING REVIEW

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

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

Date of This Review:	September 11, 2014
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 205353
Date of Submission:	March 24, 2014 and July 11, 2014
Product Name and Strength:	Farydak (Panobinostat) Capsules, 10 mg, 15 mg, 20 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novartis
OSE RCM #:	2014-691
DMEPA Primary Reviewer:	Michelle Rutledge, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD
DMEPA Deputy Director:	Todd Bridges, PharmD

1. REASON FOR REVIEW

This review evaluates the proposed product design, blister label, shell and carton labeling, physician samples labeling, and prescribing information for Farydak for areas of vulnerability that could lead to medication errors. The Applicant intends to market this product under NDA 205353 for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy, in combination with bortezomib and dexamethasone.

2. MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FAERS	B – N/A
ISMP Newsletters	C
Previous DMEPA Reviews	D
Human Factors Study (if applicable)	E – N/A
Other (if applicable)	F – N/A
Container Label, Carton Labeling, and Instructions for Use or Medication Guide (if applicable)	G

N/A = not applicable to this review

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The administration of this product is complicated due to the fact that a capsule should be taken once a day on days 1, 3, 5, 8, 10, and 12 of a 21 day cycle versus daily administration. As a result, it may be hard for patients to remember on which days they are supposed to take the drug. Therefore, Novartis placed a pre-printed dosing schedule on blister label and shell labeling. However, in some cases pre-printing dosing schedule on the labels and labeling may be problematic because some doses may have to be omitted due to suspected adverse reactions that can develop during therapy with this product, and later the same dose should be resumed (i.e., diarrhea Grade 2 and neutropenia Grade 3 or less).

We have considered whether not placing the dosing schedule on the label and labeling all together or placing a dosing schedule not tailored to dosage adjustments due to aforementioned ADEs is more error prone. Based on our risk assessment, it appears that not placing a pre-printed dosing schedule is more error-prone due to the fact that the administration of this product is complicated as explained above. Additionally, for those cases,

where dose omissions are indicated, the dosage frequently should also be reduced. Thus, a new pack of a lesser strength should be started in many cases (e.g., diarrhea Grade 3, nausea or vomiting: Grade 3 nausea or Grade ¾ vomiting, Grade 4 neutropenia, etc.). However, since there will be situations when the dose will stay the same after a single dose omission, patient education regarding the correct schedule of administration of the product is also prudent and should be labeled.

In terms of medication error prone aspects related to labels and labeling, we note that the container labels lack prominence of cautionary statements such as "Swallow capsules whole with water and not to break, crush, or chew". Addition of these statements may help reinforce correct administration of the product. Therefore, we conclude that the proposed labels and labeling can be improved to increase readability, increase prominence of important safety information, and to provide clarity in the Dosing and Administration section of the prescribing information.

4. CONCLUSION & RECOMMENDATIONS

We reviewed the label and labeling, and product design, and identified that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. The Dosing and Administration Section includes the use of error-prone symbols[1]. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations[1] appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Therefore, please revise accordingly, for example, to read "greater than and equal to" instead of the use of symbols (≥).

2. We recommend adding a statement regarding patient counseling in Section 2.1 *Recommended Dosing* immediately below Table 2, such as, "Counsel patients on the correct schedule and correct technique of administration of FARYDAK and when to take FARYDAK in case dosing adjustments are needed." We recommend the addition of this statement due to complicated administration of this product.

[1] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 April 2]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

4.2 RECOMMENDATIONS FOR THE APPLICANT

B. 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.

C. 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.

D. 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.

E. 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 further questions or need clarifications, please contact Kevin Wright, OSE Project Manager, at 301-796-3621.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Farydak that Novartis submitted on July 11, 2014.

Table 2. Relevant Product Information for Farydak	
Active Ingredient	Panobinostat
Indication	In combination with bortezomib and dexamethasone is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy
Route of Administration	Oral
Dosage Form	Capsules
Strength	10 mg, 15 mg, 20 mg
Dose and Frequency	20 mg, taken once a day, on days 1, 3, 5, 8, 10 and 12, of a 21 days cycle
How Supplied	PVC/PCTFE blister packs with 6 capsules in each blister pack
Storage	Store at 25˚C (77˚F); excursions permitted to 15-30˚C (59-86˚F)

APPENDIX C. ISMP NEWSLETTERS

C.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on July 28, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
Date Range	July 28, 2014
ISMP Newsletter Search Strategy	Match Any of the words
Search Terms	Farydak

C.2 Results

Our search of ISMP did not yield any articles of medications errors associated with Farydak.

APPENDIX D. PREVIOUS DMEPA REVIEWS

D.1 Methods

We searched the L:Drive on July 28, 2014 using the terms, Farydak, to identify reviews previously performed by DMEPA.

D.2 Results

Our search did not identify any label and labeling reviews previously performed by DMEPA.

APPENDIX G. CONTAINER LABEL, CARTON LABELING, INSTRUCTIONS FOR USE, MEDICATION GUIDE

G.1 List of Label and Labeling Reviewed

We reviewed the most recent Farydak labels and labeling submitted by Novartis on July 7, 2014.

- Container label
- Carton label
- Physician samples
- Prescribing Information (not listed)

G.2 Label and Labeling Images

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

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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/

MICHELLE K RUTLEDGE
09/11/2014

YELENA L MASLOV
09/11/2014

TODD D BRIDGES
09/18/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: September 11, 2014

TO: CAPT Diane Hanner, M.P.H., M.S.W., Regulatory Project Manager
Barry Miller, M.Sc., C.R.N.P., Clinical Analyst
Nicole Gormley, M.D., Medical Officer
Virginia Kwitkowski, M.S., A.C.N.P.-B.C., Team Leader
Division of Hematology Products (DHP)

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

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 205353

APPLICANT: Novartis Pharmaceuticals Corporation

DRUG: panobinostat

NME: yes

THERAPEUTIC CLASSIFICATION/REVIEW: priority review

INDICATION: Treatment of adult patients with relapsed multiple myeloma

CONSULTATION REQUEST DATE:	April 24, 2014
INSPECTION SUMMARY GOAL DATE (original):	August 22, 2014
INSPECTION SUMMARY GOAL DATE (extended):	September 11, 2014
DIVISION ACTION GOAL DATE	September 22, 2014
PDUFA DATE:	November 24, 2014

I. BACKGROUND:

Standard first-line treatment for multiple myeloma patients with adequate performance status is a three to four month induction therapy with thalidomide plus high-dose dexamethasone or a combination regimen consisting of vincristine, doxorubicin and high-dose dexamethasone. This treatment is followed by autologous stem cell transplantation that is effective in up to 10% of multiple myeloma patients. Multiple myeloma patients who are not candidates for stem cell transplantation who have relapses or fail therapy are given chemotherapy alone with a regimen such as lenalidomide or bortezomib. Additional novel therapeutic options for the treatment of previously treated multiple myeloma are warranted for those who relapse or fail with available therapies.

Panobinostat is a potent orally active deacetylase (DAC) inhibitor that structurally belongs to a cinnamic hydroxamic acid class of compounds. Deacetylase enzymes may also target lysine groups on various non-histone proteins such as p53, α-tubulin, Hsp90, and HIF1-α.

A single adequate and well-controlled clinical trial was submitted in support of the applicant's NDA. A single domestic and a single foreign clinical study site were selected for audit, since these sites represented the largest enrolling sites.

Protocol CLBH589D2308
Study CLBH589D2308 was a Phase 3, randomized, double-blind, placebo-controlled, parallel group, multinational study comparing progression free survival in patients who received panobinostat, bortezomib, and dexamethasone or placebo, bortezomib, and dexamethasone, following recurrence or progression of disease following one to three previous lines of therapy and not refractory to bortezomib. The primary study endpoint was PFS defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause.

II. RESULTS:

Name of CI Location	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Classification*
Robert Schlossman, M.D. Dana Farber Cancer Institute 44 Binney Street Boston, MA 02115	CLBH589D2308/ Site #561 N=11	June 18-24, 2014	Preliminary: NAI
Vania Hungria, M.D. Irmandade da Santa Casa de Misericordia de Sao Paulo Rue Cesario Mota Junior 112 Sao Paulo, Brazil 01224-000	CLBH589D2308/ Site #262 N=17	July 28-August 1, 2014	Preliminary: VAI
Sponsor: Novartis Pharmaceuticals Corporation One Health Plaza East Hanover, NJ 07936-1080	Sponsor monitoring of the clinical trial, Protocol CLBH589D2308	July 15-August 5, 2014	Preliminary: VAI

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

CLINICAL STUDY SITE INVESTIGATOR

1. Robert Schlossman, M.D./Protocol CLBH589D2308/Site 561
Boston, MA

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from June 18 to 24, 2014. A total of 12 subjects were screened and 11 subjects were enrolled. Two subjects completed Treatment Phase 1 and two subjects completed Treatment Phase 2 of the study. An audit of 12 screened subjects' records was conducted.

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

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

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Vania Hungria, M.D./Protocol CLBH589D2308/Site 262
Sao Paulo, Brazil

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from July 28 to August 1, 2014. A total of 22 subjects were screened and 17 subjects were enrolled. Five subjects completed the study. An audit of nine enrolled subjects' records was conducted.

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

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

A Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection. In general, the study was not conducted in accordance with the investigational plan. Specifically, the clinical site principal investigator (PI) did not adequately supervise the site. A sub-investigator:

i. Committed numerous protocol deviations, e.g., not performing complete physical exams at screening in 11 of the 17 enrolled subjects; not completing ECGs for five of the 17 enrolled subjects; completing treatment cycles in less

than the protocol-required 21 days in two of the 17 enrolled subjects, and not adjusting medication doses for adverse events, as per protocol, in five of the 17 study subjects.

ii. Did not accurately complete case report forms according to the data in the source documents for the five of the 17 enrolled subjects.

iii. Did not report adverse events for three of the 17 enrolled subjects in a timely manner.

The sub-investigator was dismissed from further participation in this study when the PI discovered that an SAE in a hospitalized patient was not reported. Dr. Vania Hungria notified Novartis about this incident. As a consequence the sponsor (Novartis) monitored the site closely and retrained the site.

The PI responded adequately to the Form FDA 483 in a letter dated August 15, 2014. Specifically, following the dismissal of the sub-investigator, Dr. Hungria implemented the following corrective and preventive actions: (a) To ensure data integrity for this study, all clinical research and hospital chart information were reviewed by the PI (Note: all the study subjects who were enrolled in Study CLBH589D2308 were under the PI's direct medical supervision prior to enrolling in the study), (b) A new sub-investigator who was properly trained to handle issues related to Protocol CLBH589D2308 was assigned to this study protocol, , and (c) The site staff and the PI were retrained on the following topics: (i) Good Clinical Practice-ICH, (ii) Good Documentation Practices (ALCOA- attributable, legible, contemporaneous, original and accurate), (iii) Training and Delegation , and (iv) Protocol Review in two training sessions (March 2013 and April 2013), with a required post-training examination minimum pass score.

Based on the field investigator report, data discrepancies between source documents and case report forms were recently reported to the sponsor. The database was unlocked by the sponsor and changes were made to raw data for seven of the 17 subjects at this site. Examples of the edited safety data include the following: (1) Subject 002 - Grade 1 neuropathy was not reported as continuing, (2) Subject 017 - case report form entry indicated that thrombocytopenia was not related to the study drug, but the source document stated that the adverse event was "suspected" to be related to study drug, (3) Subject 022 - Grade 1 diarrhea was not reported as "continuing". Additionally, for efficacy assessment, two subjects (Subject 012 and Subject 014) had source documentation for M-protein electrophoresis results that were not previously reported in the case report forms added to the database.

OSI reviewer comments:

As far as drug safety assessment is concerned, the recently identified discrepancies in AE reporting appear to be minor. Adverse event information has been conveyed by the site to the sponsor who has reportedly updated the database and provided the adverse events report to FDA. The DHP review team concurs with OSI.

OSI had a concern regarding the reporting of additional M-protein electrophoresis results, since these results are a component of the efficacy endpoint. On August 29, 2014, OSI and DHP had a teleconference to discuss concerns about whether recent reporting of M-protein electrophoresis might have an effect on efficacy endpoint determination (i.e. progression-free survival data). There was also a concern that there might be additional clinical sites where data were being updated. On August 29, 2014, DHP sent an Information Request to the sponsor requesting information about the reported "unlocking" of the database. DHP notified OSI on September 8, 2014, about the sponsor's response.

The sponsor acknowledged that data discrepancies at Site 262 led to a decision to "unlock" the database and this was proactively reported to the ORA field investigator conducting the sponsor inspection at Novartis. The sponsor also confirmed that no other clinical study sites notified them of any planned data changes or performed data changes.

Two subjects at Site 262 (Subjects 012 and 014) had a total of four M-protein electrophoresis results added to the database. Investigator assessment of response for these two subjects was not altered on the basis of these results.

The sponsor's next database lock and extraction of datasets is planned for September 22, 2014. This date will be the planned interim analysis for overall survival, corresponding to approximately 90% of the overall survival events. The sponsor states that they will investigate any changes made to data prior to the September 10, 2013, cut-off date (as had been done for Site 262).

Finally, the clinical investigators and the study patients in Study CLBH589D2308 remain blinded to study drug treatment, per sponsor's procedures, SOP-7012380 (PSP 009) Version 3.0, entitled "Randomization, Blinding, Unblinding and Interactive Response Technology (IRT) (PSP 009)". The study follow-up continues for all patients for overall survival.

c. Assessment of data integrity:
The regulator deficiency and protocol violations identified at this site have been attributed to a sub-investigator who was removed from the study. Data discrepancies between source documents and information reported to the sponsor are minor and have been reported to FDA by the sponsor as protocol violations. Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR

3. Novartis Pharmaceuticals Corporation
East Hanover, NJ

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.810, from July 15 to August 5, 2014. The inspection evaluated the following: documents related to

study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, training of staff and site monitors.

b. General observations/commentary:
The sponsor generally maintained adequate oversight of the clinical trial. For the most part, monitoring of the investigator sites was adequate. Appropriate steps were taken by the sponsor to bring noncompliant sites into compliance. There was no evidence of under-reporting of adverse events.

A Form FDA 483 was issued at the end of the sponsor inspection. The following observations were noted:

i. The sponsor did not provide the Agency with a written IND safety report in a timely manner. Specifically, a Suspected Adverse Reaction of pulmonary hypertension was reported to the sponsor on January 14, 2013, but the Agency was not notified until March 15, 2013 which is outside of the protocol-required 15 calendar day window. Additionally, participating investigators were not promptly informed about new adverse effects. This observation was related to the previously described event reported to investigators on March 1, 2013, outside the protocol-required 15 calendar day window.

ii. The sponsor failed to properly monitor the study. Specifically, for Site #561, there were no Monitoring Visit Reports for February 2, February 24, March 26, March 28, and May 9 and 10, 2012). Additionally, monitoring visits were not conducted every four to six weeks at Site #561 (e.g. a monitoring visit conducted on August 29, 2012 was conducted approximately 16 weeks after the last visit on May 10, 2012).

OSI reviewer comments:
The sponsor responded adequately with a corrective and preventive action plan in a letter dated August 25, 2014.

Although delayed, the pulmonary hypertension adverse event was ultimately reported to the NDA and does not impact data integrity. The sponsor conducted a root cause analysis of the delayed reporting and has modified their processing of case reporting and retrained personnel.

For the monitoring visits that were not done for Site 561, these inspectional observations were not considered critical. Based on the clinical site inspection, there were no indications that the site was noncompliant; in fact, all serious adverse events and progression free survival calendar entries in Site 561 for the primary efficacy endpoint were documented adequately, as determined by the clinical investigator response assessments (Note: per the modified EMBT criteria for multiple myeloma, [i.e., relapse from complete remission (CR) or progressive disease (PD) for those patients not in complete remission]).

Specifically, the sponsor has implemented the following corrective actions, in part, to improve control over the monitoring visit reporting process: (a) communication to all Clinical Research Associates, emphasizing that the criticality of ensuring Monitoring Visit Reports were written for each visit as required, (b) communication to all Clinical Research Associate managers, reinforcing the importance of checking for completion of Monitoring Visit Reports, and (c) implementation of quality checks by the sponsor's Oncology Global Monitoring Operations, in the two countries in which missing reports were identified (i.e., U.S. and Germany), that required managers to review monitoring logs and to ensure corresponding reports.

c. Assessment of data integrity:
Notwithstanding the above minor regulatory deficiencies, the sponsor monitoring appeared reliable. Data submitted by this sponsor appear acceptable in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this Phase 3, randomized, double-blind, placebo-controlled, parallel group study submitted in support of this NDA, two clinical sites were inspected. The sponsor (Novartis) was also inspected.

The preliminary regulatory classification for Dr. Robert Schlossman is No Action Indicated (NAI). The preliminary regulatory classification for Dr. Vania Hungria is Voluntary Action Indicated (VAI). The preliminary regulatory classification for the Novartis Pharmaceuticals Corporation audit is Voluntary Action Indicated (VAI). The study data collected from this clinical site appears reliable in support of the requested indication.

Note: *The inspectional observations noted above are based on preliminary communications with the field investigator and/or preliminary review of the EIR. A clinical inspection summary addendum will be generated, if conclusions on the current inspection report changes significantly, upon receipt the Establishment Inspection Report (EIR). CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.*

{See appended electronic signature page}

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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/

ANTHONY J ORENCIA
09/11/2014

JANICE K POHLMAN
09/11/2014

KASSA AYALEW
09/11/2014

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 30, 2014

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Diane Hanner, RPM
DHP

Subject: QT-IRT Consult to NDA 205353

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated March 27, 2014 regarding sponsor's findings on the risk of QT prolongation in their trials and proposed QT related labeling. The QT-IRT received and reviewed the following materials:

- Your consult
- QT-IRT's Previous Reviews under IND 69862 (2/11/2008, 3/19/2008, 9/23/2008, 9/28/2009 and 8/9/2010), (b) (4) and IND 67091 (5/16/2008)
- Proposed labeling
- Summary of Clinical Pharmacology Studies

QT-IRT Comments for DHP

The labeling language related to the QT risk appears to be adequate in mitigating risk after drug is approved to be marketed (please see our minor edits in the following). The sponsor's exposure-QTc analysis is not reliable because the QT prolongation is dose but not concentration dependent. Although the case of TdP was only noted with consecutive IV dosing, which has been discontinued, and plasma concentrations are lower with oral dosing, we would like to bring to

the division's attention that TdP risk has not been included in the proposed label. We defer final labeling decisions to the Division.

2 DOSAGE AND ADMINISTRATION

(b) (4)

5 WARNINGS AND PRECAUTIONS

(b) (4)

(b) (4)

6 ADVERSE REACTIONS

(b) (4)

7 DRUG INTERACTIONS

7.4 (b) (4)

Concomitant use of anti-arrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol) and other drugs that are known to prolong the QT interval (including, but not limited to chloroquine, halofantrine, clarithromycin, methadone, moxifloxacin, bepridil and pimozide) is not recommended. Anti-emetic drugs with known QT prolonging risk, such as dolasetron, ondansetron, and tropisetron should be used with careful ECG follow-up *[see Warnings and Precautions (5.4, 5.5)]*.

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

(b) (4)

17 PATIENT COUNSELING INFORMATION

(b) (4)

Inform patients to report chest pain or discomfort, changes in heart beat (fast or slow), palpitations, lightheadedness, fainting, dizziness, blue discoloration of lips, shortness of breath, and swelling of lower limbs or skin as these may be warning signs of a heart problem.

BACKGROUND

Panobinostat (LBH589) is a histone-deacetylase inhibitor (DACi). It is currently proposed, in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy. The proposed dosing regimen is 20 mg once daily orally, 3 times a week (days 1, 3, 5, 8, 10, 12), on a 2 weeks on 1 week off cycle.

The QT-IRT has been consulted on several occasions regarding ECG monitoring plans for panobinostat.

Appears This Way On Original

Panobinostat has been associated with QTc prolongation and one patient developed

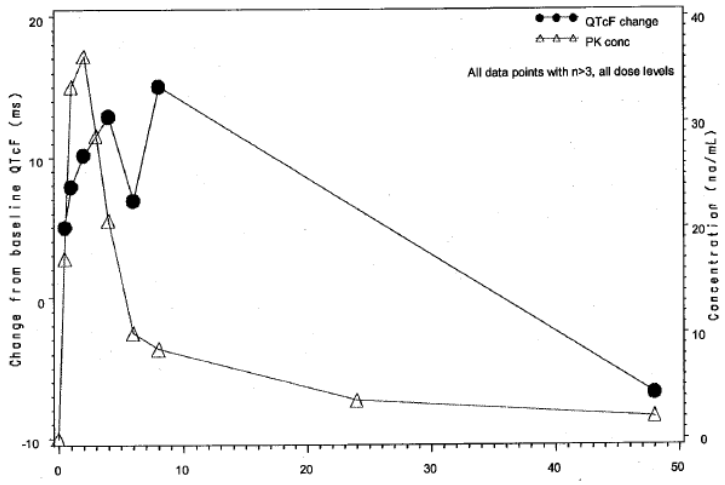
Summary of findings from previous reviews by the QT-IRT

1. Administration of panobinostat by i.v. and oral routes causes a dose-related increase in the QT interval. There has been one case of TdP TdP with the 20 mg/m^2 consecutive intravenous dosing regimen which has been discontinued. This property is probably a class effect of HDAC inhibitors.

2. The QT effect appears to occur hours after Tmax of the parent drug, so the effect is not dependent on the concentration of the parent drug (see the following figure). The mechanism for this delayed effect is unknown. It is possible that this delayed effect occurs due to metabolites, delayed myocardial distribution or due to hERG trafficking. The division (DDOP) determined that further non-clinical studies to elucidate the mechanism for this delayed effect were not required. The sponsor has conducted a hERG trafficking study for the parent drug which was negative (reviewed by DCRP pharmacologist Dr. James Willard under IND 69862).

3. Intensive ECG monitoring and other procedures for risk minimization where panobinostat is being administered as monotherapy or combination chemotherapy has been incorporated in various protocols by the sponsor in consultation with the review division.

Figure 1-3 **QTcF change from baseline over time vs. panobinostat conc-time course following the first oral panobinostat doses of a MWF schedule**



In the current NDA submission, the incidence of grade 3 QTc prologation (QTcF > 500 ms) with intermittent dosing is about 1% with the highest frequency of <5% seen in patients treated with the 60-mg oral dose. The relationship between plasma panobinostat concentration and heart-rate corrected QTc prolongation was explored using a linear mixed-effect model with the time-matched (within 60 minutes) conc-QT data in 499 patients from 12 pooled single-agent studies with oral doses between 10 and 80 mg. Contribution of BJB432, one of panobinostat's metabolites whose IC50 was 1.6 μM in the hERG channel assay towards QTcF prolongation was also investigated in 140 patients from two studies.

In the proposed label, QT related language was included in the following sections:

2 DOSAGE AND ADMINISTRATION

(b) (4)

(b) (4)

5 WARNINGS AND PRECAUTIONS

(b) (4)

6 ADVERSE REACTIONS

(b) (4)

(b) (4)

7 DRUG INTERACTIONS

7.4 (b) (4)

Concomitant use of anti-arrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol) and other drugs that are known to prolong the QT interval (including, but not limited to chloroquine, halofantrine, clarithromycin, methadone, moxifloxacin, bepridil and pimozide) is not recommended. Anti-emetic drugs with known QT prolonging risk, such as dolasetron, ondansetron, and tropisetron should be used with caution [see Warnings and Precautions (5.4, 5.5)].

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

(b) (4)

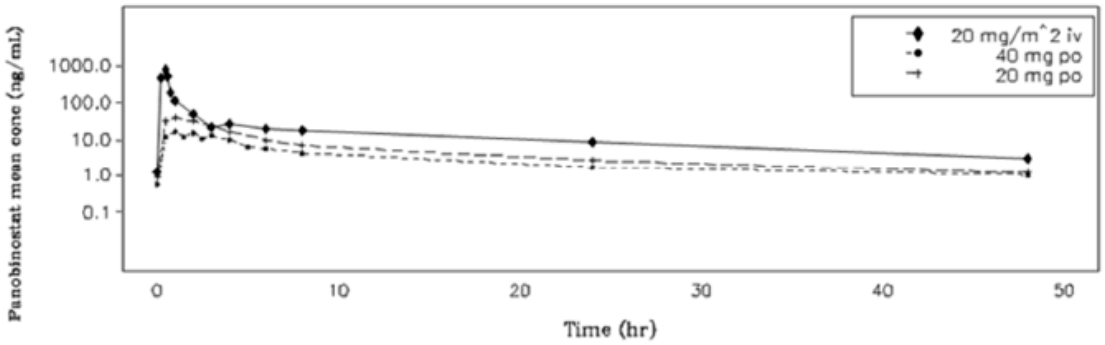
17 PATIENT COUNSELING INFORMATION

(b) (4)

Inform patients to report chest pain or discomfort, changes in heart beat (fast or slow), palpitations, lightheadedness, fainting, dizziness, blue discoloration of lips, shortness of breath, and swelling of lower limbs or skin as these may be warning signs of a heart problem.

Reviewer's comments: The labeling language related to the QT risk seems adequate in mitigating risk after drug is approved to be marketed. The sponsor's exposure-QTc analysis is not reliable because the QT prolongation is dose but not concentration dependent. Although the case of TdP was only noted with consecutive IV dosing, which has been discontinued, and plasma concentrations are lower with oral dosing (see figure below), we would like to bring to the division's attention that TdP risk has not been included in the proposed label.

Figure 3-1 **Mean panobinostat plasma concentration-time curves following a single i.v. and oral dose, full time scale**



Thank you for requesting our input into the development of this product under NDA 205353. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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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/

JIANG LIU
06/30/2014

NORMAN L STOCKBRIDGE
06/30/2014

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

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

Application: NDA 205353

Application Type: New NDA - NME

Name of Drug/Dosage Form: FARYDAK® (panobinostat) 10 mg, 15 mg, and 20 mg Capsules

Applicant: Novartis Pharmaceuticals Corporation

Receipt Date: March 24, 2014

Goal Date: November 24, 2014

1. Regulatory History and Applicant's Main Proposals

This submission is for panobinostat (LBH589), bortezomib and dexamethasone in patients with relapsed and/or refractory multiple myeloma (MM). The primary objective is to assess the safety of panobinostat in combination with bortezomib and dexamethasone in patients with multiple myeloma who have received at least 1 prior line of therapy.

The orphan drug designation in multiple myeloma was granted on August 20, 2012.
The Type C Clinical Pharmacology meeting was held on March 3, 2010.
Another Type C meeting was held on February 29, 2012 to discuss MM.
The Pre-NDA meeting for MM was held on February 5, 2014.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

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

The following minor labeling issues were identified in this PI:

1. *The revised date will need to be updated since it currently reads "Revised: 3/2014." This will be corrected upon completion of the revisions to the label.*
2. *At the end of the Table of Content (TOC): "*Sections or subsections omitted from the full prescribing information are not listed." A period needs to be added at the end of this statement.*
3. *Section 15 References is omitted which is acceptable.*

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant coveyed to the applicant during the label negotiations.

Appendix

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

Highlights

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

HIGHLIGHTS GENERAL FORMAT

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Comment: *There is white space between the HL Heading and HL Limitation Statement. The Applicant will be requested to remove the white space.*

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

Comment:

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

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Selected Requirements of Prescribing Information

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

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

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

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

Comment:

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

Comment:

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

Comment:

Indications and Usage in Highlights

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

Comment:

Dosage Forms and Strengths in Highlights

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

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

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

Comment:

Adverse Reactions in Highlights

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

Comment:

Patient Counseling Information Statement in Highlights

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

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

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

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

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

Comment:

Revision Date in Highlights

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

Comment: *The revised date will need to be updated since it currently reads "Revised: 3/2014"*

Contents: Table of Contents (TOC)

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

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

Comment:

NO 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment: *The heading was not bolded but RPM made the correction.*

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

Comment:

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

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *Subsection 7.1, 7.2, 7.3, and 7.4 need to be revised as follows:*

7.1 Agents that May Increase FARYDAK Blood Concentrations

7.2 Agents that May Increase FARYDAK Plasma Concentrations

7.3 Agents Whose Plasma Concentration May Be Increased by FARYDAK

7.4 Agents for Which Anticipated Interactions Should Be Considered

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

Comment:

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

Comment: *Need to add a period at the end of the statement "*Sections or subsections omitted from the full prescribing information are not listed."*

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

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

Comment: *Section 15 References is omitted which is acceptable.*

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

Comment:

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

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

Comment:

BOXED WARNING Section in the FPI

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

Comment:

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

Comment:

CONTRAINDICATIONS Section in the FPI

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

Comment:

ADVERSE REACTIONS Section in the FPI

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

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

Comment:

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

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

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

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

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

Comment:

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

Comment:

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
05/22/2014

PATRICIA N GARVEY
05/22/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 205353 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
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): N/A		
Date of Application: March 22, 2014 Date of Receipt: March 24, 2014 Date clock started after UN:		
PDUFA Goal Date: November 24, 2014	Action Goal Date (if different): TBD	
Filing Date: May 23, 2014	Date of Filing Meeting: April 24, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): FARYDAK®, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***		☐ 351(a) N/A ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***		☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐ (b) (4)	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate	

	products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): 069862 and 067091

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐	X	N/A not on AIP list
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		Please note that this application has an Orphan Designation

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☒	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	☒	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: N/A- # years was not specified ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	The Applicant did not specify the # years they were requesting.
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☒	☐		

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

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		Note: electronic signature
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	This is an electronic submission. However, a field certification was included in the submission.
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☒	☐	Exempt since this is an orphan designated indication
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	☐	☒	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☐	☐	☒	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	Risk Management Plan has been submitted.
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	SENT 3-27-14
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	No consult necessary for OSE/DRISK
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	No consult necessary for OSE/DMEPA
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		N/A-This is not OTC
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☒	
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☒	

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

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☒	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	QT-sent 3-27-14 DSI-sent 4-24-14
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** *Type C-clin pharm meeting March 3, 2010 *Type C-EOP3 meeting February 29, 2012 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** Pre-NDA meeting October 8, 2008 Pre-NDA meeting February 5, 2014 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☐	X	

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 24, 2014

BLA/NDA/Supp #: NDA 205353

PROPRIETARY NAME: Farydak®

ESTABLISHED/PROPER NAME: Panobinostat

DOSAGE FORM/STRENGTH: 10 mg, 15 mg, and 20 mg

APPLICANT: Novartis Pharmaceuticals Corporation

PROPOSED INDICATION: FARYDAK®, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy

BACKGROUND: The panobinostat application was received on April 24, 2014 and it is indicated for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy. The orphan-drug designation was granted for the treatment of multiple myeloma on August 20, 2012.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Diane Hanner	Y
	CPMS/TL:	Ebla Ali Ibrahim	N
Cross-Discipline Team Leader (CDTL)	Virginia Kwitkowski		Y
Clinical	Reviewers:	Barry Miller & Adam George	Y
	TL:	Virginia Kwitkowski	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Erika Pfeiler	Y
	TL:	Bryan S. Riley	N

Clinical Pharmacology	Reviewer:	Joe Grillo/ Ping Zhao	Y
	TL:	Julie Bullock	Y
Biostatistics	Reviewer:	Chia-Wen Ko	Y
	TL:	Lei Nie	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Emily Place & Luan Lee	Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:		N/A
	TL:		N/A
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		N/A this is not a BLA
	TL:		N/A this is not a BLA
Product Quality (CMC)	Reviewer:	Danuta Gromek-Woods	Y
	TL:	Janice Brown	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Erika Pfeiler	Y
	TL:	Bryan S. Riley	Y
CMC Labeling Review	Reviewer:		N/A
	TL:		N/A
Facility Review/Inspection	Reviewer:	Vipul Dholakia	Y
	TL:		N
OSE/DMEPA (proprietary name)	Reviewer:	Michelle Rutledge	N
	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:	Suzanne Berkman Robottom	N
	TL:	Cynthia Lacivita	N

OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orencia	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers			
Other attendees	Edvardas Kaminskas; Kevin Wright; Nisha Patel; Wana Manitpistkul; Peter Waldron; Diane Leaman; Angelica Dorantes		

FILING MEETING DISCUSSION:

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

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

BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: Biopharmaceutic had issues for the 74 day letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: Review issues for 74-day letter noted.	☐ Not Applicable ☒ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: 3 inspections	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**: 	 ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO ☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	N/A
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): June 5, 2014

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Note: A "No filing review issues identified" letter will be issued because so far all of the filing review issues have already been sent to the sponsor as information requests. Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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
05/22/2014

PATRICIA N GARVEY
05/22/2014

PMR/PMC Development Template

PMR #1

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	205353
Product Name:	FARYDAK® (panobinostat, LBH589) capsules, 10 mg, 15 mg and 20 mg

PMR Description of trial:

2181-1: 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 International Myeloma Working Group (IMWG) criteria by investigator assessment. The trial should 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 report with full datasets.

Preliminary Protocol Submission to Include SAP:	April 2015
Final Protocol Submission:	September 2015
Interim Analysis:	August 2017
Trial Completion:	August 2018
Final Report Submission:	August 2019

Note: [redacted] (b) (4)

NOTE: PREA PMRs require sponsor to provide schedule milestone dates in MM/DD/YYYY format.

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

Patients with Multiple Myeloma who have received both an immunomodulatory agent and bortezomib and at least 2 prior therapies have no available therapies. In spite of many approved treatments for Multiple Myeloma, nearly all patients will eventually relapse and require subsequent lines of therapy. This trial will aid further panobinostat dose selection when used in combination with a different bortezomib regimen (subcutaneous administration) as a requirement under Subpart H.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

PMR under subpart H. The Applicant conducted (and submitted to FDA) a single randomized add-on design trial PANORAMA 1 adding panobinostat to intravenous bortezomib and dexamethasone in a population of patients with relapsed/refractory Multiple Myeloma that demonstrated a statistically significant median PFS improvement of 3.9 months. PANORAMA 1 administered bortezomib intravenously and a trial comparing the intravenous and subcutaneous routes reported similar efficacy but improved thrombocytopenia and neuropathy with the subcutaneous route. The safety profile of the combination could possibly be improved by switching the bortezomib to a subcutaneous route. This trial is designed to evaluate the safety and efficacy of different doses of panobinostat in combination with once weekly subcutaneous bortezomib and dexamethasone. . The results of this trial will be used to inform the dosing selection for the confirmatory Phase 3 trial.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☒ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Multicenter, open-label, phase 2 study, randomizing to at least two doses of panobinostat in combination with dexamethasone and weekly, subcutaneous bortezomib, in patients with relapsed multiple myeloma who have been previously exposed to IMiDs. Sponsor will justify final panobinostat dosage selections for the trial to be given in combination with 1.3 mg/m^2 bortezomib by subcutaneous injection and 20 mg dexamethasone by mouth on the day of and day after each bortezomib dose. Eligible patients will have 1-3 prior lines of anti-myeloma treatment that must include an immunomodulatory agent. The primary objective is to assess the overall response rate (ORR) in both treatment arms according to IMWG criteria by investigator assessment. (b) (4)

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Subpart H

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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

QIN C RYAN
02/23/2015
Sign for Dr. Robert Kane, DDS

PMR/PMC Development Template

PMR #2

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #	205353
Product Name:	FARYDAK® (panobinostat, LBH589) capsules, 10 mg, 15 mg and 20 mg
PMR Description of trial:	2181-2 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 the interim analysis of the trial described in PMR 2181-1. 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 progression free survival (PFS) in both treatment arms by investigator assessment.

Preliminary Protocol Submission to Include SAP:	March 2017
Final Protocol Submission:	November 2017
Trial Completion:	February 2021
Final Report Submission:	December 2021

NOTE: PREA PMRs require sponsor to provide schedule milestone dates in MM/DD/YYYY format.

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

Patients with Multiple Myeloma who have received both an IMiD and bortezomib and at least 2 prior therapies have no available therapies. In spite of many approved treatments for Multiple Myeloma, nearly all patients will eventually relapse and require subsequent lines of therapy. This trial tests panobinostat when used with a different bortezomib regimen (subcutaneous administration) as a requirement under Subpart H

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Subpart H requirement: The Applicant conducted (and submitted to FDA) a single randomized add-on design trial PANORAMA 1 adding panobinostat to intravenous bortezomib and dexamethasone in a population of patients with relapsed/refractory Multiple Myeloma that demonstrated a statistically significant median PFS improvement of 3.9 months. These findings were limited by a large amount of missing and incorrectly assessed disease measurements (M Protein) as well as heavy censoring on the primary endpoint. This trial is designed to confirm and verify the clinical benefit of panobinostat when used in combination with bortezomib (when given subcutaneously) and dexamethasone in the treatment of patients with relapsed or refractory Multiple Myeloma.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☒ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Multicenter, randomized, double-blind, placebo controlled phase 3 trial of panobinostat or placebo in combination with weekly, subcutaneous bortezomib and dexamethasone in patients with relapsed multiple myeloma who have been previously exposed to IMiDs. 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.

(b) (4)

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Subpart H

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

QIN C RYAN
02/23/2015
Signing for Dr. Robert Kane, DDS