

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205353Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS)**

Date: February 22, 2015

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Subject Rationale for requiring a REMS and review REMS  
submitted February 21, 2015

Drug Name(s): Panobinostat (Farydak)

Therapeutic Class: histone deacetylase inhibitor

Dosage and Route: 20 mg by mouth once daily on day 1,3,5, 8, 10, and 12 of a  
21 day cycle

Application Type/Number: NDA 205353

Applicant/Sponsor: Novartis

OSE RCM #: 2014-690, 692

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## **EXECUTIVE SUMMARY**

This review by the Division of Risk Management (DRISK) provides the rationale for requiring a risk evaluation and mitigation strategy (REMS) for the new molecular entity panobinostat and recommends approval of the REMS submitted by Novartis on February 21, 2015.

DRISK agrees that the totality of these risks associated with panobinostat are serious and it is necessary for prescribers to understand these risks and the importance of monitoring for them. Based on the magnitude and severity of the diarrhea risk, we agree that requiring a REMS consisting of a communication plan is necessary to ensure that the benefits outweigh the risks of diarrhea. The Division of Hematology Products (DHP) has determined and DRISK aligns that the REMS must also address the cardiac toxicities (severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes) associated with panobinostat.

DRISK finds the revised REMS, REMS Supporting Document, and the REMS communication materials submitted on February 21, 2015 acceptable for approval.

### **1 INTRODUCTION**

This review by the Division of Risk Management (DRISK) provides the rationale for requiring a risk evaluation and mitigation strategy (REMS) for the new molecular entity panobinostat and recommends approval of the REMS submitted by Novartis on February 21, 2015.

### **2 BACKGROUND**

On August 28, 2014, DRISK completed a review for panobinostat. The review outlined the major risks of concern at that time were thrombocytopenia resulting in hemorrhage, infection, and gastrointestinal toxicity. The review stated, “DRISK defers a recommendation on a risk management approach pending further discussions with Division of Hematology Products (DHP) regarding the risk benefit of this product and after the Oncologic Drugs Advisory Committee (ODAC) meeting.”

On November 6, 2014, the ODAC convened to discuss panobinostat “for the treatment of patients with multiple myeloma (MM), who have received at least one prior therapy” in combination with bortezomib and dexamethasone. The committee voted five (no) to two (yes) that the benefit of panobinostat in combination “outweigh the risks for patients with relapsed multiple myeloma.” Those five members who voted that the benefit *does not* outweigh the risks cited concerns regarding the toxicity and uncertain magnitude of progression free survival (PFS) improvement. However, committee members did generally agree that panobinostat is active in this patient population.

Novartis requested a meeting with FDA which was held November 19, 2014 to discuss the safety and efficacy of panobinostat treatment in a subset of patients (relapsed patients previously exposed to immunomodulatory drug (IMiD) + bortezomib, who are bortezomib sensitive), along with the Novartis’ proposal to consider the application for

accelerated approval in this limited population with a confirmatory phase 3 study with dose finding, and additional risk management measures.

On November 21, 2014, DHP issued a Major Amendment letter for this application based on submission of the additional progression-free survival analysis performed by an Independent Review Committee<sup>1</sup> and determination that a “risk evaluation and mitigation strategy (REMS) will be necessary to ensure the benefits of FARYDAK outweigh the risks.” The major amendment extended the review goal date to February 24, 2015.

### **3 MATERIAL REVIEWED**

- Proposed REMS. Amendment submitted February 21, 2015; eCTD0066.
- Farydak final label, February 19, 2015; eCTD0065
- George A. OPDP REMS Consult Review. Signed in DARRTS on February 11, 2015. (OPDP conveyed no comments on the materials.)

#### **3.1 PREVIOUS DRISK REVIEWS**

- Proposed REMS. Submitted via email to Hanner D on February 18, 2015
  - DRISK comments provided via email to Novartis by Hanner D and signed in DARRTS on February 19, 2015.
- Proposed REMS. Amendment submitted January 13, 2015; eCTD 0058
  - DRISK comments provided via email to Novartis by Hanner D and signed in DARRTS on January 30, 2015 (general comments on materials) and February 9, 2015 (REMS Document).
- Proposed REMS submitted December 3, 2014; eCTD 0051.
  - DRISK comments provided via email to Novartis by Hanner D and signed in DARRTS on December 31, 2014 by Hanner D.
- “Core risk management plan” submitted March 24, 2014; eCTD 0000
  - DRISK review signed in DARRTS on August 28, 2014 by Robottom S and LaCivita C.

#### **3.2 OTHER MATERIAL REVIEWED**

- REMS Notification Letter signed in DARRTS on February 4, 2015.
- Kwitkowski VE. Cross Discipline Team Leader Review. Signed in DARRTS January 25, 2015 by Kwitkowski VE.
- ODAC Quick Minutes (draft) dated December 15, 2014.

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<sup>1</sup> This IRC analysis was conducted after Novartis realized that the original IRC assessment submitted did not take into account a confirmation assessment as required by modified EBMT (European Society for Blood and Marrow Transplantation) criteria. Therefore, Novartis no longer considers the original IRC assessment valid.

- Major Amendment Letter signed in DARRTS on November 21, 2014.

## 4 ANALYSIS OF NEED FOR A REMS

### 4.1 MULTIPLE MYELOMA

MM is a chronic malignancy of the plasma cells. It primarily affects older individuals. The diagnosis is most common in the 6th and 7th decades of life and approximately 75% of patients are over 70 years of age.<sup>2</sup> In comparison, the overall panobinostat clinical trial population had a median age of 63 years (sub-set population was 61 years old).

Survival has improved in recent years, both in the relapsed setting as well as at initial diagnosis.<sup>3,4</sup> However it remains a fatal disease; not curative with available therapy.

### 4.2 EXPECTED BENEFIT - UPDATE

Based on analysis of the subgroup consisting of “193 patients who had received prior treatment with both bortezomib and an immunomodulatory agent and a median of two prior therapies,” the “benefit:risk appeared to be greater in this more heavily pretreated population than the overall trial population.” The “median progression free survival (PFS) (95% CI) was 10.6 months (7.6, 13.8) in the panobinostat, bortezomib, and dexamethasone arm and 5.8 months (4.4, 7.1) in the placebo, bortezomib, and dexamethasone arm [HR: 0.52 (0.36, 0.76)].”<sup>5</sup> The median PFS benefit was 4.8 months.

For comparison, the median PFS benefit in the overall trial population was 3.9 months.<sup>5</sup>

### 4.3 SEVERITY OF RISK - UPDATE

DHP emphasized that it is the totality and magnitude of the panobinostat toxicity profile that is most concerning, weighed with an efficacy benefit of an additional 4.8 months.

Serious adverse events (SAEs) occurred in 60% of patients in the panobinostat, bortezomib, and dexamethasone arm compared to 42% of patients in the control arm. The most frequent treatment emergent SAEs reported for patients treated with panobinostat were pneumonia (18%), diarrhea (11%), thrombocytopenia (7%), fatigue (7%), and sepsis (6%). Deaths occurred in 8% of patients treated with panobinostat, bortezomib, and dexamethasone versus 5% on the control arm. The most frequent causes of death were infection and hemorrhage.

DHP noted hemorrhage, infection, diarrhea, and cardiovascular toxicities were of most concern. Given that hemorrhage (related to thrombocytopenia) and infection are basic risks associated with chemotherapy, DHP advocated for focusing increased communication efforts on the risk of diarrhea and cardiovascular toxicity as prescribers may be less aware of these risks.

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<sup>2</sup> Kane R. Farydak REMS Memo [draft] dated February 6, 2015.

<sup>3</sup> Kumar SK, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008;111(5):2516-2520.

<sup>4</sup> Pulte D et al. Improvement in survival of older adults with multiple myeloma: results of an updated period analysis of SEER Data. *The Oncologist* 2011;16:1600-1603.

(b) (4)

The FDA-revised labeling sent to Novartis on February 19, 2014, describes the risks as follows:

- **Diarrhea: Boxed Warning**



Diarrhea was the most common reason for treatment discontinuation in the panobinostat arm. Dr. Gormley noted that there were three cases of colitis and one case of bowel perforation (which was confounded).

*Reviewer Comment: In discussion with DHP, one diarrhea-related death was mentioned but this death is not mentioned in revised labeling. As noted in our August 28, 2014 review, 25% of patients had grade 3/4 diarrhea; 10.2% experiencing an SAE (compared to 2.4% in the control arm). The incidence of grade 3/4 diarrhea in the control arm is similar to the incidence reported in the bortezomib labeling (7-8%)*

*Zydelig (idelalisib), a kinase inhibitor, was approved with a REMS to address the risks of fatal and/or serious/severe diarrhea, colitis, intestinal perforation, hepatotoxicity, and pneumonitis. Fatal and/or serious/severe diarrhea or colitis occurred in 14% of Zydelig-treated patients across clinical trials.*

- **Cardiac Toxicities: Boxed Warning**



Further, the CDTL Memo states that three patients in the panobinostat arm died due to cardiac ischemia and none in the control arm. However, the difference in severe (grade 3-4) ischemic events was minimal (2% for panobinostat vs <1% for control arm).

*Reviewer Comment: The initial DRISK review cited the data available at that time which was data presented and opinions expressed during June 5, 2014 internal midcycle meeting. At that time, cardiac adverse event signal was not considered concerning. After additional review, concern has been raised about the totality of cardiovascular risk being consistently higher in the panobinostat treatment arm in comparison to the control. In addition, DHP expects that patients treated in the post-approval setting with panobinostat will be older with likely more underlying cardiac disease compared to the clinical trial population.*

*DRISK notes three drugs (carfilzomib, doxorubicin, and bortezomib) that are approved for MM and recognized treatment options for “salvage therapy” by the NCCN have cardiovascular risk listed in the Warnings and Precautions section of the labeling; one (doxorubicin) includes this risk in the Boxed Warning. Refer to Appendix A.*

- *Doxorubicin: The doxorubicin Warning states, “[m]yocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCL approaches 550mg/m<sup>2</sup>. In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at a starting dose of 50 mg/m<sup>2</sup> every 4 weeks. At all cumulative anthracycline doses between 450-500 mg/m<sup>2</sup> or between 500-550 mg/m<sup>2</sup>, the risk of cardiac toxicity for patients treated with DOXIL was 11%.”*
- *Carfilzomib: The carfilzomib Warning states, “[d]eath due to cardiac arrest has occurred within a day of KYPROLIS administration. ... Cardiac failure events (e.g., cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients.”*

*The Adverse Reactions section states, “Deaths due to all causes within 30 days of the last dose of KYPROLIS occurred in 37/526 (7%) of patients. Deaths not attributed to disease progression were cardiac in 5 patients (acute coronary syndrome, cardiac arrest, cardiac disorder)...”*

- *Bortezomib: The bortezomib Warning states, “[a]cute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during VELCADE therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction. ... In the relapsed multiple myeloma study of VELCADE versus dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5% in the VELCADE and dexamethasone groups, respectively.”*

*Of the three approved histone deacetylase inhibitors (HDAC)<sup>6</sup>, only romidepsin includes a cardiac-related Warning (“5.3 Electrocardiographic changes”). According to the label, ST-T wave changes were noted in one study (2%) and in another study (63% all grade; no grade 3/4). None of these the approved HDAC have a REMS.*

*DRISK evaluated drugs that have been approved with a REMS to address cardiac toxicity.<sup>7</sup> The indication for these drugs vary widely but none of these drugs with an approved REMS addressing cardiac toxicity are indicated for the treatment of cancer.*

*Please refer to the previous DRISK review for evaluation the QT prolongation.*

## **5 RISK MANAGEMENT ACTIVITES PROPOSED BY THE SPONSOR**

During the November 19, 2014 meeting with the Agency, Novartis outlined a proposed risk management approach which included:

- REMS consisting of a Medication Guide and communication plan

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(b) (4)

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<sup>6</sup> The approved HDAC inhibitors are approved for cutaneous t-cell lymphoma and/or peripheral t-cell lymphoma.

<sup>7</sup> Entereg, a peripherally acting opioid receptor antagonist, is approved to accelerate the time to upper and lower gastrointestinal recovery following surgeries that include partial bowel resection with primary anastomosis. The label includes a Boxed Warning regarding the potential risk of myocardial infarction with long-term use. The REMS consists of an ETASU to limit Entereg distribution to hospital pharmacies that are specially certified. Those hospital pharmacies agree to dispense no more than 15 doses in an inpatient settings.

Omontys (peginesatide) carries a Boxed Warning for increases risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence. The REMS addresses the potentially fatal cardiovascular and /or thromboembolic adverse events and the increased risk of these events in non-dialysis patients. The REMS consists of a communication plan (DHCP and society letter).

Rosiglitazone, a thiazolidinedione, approved for the treatment of type 2 diabetes *had* a REMS with ETASU to address the potential increased risk of myocardial infarction. Based on data re-adjudication, the REMS was modified to remove the ETASU and inform prescribers about the most up to date cardiovascular information. At the time the REMS was modified, the Boxed Warning was revised to remove the myocardial infarction risk.

Gilyena (fingolimod) is approved for the treatment of relapsing forms of multiple sclerosis. The labeling does not include a Boxed Warning. The REMS consists of a communication plan to address the risk of bradyarrhythmia and AV block following initiation of treatment, infections, macular edema, respiratory effects, hepatic effects, and fetal risk.

Multaq (dronedarone) is an antiarrhythmic. The labeling includes a Boxed Warning for increased risk of death, stroke, and heart failure in patients with decompensated heart failure or permanent atrial fibrillation. The REMS consists of a communication plan to address these risk along with hepatic failure and appropriate patient selection (preventing use in patients for which it is contraindicated).

- [REDACTED] (b) (4)

On December 3, 2014 Novartis submitted a proposed REMS consisting of a Medication Guide and communication plan with the following goal:

- [REDACTED] (b) (4)
- [REDACTED]

*Reviewer Comment:* [REDACTED] (b) (4)  
[REDACTED] . Currently Medication Guides are approved as labeling and are generally not part of REMS that consist of communication plans only.

The communication plan consisted of the following pieces:

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED]

*Reviewer Comment:* [REDACTED] (b) (4)  
[REDACTED] It is not clear if these measures (or others) will be employed.

It is unclear if the [REDACTED] (b) (4) primary function will be safety management or marketing liaisons.

However [REDACTED] (b) (4) are voluntary efforts proposed by Novartis were not proposed as part of the REMS.

## 6 DRISK PROPOSED REMS

### 6.1 GOAL STATEMENT

The goal of the FARYDAK REMS is to mitigate the risks of severe diarrhea and cardiac toxicities (severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes) associated with FARYDAK treatment

- by informing healthcare providers about the risks of severe diarrhea and cardiac toxicities associated with FARYDAK

*Reviewer Comment:* The goals as proposed by Novartis and were revised to reflect the risks DHP conveyed were most concerning.

## 6.2 REMS ELEMENTS

Based on DHP’s level of concern for diarrhea and cardiac toxicity, DRISK recommended a communication plan comprised of the following materials:

- A. REMS Letters to be distributed to healthcare providers who may prescribe or dispense Farydak and distribution of these letters to the corresponding professional societies for these healthcare providers
- B. REMS Factsheet to be made available to healthcare providers and disseminated through Novartis field-based sales or medical representatives during the initial discussion with health care providers within the first 12 months after the REMS approval.
- C. Scientific Meeting: Novartis will prominently display and disseminate Farydak REMS materials at scientific meetings where Novartis has a presence for the duration of the REMS.
- D. REMS Program Website to continue for the duration of the REMS. The REMS program website will include the option to print the PI, Medication Guide, REMS Letters, and *REMS Factsheet*. The FARYDAK product website will include a prominent REMS-specific link to the *FARYDAK REMS Program Website*.

*Reviewer comment: While we did not request Novartis propose a journal information piece, Novartis proposed one in their January 13, 2015 revised REMS submission and we do not object to including this in the REMS.*

## 6.3 REMS MESSAGE MAP

The following REMS message maps for healthcare providers are based on the current draft product label (February 10, 2014). The message maps contain the key risk messages addressed by the Farydak REMS. The messages included in these maps are consistent with (although not necessarily verbatim) the product label and used to guide the development of all REMS-related materials. These messages will also guide the development of the REMS assessment survey questions.

	<b>Message</b>	<b>Materials</b>	<b>Labeling</b>
<b>Key Risk Message 1</b>	Farydak has a boxed warning for severe diarrhea.	Factsheet, Journal piece REMS Letters Website	Boxed Warning
<b>Key Message 2</b>	Severe diarrhea occurred in 25% of Farydak treated patients	Factsheet Journal piece Letters	Boxed Warning, Warnings and Precautions

		website	
Supporting Message	Diarrhea occurred in 68% of patients treated with Farydak compared to 42% in the control arm	Factsheet Journal piece website	Warnings and Precautions
Supporting Messages	Severe diarrhea is defined as > 7 stools /days, IV fluids or hospitalization required	Factsheet Journal piece website	Dosage and Administration
Supporting Messages	Diarrhea can occur any time Diarrhea was the most common adverse event leading to treatment discontinuation	Factsheet	Warnings and Precautions
<b>Key Message 3 (shortened)</b>	Monitor for symptoms, institute anti-diarrheal treatment, interrupt FARYDAK and then reduce dose or discontinue FARYDAK	Journal piece website	Boxed Warning
<b>Key Message 3 (expanded with supporting messages)</b>	<p>Ensure patients have anti-diarrheal medications on hand when they start Farydak</p> <p>Inform patients to begin anti-diarrheal medication at the first sign of abdominal cramping, loose stools</p> <p>For moderate diarrhea (4 to 6 stools per day)</p> <ul style="list-style-type: none"> <li>○ Inform patients to Interrupt Farydak until resolved</li> <li>○ Consider interrupting bortezomib until resolved</li> </ul> <p>For severe diarrhea (<math>\geq 7</math> stools/day)</p> <ul style="list-style-type: none"> <li>○ Interrupt Farydak until resolved and restart at reduced dose</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>○ Interrupt bortezomib also until resolved and restart at reduced dose</li> </ul> <p>For life-threatening diarrhea permanently discontinue Farydak and bortezomib</p>	Factsheet	<p>Warnings and Precautions</p> <hr/> <p>Dosage and Administration</p>

	<p>Monitor hydration status and electrolytes (including potassium, magnesium, and phosphate)</p> <ul style="list-style-type: none"> <li>○ At baseline and weekly (or more frequently as clinically indicated) during treatment</li> <li>○ Correct to prevent dehydration and electrolyte disturbances</li> </ul>		
<b>Key Risk Message 4</b>	Farydak has a boxed warning for cardiac toxicities	Factsheet, Journal piece REMS Letters Website	Boxed Warning
<b>Key Risk Message 5</b>	Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes occurred with Farydak.	Factsheet Journal piece Letters website	Boxed Warning, Warnings and Precautions
Supporting Message	Cardiac ischemic events occurred in 4% of patients treated with Farydak compared with 1% of patients in the control arm	Factsheet Journal piece website	Warnings and Precautions
Supporting Message	Arrhythmias occurred in 12% of patients receiving Farydak compared to 5% of patients in the control arm	Factsheet Journal piece website	Warnings and Precautions
Supporting Message	Electrolyte abnormalities may exacerbate arrhythmias.		Boxed Warning, Warnings and Precautions
Supporting Messages	<p>ECG abnormalities occurred more frequently in patients receiving Farydak compared to control arm</p> <ul style="list-style-type: none"> <li>○ ST-segment depression: 22% vs 4% (control arm)</li> <li>○ T-wave abnormalities: 40% vs 18% (control arm)</li> </ul>	Factsheet	Warnings and Precautions
<b>Key Risk Message 6</b>	Do not start Farydak if patient has recent myocardial infarction, unstable angina, QTcF > 450msec or clinically significant ST segment or T wave abnormalities	Factsheet Journal ad Website	Warnings and Precautions
Supporting	<ul style="list-style-type: none"> <li>• <b>Monitor ECG</b> <ul style="list-style-type: none"> <li>○ Perform an ECG prior to start of</li> </ul> </li> </ul>	Factsheet	Boxed Warning

Messages	<p>therapy and repeat periodically during treatment as clinically indicated.</p> <ul style="list-style-type: none"> <li>○ Interrupt treatment if QTcF increases to <math>\geq 480</math> msec.</li> <li>○ If QT prolongation does not resolve, permanently discontinue Farydak</li> <li>● <b>Monitor Electrolytes</b> <ul style="list-style-type: none"> <li>○ Obtain electrolytes including potassium and magnesium at baseline and during therapy</li> <li>○ Correct abnormal electrolytes before Farydak treatment</li> </ul> </li> </ul>		<hr/> <p>Dosage and Administration</p> <hr/> <p>Boxed Warning,</p> <p>Dosage and Administration, Warnings and Precautions</p>
<b>Key Message 7</b>	<p>Farydak (panobinostat) capsules, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. The indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.</p>	<p>Factsheet</p> <p>Journal piece</p> <p>REMS Letters</p> <p>Website</p>	<p>Indications and Usage</p>

#### 6.4 REMS ASSESSMENT PLAN

The following REMS Assessment parameters will be included in the action letter:

1. Launch date of FARYDAK
2. An evaluation of healthcare providers who prescribe or dispense awareness and understanding of the risks associated with FARYDAK (panobinostat) and the management of these events:
  - Severe diarrhea
  - Severe and fatal cardiac ischemic events
  - Severe arrhythmias
  - ECG changes

3. A description of the implementation of the communication plan, including:

- Number of healthcare providers and professional societies targeted by the REMS
- Number of REMS letters sent to healthcare providers and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via mail because the emailed letter was undeliverable. Also include numbers of returned or undeliverable letters. For letters sent via email, include the number of letters successfully delivered, and number of email letters opened by the recipients.
- Which professional societies distributed the REMS letters or content of the letter to their membership
- The sources of the distribution lists
- Date journal pieces appeared in each journal or publication, including volume, issue number, and journal name
- Date and name of the scientific meetings attended and materials displayed
- Date the REMS website went live, and number of unique site visits to the FARYDAK (panobinostat)
- Number of REMS fact sheets distributed by Novartis representatives during follow-up details/visits with healthcare providers during the 12 months after approval of the REMS.

## 7 SUMMARY OF FARYDAK REMS

Novartis submitted a revised REMS on February 21, 2015 consisting of a communication plan to address the risk of severe diarrhea and cardiac toxicities (severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes).

The goal of the REMS is “to mitigate the risks of severe diarrhea and cardiac toxicities (severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes) associated with FARYDAK treatment

- by informing healthcare providers about the risks of severe diarrhea and cardiac toxicities associated with FARYDAK”

The communication plan is comprised of the following materials

- A. REMS Letters
- B. REMS Factsheet
- C. Journal Information Piece
- D. Scientific Meeting
- E. REMS Program Website

*Reviewer Comment: The sponsor’s revised submission of Farydak REMS and REMS materials on February 21, 2015 align with the risk information outlined in the Boxed Warning and Warning and Precautions sections for severe diarrhea and cardiac toxicities.*

*Novartis has incorporated all of the Agency's edits; there are no further edits or changes recommended by DRISK for these documents.*

## **8 DISCUSSION**

In considering the risks of severe diarrhea and cardiac toxicity, DRISK evaluated the merits of a communication plan. Additional communication/education efforts are necessary to highlight the increased risk and different actions practitioners should take to minimize the risk(s) associated with panobinostat.

As stated in our previous review, healthcare providers who treatment MM are generally familiar with (A) the toxicities associated with panobinostat based on the risk profiles of other MM treatments and (B) the necessity of monitoring patients.

- A. With regard to the toxicity profile: A communication concern is that practitioners may quickly dismiss a message if the severity or magnitude of the risk is not perceived significant particularly in relation to the patient's medical condition and prognosis. The cardiac events are varied and include arrhythmias, ischemic events, ECG abnormalities. There is not a specific cardiac event that stands out as opposed to the collection of the cardiac risks. Some level of awareness with considering a MM patient's cardiac health in determining the appropriate treatment option is necessary based on the risk profiles of the currently available treatment options.

However, the magnitude and severity of diarrhea associated with panobinostat is marked. Diarrhea can occur at any time during the treatment with panobinostat. Any grade diarrhea occurred in 68% of patients treated with panobinostat compared to 42% of patients in the control arm. Severe diarrhea occurred in 25% of patients treated with panobinostat. Because of the incidence and severity of diarrhea, prescribers need to be aware and provide timely interventions to minimize the risk.

- B. With regard to monitoring patients: We believe there is specific information with regard to monitoring patients and minimizing these risks. For example, we note that labeling states not to start panobinostat in patients with recent myocardial infarction, unstable angina, QTc > 450, or clinically significant ST segment or T wave abnormalities. For diarrhea, patients need anti-diarrheal medication on hand when starting panobinostat and dosing must be modified or discontinued based on the severity of the diarrhea. Other aspects such as monitoring ECG, electrolytes and hydration appear to be consistent with standard monitoring for patients treated with a chemotherapeutic agent associated with these risks.

Refer to Section 6.3 for more details regarding the key messages.

Based on the magnitude and severity of the diarrhea risk, we agree with requiring additional communication efforts to address this risk. The collection of the cardiac events are concerning; we align with DHP on including it in the REMS based on the likelihood of patients in the post-marketing setting will be older than the clinical trial population (possibly increasing the risk for cardiac sequelae) along with educating practitioners not to use panobinostat in certain patients with current or recent cardiac events/abnormalities.

## **9 CONCLUSION AND RECOMMENDATION**

DRISK agrees that the totality of the risks associated with panobinostat are serious and it is necessary for prescribers to understand these risks and the importance of monitoring for them. Based on the magnitude and severity of the diarrhea risk, we agree that requiring a REMS consisting of a communication plan is necessary to ensure that the benefits outweigh the risks of diarrhea. DHP has determined and DRISK aligns that the REMS must also address the cardiac toxicities (severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes) associated with panobinostat.

DRISK finds the revised REMS, REMS Supporting Document, and the REMS communication materials submitted on February 21, 2015 acceptable for approval.

### **ATTACHMENTS**

- A. Cardiovascular Warnings and Gastrointestinal Toxicity Warning for MM and HDAC Drugs.
- B. Farydak REMS and materials

## Attachment A: Cardiovascular Toxicities - Warnings Gastrointestinal Toxicities – Warnings

Attachment A: Cardiovascular Toxicities - Warnings		
Treatment options (“salvage therapy) according to NCCN Multiple Myeloma Guidelines <sup>1</sup> *These drugs are typically used in combination*		
Bortezomib <sup>2</sup>	Proteasome inhibitor	<p><b>Cardiac Toxicity</b></p> <p>Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during VELCADE therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the relapsed multiple myeloma study of VELCADE versus dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5% in the VELCADE and dexamethasone groups, respectively. The incidence of adverse reactions suggestive of heart failure (acute pulmonary edema, pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock) was ≤ 1% for each individual reaction in the VELCADE group. In the dexamethasone group the incidence was ≤ 1% for cardiac failure and congestive cardiac failure; there were no reported reactions of acute pulmonary edema, pulmonary edema, or cardiogenic shock. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.</p>
Carfilzomib	Proteasome inhibitor	<p><b>5.1 Cardiac Arrest, Congestive Heart Failure, Myocardial Ischemia</b></p> <p>Death due to cardiac arrest has occurred within a day of KYPROLIS administration. New onset or worsening of pre-existing congestive heart failure with decreased left ventricular function or myocardial ischemia have occurred following administration of KYPROLIS. Cardiac failure events (e.g., cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients. Monitor for cardiac complications and manage promptly. Withhold KYPROLIS for Grade 3 or 4 cardiac events until recovery and consider whether to restart KYPROLIS based on a benefit/risk assessment [see <i>Dosage and Administration (2.4)</i>].</p>

<sup>1</sup> Not all drugs recommended in the NCCN Guidelines are FDA-approved for the treatment of multiple myeloma.

<sup>2</sup> Studied in combination with panobinostat.

		<p>Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications.</p>
Doxorubicin	anthracycline	<p><b>Boxed Warning</b></p> <p>The use of DOXIL may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCL approaches 550mg/m<sup>2</sup>. In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at a starting dose of 50 mg/m<sup>2</sup> every 4 weeks. At all cumulative anthracycline doses between 450-500 mg/m<sup>2</sup> or between 500-550 mg/m<sup>2</sup>, the risk of cardiac toxicity for patients treated with DOXIL was 11%. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Cardiac toxicity may also occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy.</p> <p>5.1 Cardiac Toxicity</p> <p>Special attention must be given to the risk of myocardial damage from cumulative doses of doxorubicin HCl. Acute left ventricular failure may occur with doxorubicin, particularly in patients who have received a total cumulative dosage of doxorubicin exceeding the currently recommended limit of 550 mg/m<sup>2</sup>. Lower (400 mg/m<sup>2</sup>) doses appear to cause heart failure in patients who have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide.</p> <p>Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Congestive heart failure or cardiomyopathy may be encountered after discontinuation of anthracycline therapy. Patients with a history of cardiovascular disease should be administered DOXIL only when the potential benefit of treatment outweighs the risk.</p> <p>Cardiac function should be carefully monitored in patients treated with DOXIL. The most definitive test for anthracycline myocardial injury is endomyocardial biopsy. Other methods, such as echocardiography or multigated radionuclide scans, have</p>

		<p>been used to monitor cardiac function during anthracycline therapy. Any of these methods should be employed to monitor potential cardiac toxicity in patients treated with DOXIL. If these test results indicate possible cardiac injury associated with DOXIL therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.</p> <p>In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at starting dose of 50 mg/m<sup>2</sup> every 4 weeks. At all cumulative anthracycline doses between 450-500 mg/m<sup>2</sup>, or between 500–550 mg/m<sup>2</sup>, the risk of cardiac toxicity for patients treated with DOXIL was 11%. In this study, cardiotoxicity was defined as a decrease of &gt;20% from baseline if the resting left ventricular ejection fraction (LVEF) remained in the normal range, or a decrease of &gt;10% if the resting LVEF became abnormal (less than the institutional lower limit of normal). The data on left ventricular ejection fraction (LVEF) defined cardiotoxicity and congestive heart failure (CHF) are in the table below.</p> <p>In the randomized multiple myeloma study, the incidence of heart failure events (ventricular dysfunction, cardiac failure, right ventricular failure, congestive cardiac failure, chronic cardiac failure, acute pulmonary edema and pulmonary edema) was similar in the DOXIL+bortezomib group and the bortezomib monotherapy group, 3% in each group. LVEF decrease was defined as an absolute decrease of ≥15% over baseline or a ≥5% decrease below the institutional lower limit of normal. Based on this definition, 25 patients in the bortezomib arm (8%) and 42 patients in the DOXIL + bortezomib arm (13%) experienced a reduction in LVEF.</p>
Thalidomide	Imid	Arterial Thromboembolism
Lenalidomide	Imid	No cardiac warning
Pomalidomide	Imid	No cardiac warning
Cyclophosphamide		No cardiac warning
Etoposide		No cardiac warning
Cisplatin		No cardiac warning
<b>HDAC Inhibitors</b>		

Romidepsin	<p><b>5.3 Electrocardiographic Changes</b>  Several treatment-emergent morphological changes in ECGs (including T-wave and ST-segment changes) have been reported in clinical studies. The clinical significance of these changes is unknown [see <i>Adverse Reactions (6)</i>].</p> <p>In patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation, consider cardiovascular monitoring of ECGs at baseline and periodically during treatment.</p> <p>Confirm that potassium and magnesium levels are within normal range before administration of ISTODAX [see <i>Adverse Reactions (6)</i>].</p> <p><b>AE Section: CTCL</b></p> <ul style="list-style-type: none"> <li>• ECG ST-T wave changes: Study 1 - all grades 2% (0 grade 3/4); study 2 – all grade 63% (0 grade 3/4)</li> <li>• SAEs – ventricular arrhythmia – 4%</li> </ul> <p><b>T Cell Lymphoma</b></p> <ul style="list-style-type: none"> <li>• Tachycardia –study 3 10% (all grades); study 4 – none</li> <li>• No ECG changes included in table.</li> <li>• Ventricular arrhythmia – 4%</li> </ul>
Belinostat	No cardiac warning
Vorinostat	No cardiac warning

<b>Gastrointestinal Toxicities – Warnings</b>	
<b>Treatment options (“salvage therapy) according to NCCN Multiple Myeloma Guidelines<sup>3</sup></b> <b>*These drugs are typically used in combination*</b>	
Bortezomib <sup>4</sup>	Warnings Section: 5.6 <b>Gastrointestinal Toxicity</b> VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting [see <i>Adverse Reactions (6.1)</i> ] sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent

<sup>3</sup> Not all drugs recommended in the NCCN Guidelines are FDA-approved for the treatment of multiple myeloma.

<sup>4</sup> Studied in combination with panobinostat.

	<p>dehydration. Interrupt VELCADE for severe symptoms.</p> <p><b>AE Section – Untreated MM Study</b></p> <p>Diarrhea – 35%; grade 3 (6%), grade 4 (1%)</p> <p><b>AE Section – Relapsed</b></p> <p>Diarrhea – 52%; grade 3 (7%), grade 4 (0%)</p> <p>IV (28%) vs SC (19%)</p> <p>concerns</p>
Thalidomide	No GI warning
Lenalidomide	No GI warning
Pomalidomide	No GI warning
Cyclophosphamide	No GI warning
Carfilzomib	No GI warning
Doxorubicin	No GI warning
Etoposide	No GI warning
Cisplatin	No GI warning
<b>HDAC Inhibitors</b>	
Romidepsin	No warning
Belinostat	<p>5.5 Gastrointestinal toxicity</p> <p>Nausea, vomiting and diarrhea occur with Beleodaw and may require the use of antiemetic and antidiarrheal medications.</p> <p>AE Section – Diarrhea</p> <p>All grades (23%); Grade 3-4 (2%)</p>
Vorinostat	<p><b>5.3 Gastrointestinal Toxicity</b></p> <p>Gastrointestinal disturbances, including nausea, vomiting and diarrhea, have been reported [see Adverse Reactions (6)] and may require the use of antiemetic and antidiarrheal medications.</p>

	<p>Fluid and electrolytes should be replaced to prevent dehydration [see <i>Adverse Reactions (6.1)</i>]. Pre-existing nausea, vomiting, and diarrhea should be adequately controlled before beginning therapy with ZOLINZA.</p> <p>AE Section - Diarrhea</p> <p>All grades 52.3% (no grade 3-5)</p>
<b>Drugs with approved REMS for diarrhea</b>	
Zydelig	<p><b>5.2 Severe Diarrhea or Colitis</b></p> <p><b>Severe diarrhea or colitis (Grade 3 or higher) occurred in 14% of Zydelig-treated patients across clinical trials [see <i>Adverse Reactions (6.1)</i>].</b> Diarrhea can occur at any time. Avoid concurrent use of Zydelig and other drugs that cause diarrhea. Diarrhea due to Zydelig responds poorly to antimotility agents. Median time to resolution ranged between 1 week and 1 month across trials, following interruption of Zydelig therapy and in some instances, use of corticosteroids [see <i>Dosage and Administration (2.2)</i>].</p> <p><i>CLL Patients – 5% grade 3 or higher (21% all grades)</i>  <i>NHL – 14% grade 3 or higher (47% all grades)</i></p>

## Initial REMS Approval 02/2015

### NDA 205353 FARYDAK (panobinostat)

histone deacetylase inhibitor

Novartis Pharmaceuticals Corporation

One Health Plaza

East Hanover, NJ 07936

Phone: 1-888-669-6682

## RISK EVALUATION AND MITIGATION STRATEGY (REMS)

### I. Goal(s)

The goal of the FARYDAK REMS is to mitigate the risks of severe diarrhea and cardiac toxicities (severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes) associated with FARYDAK treatment

- by informing healthcare providers about the risks of severe diarrhea and cardiac toxicities associated with FARYDAK

### II. REMS elements

#### Communication Plan

Novartis will implement the following communication plan for healthcare providers who are likely to prescribe and dispense FARYDAK. This communication plan will include:

#### 1. REMS Letters

Novartis will send *REMS Letter to Healthcare Providers* and *REMS Letter for Professional Societies* within 30 days of REMS approval (02/23/2015). Novartis will send a second emailing 12 months from the date of the REMS approval. The REMS Letters will address the risks of severe diarrhea and severe and fatal cardiac toxicities associated with FARYDAK. Email will be used as the primary method to disseminate the REMS Letters. If email is marked unopened, a second email will be sent within 30 calendar days of the date the first email was sent. If the second email is marked unopened, the REMS Letters will be mailed within 30 calendar days of the date of the second email was sent. If a healthcare provider's or professional society's email address is not available, or if an email is undeliverable, the REMS Letter will be mailed within 30 calendar days of the date of the bulk mailing. A copy or link to the Prescribing Information (PI) and *REMS Factsheet* will accompany each *REMS Letter for Healthcare Providers*. A copy or link to the *REMS Factsheet* will accompany each *REMS Letter for Professional Societies*.

#### a. REMS Letter for Healthcare Providers

The intended audience for the *REMS Letter for Healthcare Providers* will be oncologists, oncology physician assistants, oncology nurse practitioners, hematologists, oncology nurses, and pharmacists.

## **b. REMS Letter for Professional Societies**

The intended audience for the *REMS Letter for Professional Societies* will be the following professional societies and organizations, in which Novartis requests the letter or content be provided to their membership:

- American Society of Clinical Oncology (ASCO)
- American Society of Hematology (ASH)
- Oncology Nursing Society (ONS)
- National Comprehensive Cancer Network (NCCN)
- Hematology Oncology Pharmacy Association (HOPA)
- American Pharmacists Association (APhA)
- American Society of Health-System Pharmacists (ASHP)

## **2. REMS Factsheet**

A *REMS Factsheet* will be made available for healthcare providers and disseminated through Novartis field-based sales or medical representatives during the initial discussion with healthcare providers within the first 12 months after the approval of this REMS. Novartis field-based sales or medical representatives will orally discuss the risk messages contained in the *Factsheet* during the visit with the healthcare provider.

## **3. Journal Information Piece**

Novartis will publish in the following professional journals an *information piece* that includes the risks of serious and severe diarrhea associated with FARYDAK treatment.

- Journal of Clinical Oncology
- Blood
- New England Journal of Medicine
- Hematology Oncology Today
- Oncology & Hematology Review
- Leukemia and Lymphoma

The *information piece* will be published quarterly in each publication for one year following the REMS approval.

## **4. Scientific Meetings**

FARYDAK REMS materials will be prominently displayed and disseminated at relevant scientific meetings where Novartis has a presence (e.g., booth) for the duration of the REMS.

## **5. REMS Program Website**

The FARYDAK *REMS Website* ([www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com)) will continue for the duration of the REMS. The REMS program website will include the option to print the PI, Medication Guide, REMS Letters, and *REMS Factsheet*. The FARYDAK product website will include a prominent REMS-specific link to the *FARYDAK REMS Program Website*.

The following are part of the REMS and are appended:

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

### **III. Timetable for Submission of Assessments**

Novartis will submit REMS assessments to FDA 18 months, 3 years and 7 years from the date of the initial approval of the REMS [02/23/2015]. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for each assessment time interval. Novartis will submit each assessment so that it will be received by FDA on or before the due date.

## FDA-REQUIRED REMS\* SAFETY INFORMATION

**Boxed Warning: Severe Diarrhea and Cardiac Toxicities With FARYDAK Treatment**

### Severe Diarrhea

#### What is the risk?

- Diarrhea occurred in 68% of patients treated with FARYDAK compared with 42% in the control arm
- **Severe diarrhea occurred in 25% of FARYDAK-treated patients.** Severe diarrhea is defined as  $\geq 7$  stools/day, IV fluids, or hospitalization required
  - Diarrhea can occur at any time
  - Diarrhea was the most common adverse event leading to treatment discontinuation

#### How can I minimize this risk?

- Ensure patients have **anti-diarrheal medications on hand when they start FARYDAK**
- Inform patients to begin **anti-diarrheal medication** at the first sign of abdominal cramping, loose stools
- **For moderate diarrhea** (4 to 6 stools per day)
  - **Inform patients to interrupt FARYDAK** until resolved and restart at the same dose
  - **Consider interrupting bortezomib** until resolved and restart at the same dose
- **For severe diarrhea** ( $\geq 7$  stools/day)
  - **Interrupt FARYDAK** until resolved and restart at reduced dose
  - AND**
  - **Interrupt bortezomib** also until resolved and restart at reduced dose
- **For life-threatening diarrhea, permanently discontinue** FARYDAK and bortezomib
- **Monitor hydration status and electrolytes** (including potassium, magnesium, and phosphate)
  - At baseline and weekly (or more frequently as clinically indicated) during treatment
  - Correct to prevent dehydration and electrolyte disturbances

**Cardiac Toxicities Risk information on Other Side** 

# Cardiac Toxicities

## What is the risk?

- **Severe and fatal cardiac ischemic events**, severe arrhythmias, and ECG changes occurred in patients receiving FARYDAK® (panobinostat) capsules. Electrolyte abnormalities may exacerbate arrhythmias
  - **Cardiac ischemic events** occurred in 4% of patients treated with FARYDAK compared with 1% of patients in the control arm
  - **Arrhythmias** occurred in 12% of patients receiving FARYDAK compared with 5% of patients in the control arm
  - **ECG abnormalities** occurred more frequently in patients receiving FARYDAK compared with control arm
    - ST-segment depression: 22% vs 4% (control arm)
    - T-wave abnormalities: 40% vs 18% (control arm)

## How can I minimize this risk?

- **Patient selection and evaluation**
  - **Do not start** FARYDAK if patient has
    - Recent myocardial infarction
    - Unstable angina
    - QTcF >450 msec
    - Clinically significant ST-segment or T-wave abnormalities
- **Monitor ECG**
  - Perform an ECG prior to start of therapy and repeat periodically during treatment as clinically indicated
  - Interrupt treatment if QTcF increases to >480 msec
  - If QT prolongation does not resolve, permanently discontinue FARYDAK
- **Monitor electrolytes**
  - Obtain electrolytes including potassium and magnesium at baseline and during therapy
  - Correct abnormal electrolytes before FARYDAK treatment

# Indication

FARYDAK is used in combination with bortezomib and dexamethasone to treat patients with multiple myeloma **who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.**

This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

**\*A REMS (Risk Evaluation and Mitigation Strategy)** is a program required by the FDA to manage known or potential serious risks associated with a drug product. FDA has determined that a REMS is necessary to ensure that the benefits of FARYDAK outweigh the risks of severe diarrhea and cardiac toxicity. This factsheet is required by the FDA as part of the FARYDAK REMS program.

You are encouraged to report adverse reactions of FARYDAK to Novartis at 1-888-669-6682 and/or the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

*This factsheet does not contain the complete safety profile for FARYDAK. For complete safety information, please see the full Prescribing Information, including Boxed Warning, available at [www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com).*



## FDA-REQUIRED REMS\* SAFETY INFORMATION

### Boxed Warning: Severe Diarrhea and Cardiac Toxicities with FARYDAK Treatment

#### Dear Healthcare Provider:

The FDA has required this safety notice as part of the FARYDAK<sup>®</sup> REMS (Risk Evaluation and Mitigation Strategy) to inform you about the following serious risks of FARYDAK:

#### Severe Diarrhea

- Severe diarrhea occurred in 25% of FARYDAK-treated patients

#### Cardiac Toxicities

- Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred with FARYDAK

Please see the enclosed **REMS Factsheet**, a non-promotional factsheet reviewed by the FDA, for more detailed safety information. The factsheet and other important information are also available at [www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com).

#### Indication

FARYDAK, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma **who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.**

This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

\*A **REMS (Risk Evaluation and Mitigation Strategy)** is a program required by the FDA to manage known or potential serious risks associated with a drug product. Please visit [www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com) for more information.

For the complete safety profile of FARYDAK, please see the enclosed:

- Prescribing Information
- Medication Guide

#### Adverse Event Reporting

You are encouraged to report adverse reactions of FARYDAK to Novartis at 1-888-669-6682 and/or the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

Sincerely,

Novartis Pharmaceuticals Corporation



From: Novartis Pharmaceuticals Corporation <info@email.novartis.com> Sent: Wed 4/15/2014 10:39 AM  
To: John Doe  
Cc:  
Subject: FDA Required REMS Safety Information for FARYDAK® (panobinostat)

**FARYDAK®**  
(panobinostat) capsules  
10mg/15mg/20mg

If you have trouble viewing this email, [click here](#)  
To ensure proper delivery, please add  
<info@email.novartis.com> to your address book

## FDA REQUIRED REMS\* SAFETY INFORMATION

### Boxed Warning: Severe Diarrhea and Cardiac Toxicities with FARYDAK

#### Dear Healthcare Provider:

The FDA has required this safety notice as part of the FARYDAK® REMS (Risk Evaluation and Mitigation Strategy) to inform you about the following serious risks of FARYDAK:

#### Severe Diarrhea

- Severe diarrhea occurred in 25% of FARYDAK-treated patients

#### Cardiac Toxicities

- Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred with FARYDAK

Please see the [REMS Factsheet](#), a non promotional factsheet reviewed by the FDA, for more detailed safety information. The factsheet and other important information are also available at [www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com).

#### Indication

FARYDAK, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma **who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.**

This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

\*A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. Please visit [www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com) for more information.

For the complete safety profile of FARYDAK, please see the:

- [Prescribing Information](#)
- [Medication Guide](#)

#### Adverse Event Reporting

You are encouraged to report adverse reactions of FARYDAK to Novartis at 1-888-669-6682 and/or the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

Sincerely,

Novartis Pharmaceuticals Corporation

[Full Prescribing Information](#) | [Medication Guide](#) | [Factsheet](#)



Novartis Pharmaceuticals Corporation  
East Hanover, New Jersey 07936-1080

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## FDA-REQUIRED REMS\* SAFETY INFORMATION

### Boxed Warning: Severe Diarrhea and Cardiac Toxicities with FARYDAK Treatment

Dear <<insert contact name here>>:

The FDA has required Novartis to distribute this safety notice as part of the FARYDAK<sup>®</sup> REMS (Risk Evaluation and Mitigation Strategy) program. We request that you inform your members about the following serious risks of FARYDAK.

### Severe Diarrhea

- Severe diarrhea occurred in 25% of FARYDAK-treated patients

### Cardiac Toxicities

- Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred with FARYDAK

Please see the enclosed **REMS Factsheet**, a non-promotional factsheet reviewed by the FDA, for more detailed safety information. The factsheet and other important information are also available at [www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com).

### Indication

FARYDAK, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma **who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.**

This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

\*A REMS (**R**isk **E**valuation and **M**itigation **S**trategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. Please visit [www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com) for more information.

Sincerely,

Novartis Pharmaceuticals Corporation





If you have trouble viewing this email, [click here](#)  
To ensure proper delivery, please add <info@email.novartis.com> to your address book.

## FDA REQUIRED REMS\* SAFETY INFORMATION

**Boxed Warning: Severe Diarrhea and Cardiac Toxicities with FARYDAK**

Dear <<insert contact name here>>

The FDA has required this safety notice as part of the FARYDAK® REMS (Risk Evaluation and Mitigation Strategy) program. We request that you inform your members about the following serious risks of FARYDAK.

### Severe Diarrhea

- Severe diarrhea occurred in 25% of FARYDAK-treated patients

### Cardiac Toxicities

- Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred with FARYDAK

Please see the [REMS Factsheet](#), a non-promotional factsheet reviewed by the FDA, for more detailed safety information. The factsheet and other important information are also available at [www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com)

### Indication

FARYDAK, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.

This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

\*A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. Please visit [www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com) for more information.

Sincerely,

Novartis Pharmaceuticals Corporation

[Full Prescribing Information](#) | [Medication Guide](#) | [Factsheet](#)



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Novartis Pharmaceuticals Corporation  
East Hanover, New Jersey 07936-1080

## FDA-REQUIRED REMS\* SAFETY INFORMATION

### Boxed Warning: Severe Diarrhea and Cardiac Toxicities With FARYDAK Treatment

#### Severe Diarrhea

- **Severe diarrhea occurred in 25% of FARYDAK-treated patients**
  - Severe diarrhea is defined as >7 stools/day, IV fluids or hospitalization
- Diarrhea occurred in 68% of patients treated with FARYDAK compared with 42% in the control arm
- Monitor for symptoms, institute anti-diarrheal treatment, interrupt FARYDAK, and then reduce dose or discontinue FARYDAK. Refer to Factsheet for diarrhea management information available at [www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com)

#### Serious Cardiac Toxicities

- **Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes occurred with FARYDAK**
- **Cardiac ischemic events** occurred in 4% of patients treated with FARYDAK compared with 1% of patients in the control arm
- **Arrhythmias** occurred in 12% of patients receiving FARYDAK, compared with 5% of patients in the control arm
- **Do not start FARYDAK** if patient has
  - Recent myocardial infarction
  - Unstable angina
  - QTcF >450 msec
  - Clinically significant ST-segment or T-wave abnormalities

#### Indication

FARYDAK<sup>®</sup> (panobinostat) capsules, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received **at least 2 prior regimens, including bortezomib and an immunomodulatory agent.**

This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

You are encouraged to report adverse reactions of FARYDAK to Novartis at 1-888-669-6682 and/or the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

\*This journal piece is part of the FDA-required FARYDAK REMS. A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. Visit [www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com) for more information.

For complete safety information, please see the full Prescribing information, including Boxed Warning, available at [www.FARYDAK-REMS.com](http://www.FARYDAK-REMS.com).

# Risk Evaluation and Mitigation Strategy (REMS)

## What is the FARYDAK REMS?

A REMS (**R**isk **E**valuation and **M**itigation **S**trategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. FDA has determined that a REMS is necessary to ensure that the benefits of FARYDAK outweigh the risks.

FARYDAK has a Boxed Warning for the following risks:

## Severe Diarrhea

- **Severe diarrhea occurred in 25% of FARYDAK-treated patients**
  - Severe diarrhea is defined as >7 stools/day, IV fluids, or hospitalization
- Diarrhea occurred in 68% of patients treated with FARYDAK compared with 42% in the control arm
- Monitor for symptoms, institute anti-diarrheal treatment, interrupt FARYDAK, and then reduce dose or discontinue FARYDAK. Refer to the Factsheet for detailed diarrhea management information

## Cardiac Toxicities

- **Severe and fatal cardiac ischemic events**, severe arrhythmias, and ECG changes have occurred with FARYDAK
- **Cardiac ischemic events** occurred in 4% of patients treated with FARYDAK compared with 1% of patients in the control arm
- Arrhythmias occurred in 12% of patients receiving FARYDAK, compared with 5% of patients in the control arm
- **Do not start FARYDAK** if patient has
  - Recent myocardial infarction
  - Unstable angina
  - QTcF  $\geq$ 450 msec
  - Clinically significant ST-segment or T-wave abnormalities

## INDICATION

FARYDAK, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma **who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent.**

This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

## Materials for Health Care Providers

### Fact Sheet for Health Care Providers

[DOWNLOAD PDF](#) 

### Letter to Health Care Providers

[DOWNLOAD PDF](#) 

### Letter to Professional Societies

[DOWNLOAD PDF](#) 



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02/22/2015  
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## **Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF HEMATOLOGY ONCOLOGY PRODUCTS (OHOP)  
DIVISION OF HEMATOLOGY PRODUCTS (DHP)**

---

**NDA #s:** 205353  
**Product:** Farydak® (panobinostat, LBH589) capsules, 10 mg, 15 mg and 20 mg  
**Applicant:** Novartis  
**From:** Qin Ryan, MD, PhD, Medical Officer  
**Through:** Robert Kane, MD, Deputy Division Director for Safety  
**To:** Dr. Ann Farrell, MD, Division Director  
**DATE:** February 18, 2015

---

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

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

This memorandum describes the basis for implementing a REMS for Farydak® (panobinostat, LBH589) with the expected initial approval of the NDA. Farydak is a NME, an oral histone deacetylase inhibitor, in its first cycle review for the indication of the treatment of patients with multiple myeloma who have received at least 2 prior therapies including bortezomib and an immunomodulatory agent. After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Farydak to ensure that the benefits of the drug outweigh the risks of: severe and life-threatening diarrhea and severe and fatal cardiac ischemic events and arrhythmias. In reaching this determination, we considered the following:

A. Multiple myeloma (MM) accounts for approximately 1% of all cancers and 10% of hematologic malignancies. An estimated 24,000 new cases of MM will occur in the U. S. in 2014 with an estimated 11,000 deaths, reported by National Cancer Institute. The diagnosis is most common in the 6<sup>th</sup> and 7<sup>th</sup> decades of life and approximately 75% of patients are over 70 years of age.

B. MM is a serious and ultimately fatal disease, not curative with available therapy. Treatment of MM involves combinations of chemotherapy and stem cell/marrow transplantation for patients with good performance status. However, treatment is not curative and recurrence is expected, leading to further courses of palliative chemotherapy and/or radiation therapy of limited benefit.

C. Farydak (Panobinostat) has shown an improvement in progression-free survival (PFS), a clinical endpoint, in oncology trials, in a trial of patients with relapsed and progressive myeloma. In a multi-center, international trial, 768 eligible patients were randomized to receive panobinostat or placebo, added to the combination of IV bortezomib and oral dexamethasone (BD) therapy. The median PFS difference was 3.9 months; 12.0 months in the panobinostat + BD arm vs. 8.1 months in the placebo + BD arm, with a PFS hazard ratio of 0.63 (95% CI: 0.52, 0.76), p-value <0.0001. Interim analysis for OS (69% of needed events) is considered not mature but did not demonstrate a statistically significant difference between treatments. In a protocol specified trial subpopulation of 193 patients who had received prior treatment with both bortezomib and an immunomodulatory agent, the median number of prior treatments was two, the median PFS difference was 4.8 months: 10.6 months in the panobinostat + BD arm vs. 5.8 months in the placebo + BD arm. The hazard ratio was 0.52 (95% CI: 0.36, 0.76). This subpopulation is considered to be more representative of a U.S. population with advanced, relapsed myeloma in which to assess efficacy and supports the labeled indication.

D. Treatment may continue until toxicity or progression. 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. Patients who enrolled in the randomized clinical trial, Study D2308, were treated for a maximum of 48 weeks or until the development of progressive disease (PD), unacceptable toxicity, or consent withdrawal. Treatment was split in two 24-week phases. Treatment phase 1 comprised eight 3-week cycles of panobinostat 20 mg orally 3 times a week for two weeks of 3-week cycles or identical placebo. All patients were given bortezomib 1.3mg/m<sup>2</sup> intravenous (IV) administration twice weekly for 2 of 3 weeks with dexamethasone 20 mg per day for two days with each dose of bortezomib.

E. The decision to implement a REMS is based on the following observed adverse reactions, which are frequent, severe and serious, and included fatal cases, and may not be sufficiently anticipated and managed in a hematology-oncology practice environment:

### Diarrhea

The draft prescribing information describes the following: *Severe diarrhea occurred in 25% of patients treated with Farydak. Diarrhea of any grade occurred in 68% of patients treated with Farydak. Diarrhea can occur at any time. Monitor patient hydration status and electrolyte blood levels, including potassium, magnesium and phosphate, at baseline and weekly (or more frequently as clinically indicated) during therapy and correct to prevent dehydration and electrolyte disturbances. Initiate anti-diarrheal medication at the onset of diarrhea. Interrupt Farydak at the onset of moderate diarrhea (4 to 6 stools per day.) [see Dosage and Administration (2.2)]. Ensure that patients initiating therapy with Farydak have anti-diarrheal medications on hand.*

Grade 1 or 2 diarrhea was managed with anti-diarrheal medication in 50%-60% of patients overall. Dose interruption and dose adjustment occurred in the 20% of patients with grade 2 diarrhea ( $\geq 4$  stools/day). Grade 3 or 4 diarrhea required dose interruption, dose reduction, and/or drug discontinuation. Overall, 26% of patients receiving Farydak required treatment interruption and/or dose modification, and 5% of patients permanently discontinued Farydak treatment due to diarrhea.

The management of diarrhea requires early introduction of anti-diarrheal therapy, including loperamide and adequate fluid intake at onset of symptoms, and interruption, dose adjustment, or discontinuation of panobinostat. This is especially true for elderly patients, given the increased risk of diarrhea identified in this population.

### Cardiac Toxicities

The prescribing information describes the following: *Severe and fatal cardiac ischemic events, as well as arrhythmias, and ECG changes occurred in patients receiving Farydak. Arrhythmias occurred in 12% of patients receiving Farydak, compared to 5% of patients in the control arm. Cardiac ischemic events occurred in 4% of patients treated with Farydak compared with 1% of patients in the control arm.* (b) (4) *in patients with history of recent myocardial infarction or unstable angina.*

*Electrocardiographic (ECG) abnormalities such as ST-segment depression and T-wave abnormalities also occurred more frequently in patients receiving Farydak compared to the control arm: 22% vs 4% and 40% vs 18%, respectively. Farydak may prolong cardiac ventricular repolarization (QT interval).* (b) (4) *in patients with a QTcF >450 msec or clinically significant baseline ST segment or T wave abnormalities. Arrhythmias may be exacerbated by electrolyte abnormalities.*

*Obtain ECG at baseline and periodically during treatment as clinically indicated. Monitor electrolytes during treatment with Farydak and correct abnormalities as clinically indicated.*

Management includes evaluating cardiac status prior to therapy, including electrocardiogram to verify that the QTcF is less than <450 msec prior to initiation of treatment with FARYDAK. Also, evaluate serum electrolytes and magnesium at baseline and correct abnormal values prior to therapy and periodically during therapy.

F. Farydak is a NME.

The goal of the Farydak REMS is to inform prescribers of the serious risks of diarrhea and cardiac toxicities associated with FARYDAK treatment.

The elements of the REMS will be a Communication Plan and a timetable for submission of assessments of the REMS.

The sponsor will submit REMS assessments to FDA at 18 months, 3 years and 7 years from the initial date of approval of the REMS.

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/s/  
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QIN C RYAN  
02/19/2015

# Internal Consult

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

**Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.**

To: Kate Heinrich Oswell, Health Communications Analyst, DRISK

From: Adam George, PharmD., Regulatory Review Officer

CC: Kathleen Davis, Acting Team II Leader, OPDP  
Kevin Wright, PharmD., SRPM, OSE  
Carole Broadnax, Regulatory Review Officer  
CDER-OPDP-RPM  
Michael Wade

Date: February 11, 2015

Re: NDA #205353  
Farydak<sup>®</sup> (panobinostat) capsules, for oral use  
Comments on draft Risk Evaluation and Mitigation Strategies (REMS)  
Materials

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## **Materials Reviewed**

OPDP has reviewed the following proposed REMS materials for Farydak:

- Healthcare Provider (HCP) REMS Materials:
  - Farydak REMS webpage
  - REMS Letter to Healthcare Providers
  - REMS Letter to Professional Societies
  - Farydak REMS FACT Sheet
  - REMS Journal Information Piece

The version of the draft REMS materials used in this review were sent from DRISK by Kate Heinrich Oswell via email on February 10, 2015. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Farydak:

**General Comment**

Please remind Novartis that REMS materials are not appropriate for use in a

(b) (5)

**REMS Materials**

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Farydak REMS webpage
- REMS Letter to Healthcare Providers
- REMS Letter to Professional Societies
- Farydak REMS FACT Sheet
- REMS Journal Information Piece

**Specific Comments**

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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ADAM N GEORGE  
02/11/2015

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: August 27, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Team Leader: Doris Auth, Pharm.D.  
DRISK

Division Director: Cynthia LaCivita, Pharm.D.  
DRISK

Subject: Risk evaluation and mitigation strategy – deferral on final comments

Drug Name(s): Panobinostat (Farydak)

Therapeutic Class: histone deacetylase inhibitor

Dosage and Route: 20 mg by mouth once daily on day 1, 3, 5, 8, 10, and 12 of a 21 day cycle

Application Type/Number: NDA 205353

Applicant/Sponsor: Novartis

OSE RCM #: 2014-690, 692

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## **EXECUTIVE SUMMARY**

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity panobinostat. The Agency received the new drug application (NDA) from Novartis for panobinostat on March 24, 2014. The proposed indication is “for the treatment of patients with multiple myeloma(MM), who have received at least one prior therapy” in combination with bortezomib and dexamethasone. Panobinostat has orphan designation and is under priority review. Panobinostat is not approved in any country. While survival has improved in recent years for people diagnosed with MM, it remains an incurable cancer with an estimated 10 year survival rate of 20.8%.<sup>1,2</sup>

The phase 3 panobinostat development program for MM consisted of one trial, D2308 and included a total of 768 patients with multiple myeloma (MM) who relapsed after one to three prior treatments (and not refractory to bortezomib). The FDA analysis demonstrated a 2 to 4 month increase in median progression free survival (PFS; median 10 to 12 months, respectively) for relapsed patients treated with panobinostat in combination with bortezomib and dexamethasone compared to bortezomib and dexamethasone alone (median 8 month PFS). This increase in PFS was statistically significant.

The Agency’s safety review of panobinostat presented during the midcycle meeting included the following adverse events of interest; myelosuppression, hemorrhage, infection, and gastrointestinal toxicities. Most notable, grade 3/4 thrombocytopenia occurred in 57% of patients in the panobinostat arm compared to 25% in the standard of care arm. The number of patients who experienced a serious hemorrhage adverse event doubled for patients treated with panobinostat (4% compared to standard of care, 2%) with 6 fatal hemorrhagic events in the panobinostat arm compared to 1 hemorrhagic death in the standard of care arm.

Thrombocytopenia resulting in serious hemorrhagic events along with increased infection and gastrointestinal toxicity combined with a modest improvement in progression free survival compared to the standard of care is the center of the risk/benefit calculus for this application. DHP will be presenting panobinostat to the Oncology Drugs Advisory Committee on November 5, 2014.

In general, healthcare practitioners who treat MM are familiar with thrombocytopenia/hemorrhage (as well as the other adverse events of interest associated with panobinostat) and the importance of close patient monitoring. At this time it has not been determined that the benefits of panobinostat outweigh the risks or if there are risks that may require additional risk mitigation strategies beyond labeling.

DRISK defers a recommendation on a risk management approach pending further discussions with DHP regarding the risk benefit of this product and after the ODAC meeting on November 5, 2014.

## **1 INTRODUCTION**

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity panobinostat. The Agency received the new drug application (NDA) from Novartis for panobinostat on March 24, 2014. The proposed indication is “for the treatment of patients with multiple myeloma, who have received at least one prior therapy” in combination with bortezomib and dexamethasone. Panobinostat is not approved in any country.

Panobinostat is an oral capsule with a proposed recommended starting dose of 20 mg by mouth on days 1, 3, 5, 8, 10, and 12 of a 21 day cycle.

Novartis submitted a “core safety risk management plan;” but did not include a REMS.

## **1.1 BACKGROUND**

Multiple myeloma (MM) is a chronic, incurable, malignancy of the plasma cells. It primarily affects older individuals. The median age at diagnosis is 70 years and two-thirds of MM patients are more than 65 years of age at the time of initial diagnosis. Survival has improved in recent years, both in the relapsed setting as well as at initial diagnosis. At a single institution,<sup>1</sup> median overall survival from the time of relapse improved from 11.8 to 23.9 months in patients relapsing after 2000. In newly diagnosed patients, those diagnosed in the last decade had a 50% improvement in overall survival (44.8 vs 29.9 months). Another paper<sup>2</sup> examined the Surveillance, Epidemiology, and End Results (SEER) database from 1998-2002 and 2003-2007. The 5- and 10-year relative survival rate improved for from 32.8% and 15% in 1998-2002 to 40.3% and 20.8%, respectively, in 2003-2007.

The treatment options for MM and their associated risks and benefits are considered in the context of evaluating the risks and benefits of panobinostat. Initial treatment decisions depend on the patient’s eligibility for stem cell transplant. The National Comprehensive Cancer Network (NCCN) Treatment Guidelines for MM recommend bortezomib/dexamethasone alone or in combination with cyclophosphamide, doxorubicin, lenalidomide, or thalidomide as primary treatment. Recommended maintenance treatment consists of bortezomib, lenalidomide or thalidomide. For the treatment of relapsed myeloma (“salvage therapy”), NCCN recommends repeating the primary induction therapy or a variety of combinations of the drugs listed above (See Appendix D).

## **2 REGULATORY HISTORY**

- March 24, 2014: NDA submission
- February 5, 2014: Pre-NDA meeting

## **3 MATERIALS REVIEWED**

- March 24, 2014 NDA 205353 panobinostat “core risk management plan”
- March 24, 2014. Proposed panobinostat labeling
- June 5, 2014 internal midcycle meeting slides

## **4 RESULTS OF REVIEW**

### **4.1 OVERVIEW OF CLINICAL PROGRAM**

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<sup>1</sup> Kumar SK, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008;111(5):2516-2520.

<sup>2</sup> Pulte D et al. Improvement in survival of older adults with multiple myeloma: results of an updated period analysis of SEER Data. *The Oncologist* 2011;16:1600-1603.

The phase 3 panobinostat development program for MM consisted of one trial, D2308. The trial was a multicenter, 1:1 randomized, double-blind, placebo-controlled trial comparing 20 mg panobinostat in combination with bortezomib and dexamethasone (Pan+BTZ+Dex) versus placebo/bortezomib/dexamethasone (Placebo+BTZ+Dex; standard of care). The primary endpoint was progression free survival (PFS) as assessed by the investigator.

According to the preliminary analysis presented at the midcycle meeting, the trial included a total of 768 patients with MM who relapsed after one to three prior treatments (and not refractory to bortezomib). The median age was 63 years diagnosed approximately 37 months prior to study enrollment. Approximately half of patients had one prior treatment with the other half receiving two or three prior treatments. Between 55-58% of patients had a stem cell transplant.

According to the midcycle meeting slides, the median PFS for the panobinostat arm was 11.99 months compared to 8.08 months in the standard of care arm ( $\Delta$  3.91 months,  $p < 0.0001$ ). Further statistical analysis examined the robustness of the PFS result and determined a “worst case scenario” median PFS for the panobinostat arm was 10.2 months compared to 8.3 months ( $\Delta$  1.9,  $p = 0.0074$ ).

## 4.2 SAFETY CONCERNS

The primary safety evaluation is derived from the phase 3 trial described in Section 3.1 of this review. Supportive safety information was also provided from a single arm phase 2 study (N=55 relapsed/refractory MM patients), and a phase 1 single arm dose escalation trial (N=62 relapsed/refractory MM patients).

Based on data from Study D2308, the median duration of exposure was 152 days (range 3, 411 days) in contrast to a median of 187 days (range 3, 443 days) in the standard of care arm.

The Sponsor states that on-treatment deaths, regardless of causality, were reported in 7.9% of panobinostat-treated patients versus 4.8% of placebo-treated patients. The most frequent treatment related causes of deaths for the panobinostat arm included infection and hemorrhage.

The following table<sup>3</sup> illustrates the higher incidence of serious adverse events in the panobinostat arm.

<b>Serious adverse events &gt; 2%</b>		
<b>Preferred term</b>	<b>Pan+BTZ+Dex (n=381)</b>	<b>Placebo+BTZ+Dex (n=377)</b>
Pneumonia	57 (15%)	40 (11%)
Diarrhea	43 (11%)	9 (2%)
Thrombocytopenia	28 (7%)	8 (2%)
Asthenia	15 (4%)	6 (2%)
Anemia	14 (4%)	3 (1%)
Vomiting	12 (3%)	3 (1%)
Dehydration	11 (3%)	5 (1%)
Fatigue	11 (3%)	2 (1%)

<sup>3</sup> Internal midcycle meeting slide presentation. June 5, 2014.

Reasons for discontinuation were as follows:

	<u>Pan+BTZ+Dex</u>	<u>Placebo+BTZ+Dex</u>
Discontinuation for AE	130 (33.6%)	66 (17.3%)
Discontinuation for Progression of Disease	82 (21.2%)	153 (40.2%)
Died	21 (5.4%)	17 (4.5%)

Sections 3.2.1 through 3.2.6 highlight the risks of interest presented during the June 5, 2014 internal midcycle meeting.<sup>4</sup>

#### 4.2.1 Myelosuppression

##### *Sponsor Summary*

Almost three quarters of the myelosuppression adverse events were grade 3/4. The Sponsor states “given that both panobinostat and bortezomib can cause hematologic toxicity...there is likely an additive effect when the two are combined.” The Sponsor also states that thrombocytopenia appears to be dose related and “generally rapidly reversible upon dosing interruption or dose reduction.” The median time to onset of grade 3/4 was around 1.08 months, no dosing adjustment/interruption was required for grade 3 thrombocytopenia, and the duration of grade 3/4 myelosuppression was 12 days in both treatment arms. Dose modification or adjustment was required for 31.0% of patients due to thrombocytopenia and 29.4% were managed with platelet transfusion.

<b>All events</b>	Pan+BTZ+Dex	Placebo+BTZ+Dex
Grade 3/4 AEs	73.2%	45.1
SAEs	15.5%	3.7%
AEs leading to d/c	2%	0.8%
AEs leading to hospitalization	8%	2.1%
<b>Thrombocytopenia</b>		
Grade 3/4 AEs	63.4%	44.6%
SAEs	11.8%	2.1%
AEs leading to d/c	1.3%	0.5%
AEs leading to	4.7%	1.1%

<sup>4</sup> Percentages and numbers may differ in this section from the Sponsor analysis as the information included reflects the Division of Hematology’s analysis of the application at the point of the midcycle meeting.

hospitalization		
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The Sponsor proposes recommendations for dose adjustment for thrombocytopenia and neutropenia in labeling. They also propose to include myelosuppression in the Warnings and Precautions section of labeling.

*DHP Assessment:* As stated above, the primary concern with myelosuppression is the resulting increased risk of hemorrhage and infection.

*DRISK Comment:* Typically, the goal(s) of a REMS address a specific serious outcome (e.g., hemorrhage, infection) resulting from laboratory abnormalities rather than addressing risk of thrombocytopenia, neutropenia, etc.

#### 4.2.2 Hemorrhage

##### Sponsor Summary

The Sponsor states that “the hemorrhage observed among patients treated with panobinostat in combination with bortezomib appears to be consistent with what was reported for MM patients in general. The thrombocytopenia induced by panobinostat and bortezomib, although very frequent and severe in many patients, does not apparently increase the risk of hemorrhage beyond what could be expected for patients with thrombocytopenia caused by other chemotherapies.”

Severe Hemorrhage	Pan+BTZ+Dex	Placebo+BTZ+Dex
Grade 3/4 AEs	4%	2.4%
SAEs	4%	2.1%
AEs leading to d/c	0.7%	0.3%
AEs leading to hospitalization	4%	1.6%
Deaths	5 patients (1.3%)	0

The Sponsor proposes to include hemorrhage in the Warnings and Precautions section of labeling.

*DHP Assessment:* The incidence of severe thrombocytopenia (grade 3/4 Pan+BTZ+Dex (57%) vs Placebo+BTZ+Dex (25%) is of the greatest concern with this application because of the number of severe hemorrhage cases. Six patients died of hemorrhage who were treated with panobinostat compared to one death in the placebo arm. All patients who died from hemorrhage in Study D2308 (N=5) had grade 3/4 thrombocytopenia at the time of the event. Including hemorrhage as a Boxed Warning has been discussed. However, review of the label is ongoing.

The number of patients who experienced a serious hemorrhage adverse event doubled for patients treated with panobinostat (4% compared to standard of care, 2%).

Further, thrombocytopenia was the most frequent reason for dose modification.

*DRISK Comment:* Many chemotherapeutic agents include myelosuppression and its related serious sequelae with labeling (including Boxed Warnings) to address this risk. However, there or no drugs approved for oncology indications with an approved REMS to address hemorrhage.

*There have been three drug products approved with a REMS to address bleeding. All of these products were approved for cardiovascular indications and addressed the increased risk of*

bleeding compared to standard therapy. Two of the three include Boxed Warning for bleeding which can be fatal. All three products were approved with a Medication Guide. In addition, two of the products were approved with a REMS including a communication plan (e.g., dear healthcare provider/professional society letters, prescriber brochure). Subsequently, the REMS were released because the goals of the REMS were met and the communication activities were complete. The Medication Guides are still required as part of labeling.

### 4.2.3 Infection

#### Sponsor Summary

The overall incidence of infection was slightly higher in the panobinostat arm (27.1%) compared to the placebo arm (21.5%). Pneumonia was the third most common adverse drug reaction leading to treatment discontinuation (1.3%). Death from pneumonia or sepsis was reported. The Sponsor states again that the combination of panobinostat with bortezomib and dexamethasone may have an additive effect.

<b>Severe infection</b>	<b>Pan+BTZ+Dex</b>	<b>Placebo+BTZ+Dex</b>
Grade 3/4 AEs	20.8%	15.6%
SAEs	22.2%	16.2%
AEs leading to d/c	3.5%	3.7%
AEs leading to hospitalization	21.3%	15.9%
<b>Sepsis</b>		
Grade 3/4 AEs	7.3%	3.7%
SAEs	6.7%	3.2%
AEs leading to d/c	0.7%	0.5%
AEs leading to hospitalization	6.2%	2.9%

The Sponsor proposes to include infections in the Warnings and Precautions section of labeling. Further, the proposed labeling states that the most frequent treatment related causes of death for patients in the panobinostat arm included infections and hemorrhage.

*DHP Assessment:* The medical officer noted that ten patients died from infection in the panobinostat treatment arm compared to five patients in the placebo arm. Further, the rate of severe infections due to infection was higher in the panobinostat arm. However, the overall rate of infections for all grade events was similar between the two arms (69% for panobinostat vs. 67% for placebo). The medical officer noted that use of GCSF was 13.1% in the panobinostat arm compared to the 4.2% in the placebo arm which may explain the modest increase in severe infections (panobinostat 31% vs placebo 24%) despite the marked increase in the rate of severe neutropenia.

***DRISK Comment:** There are several REMS approved that address a variety of infections.<sup>5</sup> Most of the drugs treat chronic conditions (e.g., multiple sclerosis, rheumatoid arthritis, osteoporosis, psoriasis) and are treated by practitioners who may not routinely prescribe medications associated with an increased infection risk, or there are certain preventative measures that can be taken to reduce the risk (e.g., vaccination prior to initiating treatment (Soliris, TNF inhibitors, Stelara) testing for viral exposure (Nulojix, Tysabri), or the infection and/or its presentation associated with the drug is unusual (Nulojix, Tysabri).*

*None of the drugs with an approved REMS addressing infection are indicated for the treatment of cancer.<sup>6</sup>*

*The majority of these REMS consist of a communication plan with the exception of the REMS for Tysabri.*

#### **4.2.4 Gastrointestinal Toxicity**

##### Sponsor Summary

Gastrointestinal toxicities, primarily diarrhea, nausea and vomiting are among the most frequently reported adverse reactions. Diarrhea was the most common adverse drug reaction leading to treatment discontinuation (4.5%). According to the Sponsor, diarrhea (non-infective) was reported in 69.2% of Pan+BTZ+Dex-treated patients (grade 3/4 24.6%), compared to 41.6% (grade 3/4 8.2%) in the patients from the Placebo+BTZ+Dex arm. No patients died due to diarrhea-related causes.

<b>Diarrhea</b>	<b>Pan+BTZ+Dex</b>	<b>Placebo+BTZ+Dex</b>
Grade 3/4 AEs	24.6%	8.2%
SAEs	10.2%	2.4%
AEs leading to d/c	4.2%	1.6%
AEs leading to hospitalization	8.6%	2.4%

The Sponsor proposes to include diarrhea in the Warnings and Precautions section of labeling

(b) (4)

<sup>5</sup> Enbrel/Humira/Remicade/Symponi (TNF inhibitors / histoplasmosis and other serious invasive fungal infections), Xeljanz (rheumatoid arthritis / serious infections, malignancies, decreased hematologic parameters, increased lipids), Stelara (psoriasis / infection/reactivation of latent infections, TB, RPLS), Tysabri (multiple sclerosis / PML), Nulojix (renal transplant / PTLD and PML), Prolia (osteoporosis / serious infections, hypocalcemia, dermatologic adverse reactions, suppression of bone turnover including ONJ and atypical femur fractures), Soliris (paroxysmal nocturnal hemoglobinuria / meningococcal infection). The labeling for most of these drugs includes a Boxed Warning addressing the risk of infection.

<sup>6</sup> We note that denosumab is approved for cancer treatment (under the trade name Xgeva) and only the osteoporosis indication (under the trade name Prolia) has an approved REMS. Reasons for not requiring a REMS for Xgeva include the advance nature of the (cancer) disease, increased, more regular monitoring in patients with cancer, and different risk/benefit calculus for patients with cancer compared to post-menopausal women with osteoporosis. Donohue E. DRISK review for Xgeva. Signed October 27, 2010.

*DHP Assessment:* Diarrhea was one of the main reasons for discontinuation of therapy (5%). Diarrhea also led to dose modification or delay in 26% of patients treated with panobinostat compared to 11% of patients in the placebo arm.

*DRISK Comment:* DRISK evaluated drugs that have been approved with a REMS to address diarrhea, nausea/vomiting risk. Zydelig (idelalisib), a kinase inhibitor, is indicated for the treatment of relapsed chronic lymphocytic leukemia, relapsed follicular B-cell non-Hodgkin lymphoma, and relapsed small lymphocytic lymphoma was approved on July 23, 2014, with a REMS consisting of a communication plan (REMS Letters for healthcare providers and professional societies, Fact Sheet, Journal Information piece, website, and patient safety card). The REMS addresses the risks of *fatal/serious* hepatotoxicity, diarrhea/colitis, pneumonitis, and intestinal perforation. These risks are all addressed in a Boxed Warning in labeling. According to the Zydelig label, fatal and/or serious and severe diarrhea or colitis occurred in 14% of Zydelig-treated patients.

#### 4.2.5 Cardiac Ischemic Disease

##### Sponsor Summary

The sponsor identified cardiac ischemic events as a “potential risk.” As reported in the pivotal study D2308, 16.8% of patients treated with Pan+BTZ+Dex had underlying cardiac disorders as part of their medical histories vs. 13.9% in the Placebo+BTZ+Dex arm. In addition, medical history of hypertension was reported in 42.6% of patients from the Pan+BTZ+Dex arm vs. 36.5% from the Placebo+BTZ+Dex arm.

	Pan+BTZ+Dex	Placebo+BTZ+Dex
Grade 3/4 AEs	2%	0.3%
SAEs	2%	0.5%
AEs leading to d/c	0.4%	0
AEs leading to hospitalization	1.6%	0.5%

*DHP Assessment:* Serious adverse events related to ischemic heart disease were more frequent in the panobinostat arm (2%) compared to placebo (0.5%). Many of these cases were confounded.

There were three cardiac related deaths in the panobinostat arm and none in the placebo arm. Deaths were confounded by prior medical history. After further evaluation, DHP determined that this is no longer a risk of concern.

#### 4.2.6 QT Prolongation

##### Sponsor Summary

Non-clinical reports and literature postulate QTc prolongation is a class effect. Three of 449 panobinostat patients had a QTc change of greater than 60ms and 1.3% of patients had a QTcF recorded between 480-500msec. One case of sudden death and two cases of cardiac arrest were reported in the panobinostat treatment arm. None of these patients had apparent QTc prolongation during the studies. No cases of Torsades de pointes were reported. In addition, 3 panobinostat patients were reported to experience ventricular tachycardia or arrhythmia but QTc prolongation was not reported.

<b>QTc prolongation</b>	<b>Pan+BTZ+Dex</b>	<b>Placebo+BTZ+Dex</b>
Grade 3/4 AEs	5.8%	2.9%
SAEs	3.3%	1.9%
AEs leading to d/c	1.6%	1.1%
AEs leading to hospitalization	2.4%	0.5%

The Sponsor proposes to recommend ECG monitoring before initiation of treatment and to delay treatment until the QTcF is less than 480msec. The proposed labeling also addresses QT prolongation in the Warnings and Precautions section of labeling.

*DHP Assessment:* Rates of adverse events were identical for both treatment arms (2%) and no SAEs were reported in Study D2308. After further evaluation, DHP determined that this is no longer a risk of concern.

*DRISK Comment:* 0.7% of patients treated with panobinostat experienced a QTcF > 60msec. Vandetanib (Caprelsa) and nilotinib (Tasigna) are two oncologic drugs approved with a REMS to address the risk of QT prolongation/sudden death. For context, 35% of patients treated with vandetanib experienced a change in QTcF > 60msec. Patients treated with nilotinib, increase in QTcF > 60msec was observed in 4.1% of patients.

#### 4.2.7 Other Safety Concerns

The sponsor also identified the risks outlined below. These risks were not identified as remarkably concerning by DHP:

- **Hepatic dysfunction:** The Sponsor states that “hepatic dysfunction was common among patients treated with Pan+BTZ+Dex, which was largely compatible with the Placebo+BTZ+Dex arm; bilirubin elevation was slightly higher for the Pan+BTZ+Dex-treated patients. The vast majority of such abnormalities, including hyperbilirubinemia, were of low grade in severity and rarely such abnormal LFTs would require dose adjustment or treatment discontinuation.

<b>Hepatic dysfunction</b>	<b>Pan+BTZ+Dex</b>	<b>Placebo+BTZ+Dex</b>
Grade 3/4 AEs	4%	3.4%
SAEs	0.9%	0.8%
AEs leading to d/c	0.2%	0.3%
AEs leading to hospitalization	0.9%	0.8%

The Sponsor proposes to include hepatotoxicity in the Warnings and Precautions section of labeling stating that hepatic dysfunction (b) (4)

- **Renal dysfunction:** According to the Sponsor, among patients treated with Pan+BTZ+Dex in the 3 studies, renal dysfunction adverse events were reported in 85 (18.8%) patients of which

20 (4.4%) were of grade 3/4 severity. Grade 3/4 adverse events were similar between treatment arms.

<b>Renal dysfunction</b>	<b>Pan+BTZ+Dex</b>	<b>Placebo+BTZ+Dex</b>
Grade 3/4 AEs	4.4%	4.5%
SAEs	4.2%	4.0%
AEs leading to d/c	0%	0.8%
AEs leading to hospitalization	3.8%	3.7%

The Sponsor does not propose to include renal dysfunction in the Warning and Precautions section of labeling or specific information in the Adverse Reactions section.

- **Embryo-fetal toxicity:** We note that the Sponsor’s proposed labeling includes “embryo-fetal toxicity” in the Warnings and Precautions section. However, this risk was not included as an “identified” or “potential” risk by the Sponsor nor was it discussed during the midcycle meeting. The Sponsor proposes Pregnancy Category D based on the mechanism of action and animal studies that demonstrated reproductive and embryo-fetal toxicity.
- ***DRISK Comment:** While this is an important risk, it must be put in context with the treated population whose median age exceeds 60 years old. Therefore, most patients are not of reproductive potential. There are many chemotherapeutic agents that are known or suspected teratogens and this risk for most oncology drugs is communicated through professional labeling only. However, we note that three drugs (thalidomide, lenalidomide, and pomalidomide) approved for the treatment of MM (among other indications) and are approved with a REMS that includes elements to assure safe use to address the risk of teratogenicity. All three of these drugs are contraindicated in pregnancy and labeled Pregnancy Category X, opposed to Category D as proposed for panobinostat.*

## **5 SPONSOR’S PROPOSED RISK MANAGEMENT APPROACH**

Novartis proposes labeling and routine pharmacovigilance are sufficient to address the risks with panobinostat. (b) (4)

## **6 DISCUSSION**

### **6.1 BENEFIT**

While survival has improved in recent years for people with MM, it remains an incurable cancer with an estimated 10 year survival rate of 20.8%. Novartis is seeking approval of panobinostat for patients who have relapsed. FDA analysis demonstrated a 2 to 4 month increase in PFS (to a median of 10 to 12 months) for relapsed patients treated with panobinostat in combination with bortezomib and dexamethasone compared to bortezomib and dexamethasone alone (median 8 month PFS). This increase in PFS was statistically significant.

If approved, panobinostat will be the first histone deacetylase inhibitor approved for the treatment of MM; offering a different mechanism of action to target MM compared to current treatment options.

## 6.2 RISKS

Adverse events of interest based on the DHP review of panobinostat presented during the midcycle meeting include myelosuppression, hemorrhage, infection, and gastrointestinal toxicities. Grade 3/4 thrombocytopenia occurred in 57% of patients in the panobinostat arm (compared to 25% in the standard of care arm). The number of patients who experienced a serious hemorrhage adverse event doubled for patients treated with panobinostat (4% compared to standard of care, 2%) with 6 fatal hemorrhagic events (compared to 1 hemorrhagic death in the standard of care arm) all of whom had grade 3/4 thrombocytopenia. While thrombocytopenia can be monitored, monitoring in the clinical trial was unable to prevent serious adverse events, including death.

The incidence of severe infection was higher in patients treated with panobinostat and infection was the leading cause of treatment-related death. However, the numbers/incidence was not as striking between the two treatment arms with the overall rate of infections for all grade events similar between the two arms (69% for panobinostat vs. 67% for placebo) but serious adverse events were more common in the panobinostat-treated patients (infections ( 22.2% Pan+BTZ+Dex vs 16.2% placebo+BTZ+Dex), sepsis SAE ( 6.7% Pan+BTZ+Dex vs 3.2% placebo+BTZ+Dex).

The incidence of diarrhea was also higher in patients treated with panobinostat but there were no reports of death related to diarrhea. In contrast, for example, there were fatal events in patients treated with idelalisib.

With these risks in mind, DRISK considered the safety profiles and risk management approaches for the approved histone deacetylase inhibitors as well as the recommended treatment options for multiple myeloma.

- **Approved histone deacetylase inhibitors (vorinostat, romidepsin, belinostat):** There are some similarities and some differences in grossly comparing the risk profiles of the approved deacetylase inhibitors to each other and to panobinostat. There are three approved histone deacetylase inhibitors are approved for cutaneous and/or peripheral t-cell lymphoma and all three include Warnings and Precautions regarding myelosuppression/hematologic toxicity and embryo-fetal toxicity. None include hemorrhage as a separate Warning. The labeling for romidepsin and belinostat contain no mention of hemorrhage/death while vorinostat includes one mention of a single case of gastrointestinal hemorrhage. Two of the three approved drugs include Warnings regarding gastrointestinal toxicity, infection, and tumor lysis syndrome.

None of these drugs have a Boxed Warning or are approved with a REMS. See Appendix A/Table A.

- **Treatment options for multiple myeloma:** According to the NCCN Treatment Guidelines, there are several drugs recommended for “salvage treatment” for patients who relapse and treatment typically involves a combination of these products. These drugs have anywhere from four to twelve risks listed in the Warnings and Precautions and several carry Boxed Warnings. Three drugs (thalidomide, lenalidomide, and pomalidomide) are approved with a REMS that includes elements to assure safe use to

address the risk of teratogenicity. None of the other treatment options are approved with a REMS. See Appendix B/Table B.

In particular we considered the risk of myelosuppression as described in the labeling for each of the recommended treatment options for MM. In general, thrombocytopenia occurred in roughly 25% of patients (all grade) compared to more than fifty percent of patients treated with Pan+BTZ+Dex experienced grade 3/4 thrombocytopenia. Two of the drugs (lenalidomide and doxorubicin) had Boxed Warnings for hematologic toxicity. See Appendix C/Table C.

Based on the mechanism of action, many chemotherapeutic agents are toxic to the bone marrow, the gastrointestinal tract as well as other organ systems. Myelosuppression/hematologic toxicity, infection, gastrointestinal toxicity, hepatotoxicity, cardiac toxicity, and embryo-fetal toxicity are well-documented adverse events to chemotherapeutic agents, other histone deacetylase inhibitors, and are recognized risks with a number of the treatment options for MM, including panobinostat. Correspondingly, healthcare providers who treat MM are familiar with these toxicities, the necessity of monitoring, and the associated sequelae. However, in particular, the increased frequency and severity of thrombocytopenia, hemorrhage, infection, and gastrointestinal toxicity in patients treated with panobinostat when compared to standard treatment (bortezomib+dexamethasone) cannot be marginalized.

### **6.3 SUMMARY**

Thrombocytopenia resulting in serious hemorrhagic events along with increased infection and gastrointestinal toxicity combined with a modest improvement in progression free survival compared to the standard of care is the center of the risk/benefit calculus for this application. DHP will be presenting panobinostat to the Oncology Drugs Advisory Committee on November 5, 2014.

If approved, it will be important that prescribers are aware of the increased risk of serious adverse events (e.g., hemorrhage and thrombocytopenia) when panobinostat is used in combination bortezomib and dexamethasone. In considering this risk and risk management options, it is important to ensure that the labeling supports the risk management approach. Ticagrelor and prasugral were approved with a REMS including a communication plan to address bleeding and include a Boxed Warning. Two treatment options included in the NCCN Treatment Guidelines carry a Boxed Warning for hematologic toxicity. Second, the merits of additional communication efforts beyond labeling should be discussed especially if DHP recommends that practitioners monitor patients differently than is the typical standard of care for patients with MM. Third, it is important to keep in mind that, in general, healthcare providers who treat MM are familiar with thrombocytopenia/hemorrhage and infection (as well as the other adverse events of interest associated with panobinostat) and the importance of close patient monitoring. A communication concern is that practitioners may quickly dismiss a message if it is not focused on information unique to panobinostat.

If it is determined that a REMS is necessary in order to ensure that the benefits outweigh the risks for panobinostat, additional communication/education efforts may have more impact if they highlight the increased risk and different actions practitioners should take to minimize the risk associated with panobinostat, if any exist.

## **7 CONCLUSION AND RECOMMENDATION**

At this time it has not been determined that the benefits of panobinostat outweigh the risks or if there are risks that may require additional risk mitigation strategies beyond labeling. DHP and DRISK should discuss the merits of additional risk management strategies beyond labeling especially if DHP is considering a recommendation to practitioners to monitor patients differently than the typical standard of care because, in general, healthcare practitioners who treat MM are familiar with thrombocytopenia/hemorrhage (as well as the other adverse events of interest associated with panobinostat) and the importance of close patient monitoring.

DRISK defers a recommendation on a risk management approach pending further discussions with DHP and the Advisory Committee meeting on November 5, 2014.

**Table A: Warnings and Precautions for the approved histone deacetylase inhibitors**

	Route of Administration	Boxed Warning	Approved Indication	Warnings and Precautions	Patient Information	REMS
<b>Vorinostat</b>	Oral capsule	No	<ul style="list-style-type: none"> <li>Cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies</li> </ul>	<ul style="list-style-type: none"> <li>Thromboembolism</li> <li>Myelosuppression</li> <li>Gastrointestinal toxicity</li> <li>Hyperglycemia</li> <li>Clinical chemistry abnormalities</li> <li>Severe thrombocytopenia w other HDACi</li> <li>Pregnancy</li> </ul>	Yes	No
<b>Romidepsin</b>	IV	No	<ul style="list-style-type: none"> <li>Treatment of cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy</li> <li>Treatment of peripheral T-cell lymphoma in patients who have received at least one prior therapy</li> </ul>	<ul style="list-style-type: none"> <li>Hematologic</li> <li>Infection</li> <li>EKG Changes</li> <li>Tumor Lysis Syndrome</li> <li>Use in Pregnancy</li> </ul>	No?	No
<b>Belinostat</b>	IV	No	<ul style="list-style-type: none"> <li>Relapsed/refractory peripheral T-cell lymphoma</li> </ul>	<ul style="list-style-type: none"> <li>Hematologic toxicity</li> <li>Infections</li> <li>Hepatotoxicity</li> <li>Tumor lysis syndrome</li> <li>Gastrointestinal toxicity</li> <li>Embryo-fetal toxicity</li> </ul>	Yes	No

**Table B: Treatment options (“salvage therapy”) according to the *NCCN Multiple Myeloma Guidelines*.<sup>1</sup>**

\*These drug are typically used in combination\*

	Route of Administration	Boxed Warning	Warnings and Precautions	REMS
<b>Bortezomib<sup>2</sup></b>	IV	No	<ul style="list-style-type: none"> <li>• Peripheral neuropathy</li> <li>• Hypotension</li> <li>• Cardiac toxicity</li> <li>• Pulmonary toxicity</li> <li>• PRES</li> <li>• Thrombocytopenia/Neutropenia</li> <li>• Tumor Lysis Syndrome</li> <li>• Hepatic toxicity</li> <li>• Embryo-fetal risk</li> </ul>	No
<b>Thalidomide</b>	Oral	Yes <ul style="list-style-type: none"> <li>• Fetal toxicity</li> <li>• VTE</li> </ul>	<ul style="list-style-type: none"> <li>• Fetal toxicity</li> <li>• Venous and Arterial TE</li> <li>• Drowsiness and somnolence</li> <li>• Peripheral neuropathy</li> <li>• Dizziness and orthostatic hypotension</li> <li>• Neutropenia</li> <li>• Increased HIV viral load</li> <li>• Bradycardia</li> <li>• Stevens-Johnson Syndrome and TEN</li> <li>• Seizures</li> <li>• Contraceptive risks</li> <li>• Hypersensitivity</li> </ul>	Yes - teratogenicity
<b>Lenalidomide</b>	oral	Yes	<ul style="list-style-type: none"> <li>• Fetal toxicity</li> </ul>	Yes - teratogenicity

<sup>1</sup> Not all drugs recommended in the NCCN Guidelines are FDA-approved for the treatment of multiple myeloma.

<sup>2</sup> Studied in combination with panobinostat.

		<ul style="list-style-type: none"> <li>• Fetal toxicity</li> <li>• Hematologic</li> <li>• VTE</li> </ul>	<ul style="list-style-type: none"> <li>• Hematologic toxicity</li> <li>• VTE</li> <li>• Increased death in pts with CLL</li> <li>• 2nd primary malignancies</li> <li>• Hepatotoxicity</li> <li>• Allergic rxn</li> <li>• Tumor lysis syndrome</li> <li>• Tumor Flare Reaction</li> </ul>	
<b>Pomalidomide</b>	oral	<p>Yes</p> <ul style="list-style-type: none"> <li>• Fetal toxicity</li> <li>• VTE</li> </ul>	<ul style="list-style-type: none"> <li>• Embryo-fetal toxicity</li> <li>• POMALYST REMS Program</li> <li>• Venous thromboembolism</li> <li>• Hematologic toxicity</li> <li>• Hypersensitivity rxns</li> <li>• Dizziness and confusional state</li> <li>• Neuropathy</li> <li>• Risk of second primary malignancies</li> <li>•</li> </ul>	Yes - teratogenicity
<b>Cyclophosphamide</b>	Oral, IV	No	<ul style="list-style-type: none"> <li>• Myelosuppression</li> <li>• Urinary tract and renal toxicity</li> <li>• Pulmonary toxicity</li> <li>• 2nd malignancies</li> <li>• Veno-occlusive liver disease</li> <li>• Fetal toxicity</li> <li>• Infertility</li> <li>• Impaired wound healing</li> <li>• Hyponatremia</li> </ul>	
<b>Carfilzomib</b>	IV	No	<ul style="list-style-type: none"> <li>• Cardiac arrest, CHF, Myocardial ischemia</li> <li>• Pulm hypertension</li> <li>• Pulm complications</li> <li>• Infusion rxns</li> <li>• Tumor lysis syndrome</li> <li>• Thrombocytopenia</li> <li>• Hepatotoxicity and hepatic failure</li> <li>• Fetal toxicity</li> </ul>	<b>No</b>

Doxorubicin lioposome		Yes <ul style="list-style-type: none"> <li>• Infusion rxn</li> <li>• Myelosuppression</li> <li>• Cardiotoxicity</li> <li>• Liver impairment</li> <li>• Substitution</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiac toxicity</li> <li>• Infusion rxns</li> <li>• Myelosuppression</li> <li>• Hand-Foot Syndrome</li> <li>• Radiation recall rxn</li> <li>• Fetal Mortality</li> <li>• Toxicity Potentiation</li> <li>• Monitoring: Laboratory Tests</li> <li>• Secondary oral neoplasms</li> </ul>	PI - Warnings
Etoposide	IV	Yes Qualified physician	<ul style="list-style-type: none"> <li>• Myelosuppression</li> <li>• Anaphylactic rxn</li> <li>• Injection site rxn</li> <li>• Fetal toxicity</li> </ul>	No
Cisplatin	IV	Yes <ul style="list-style-type: none"> <li>• Qualified physician</li> <li>• Renal toxicity</li> <li>• Ototoxicity</li> <li>• Anaphylactic like rxn</li> <li>• Overdose</li> </ul>	<ul style="list-style-type: none"> <li>• Renal toxicity</li> <li>• Neuropathy</li> <li>• Anaphylactic like rxn</li> <li>• Ototoxicity</li> <li>• Fetal toxicity</li> <li>• Carcinogenic effect</li> <li>• Injection site rxn</li> </ul>	No

**Table C: Myelosuppression text in approved labeling for other MM Treatment Options**

	Myelosuppression Text	Source
Panobinostat	Grade 3/4 57% (Pan+BTZ+Dex) vs 25% (Placebo+BTZ+Dex)	Internal midcycle meeting
Bortezomib	In the relapsed multiple myeloma study of VELCADE versus dexamethasone, the incidence of bleeding (≥ Grade 3) was 2% on the VELCADE arm and was < 1% in the dexamethasone arm.  <b>Table 6: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the</b>	PI – Warnings (MM)

	<p><b>Relapsed Multiple</b></p> <hr/> <p style="text-align: center;"><b>Myeloma Study of VELCADE versus Dexamethasone</b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">Pretreatment Platelet Count*</th> <th style="text-align: center;">Number of Patients (N=331)**</th> <th style="text-align: center;">Number (%) of Patients with Platelet Count &lt; 10,000/<math>\mu</math>L</th> <th style="text-align: center;">Number (%) of Patients with Platelet Count 10,000-</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;"><math>\geq 75,000/\mu</math>L</td> <td style="text-align: center;">309</td> <td style="text-align: center;">8</td> <td style="text-align: center;">36</td> </tr> <tr> <td style="text-align: center;"><math>\geq 50,000/\mu</math>L- &lt; 75,000/<math>\mu</math>L</td> <td style="text-align: center;">14</td> <td style="text-align: center;">2 (14%)</td> <td style="text-align: center;">11 (79%)</td> </tr> <tr> <td style="text-align: center;"><math>\geq 10,000/\mu</math>L- &lt; 50,000/<math>\mu</math>L</td> <td style="text-align: center;">7</td> <td style="text-align: center;">1 (14%)</td> <td style="text-align: center;">5 (71%)</td> </tr> </tbody> </table> <p>* A baseline platelet count of 50,000/<math>\mu</math>L was required for study eligibility  ** Data were missing at baseline for 1 patient</p>	Pretreatment Platelet Count*	Number of Patients (N=331)**	Number (%) of Patients with Platelet Count < 10,000/ $\mu$ L	Number (%) of Patients with Platelet Count 10,000-	$\geq 75,000/\mu$ L	309	8	36	$\geq 50,000/\mu$ L- < 75,000/ $\mu$ L	14	2 (14%)	11 (79%)	$\geq 10,000/\mu$ L- < 50,000/ $\mu$ L	7	1 (14%)	5 (71%)	
Pretreatment Platelet Count*	Number of Patients (N=331)**	Number (%) of Patients with Platelet Count < 10,000/ $\mu$ L	Number (%) of Patients with Platelet Count 10,000-															
$\geq 75,000/\mu$ L	309	8	36															
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$\geq 10,000/\mu$ L- < 50,000/ $\mu$ L	7	1 (14%)	5 (71%)															
<p><b>Doxorubicin hydrochloride</b></p>	<p>Leukopenia</p> <ul style="list-style-type: none"> <li>- Grade 3 or 4: 3.7%</li> </ul> <p>Thrombocytopenia</p> <ul style="list-style-type: none"> <li>- Grade 4: 0.1%</li> </ul>	<p>PI – AE section (early breast cancer)</p>																
<p><b>Doxorubicin, liposomal</b></p>	<p>DOXIL may potentiate the toxicity of other anticancer therapies. In particular, hematologic toxicity may be more severe when DOXIL is administered in combination with other agents that cause bone marrow suppression.</p> <p>In patients with relapsed ovarian cancer, myelosuppression was generally moderate and reversible. In the three single-arm studies, anemia was the most common hematologic adverse reaction (52.6%), followed by leukopenia (WBC &lt; 4,000 mm<sup>3</sup>; 42.2%), thrombocytopenia (24.2%), and neutropenia (ANC</p>	<p>PI- Warnings</p>																

	<1,000; 19.0%). In the randomized study, anemia was the most common hematologic adverse reaction (40.2%), followed by leukopenia (WBC <4,000 mm <sup>3</sup> ; 36.8%), neutropenia (ANC <1,000; 35.1%), and thrombocytopenia (13.0%) [see Adverse Reactions (6.2)].	
<b>Carfilzomib</b>	In patients with multiple myeloma, 36% of patients experienced thrombocytopenia, including Grade 4 in 10%. Thrombocytopenia following KYPROLIS administration resulted in a dose reduction in 1% of patients and discontinuation of treatment with KYPROLIS in < 1% of patients.	PI – Warnings (MM)
<b>Cyclophosphamide</b>	Data not provided	PI
<b>Thalidomide</b>	Thrombocytopenia rate not reported.  Neutropenia – 31% (all grades) / 10% (grade 3/4)	PI
<b>Lenalidomide</b>	REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction.  Grade 3 or 4 <u>hematologic</u> toxicity was seen in 80% of patients enrolled in the MDS study. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median time to documented recovery was 17 days (range, 2-170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8-290 days), and the median time to documented recovery was 22 days (range, 5-224 days [see Boxed Warning and Dosage and Administration (2.2)].  In the pooled <b>MM</b> trials Grade 3 and 4 hematologic toxicities were more frequent in patients treated with the combination of REVLIMID and dexamethasone than in patients treated with dexamethasone alone  In the <b>MCL</b> trial, Grade 3 or 4 neutropenia was reported in 43% of the patients. Grade 3 or 4 thrombocytopenia was reported in 28% of the patients.	PI – Warnings
	Thrombocytopenia	PI – AR section

	<ul style="list-style-type: none"> <li>- 21.5% (all grades) / 12.2% (Grade 3/4)</li> </ul> <p>Neutropenia</p> <ul style="list-style-type: none"> <li>- 42.2% (all grades) / 33.4% (Grades 3/4)</li> </ul>	(MM)
<b>Pomalidomide</b>	Neutropenia of any grade was reported in 50% of patients in the trial.  The rate of Grade 3/4 neutropenia was 43%. The rate of febrile neutropenia was 3%.	PI- Warnings
	Thrombocytopenia	PI – AR section
	<ul style="list-style-type: none"> <li>- 25% (All grades) / 19-22% (Grade 3/4)</li> </ul>	

### D. NCCN Guidelines – Multiple Myeloma (version 2.2014)

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**MYELOMA THERAPY<sup>1-3</sup>**

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

Salvage Therapy <sup>7</sup>	Preferred Regimens	Other Regimens
	<ul style="list-style-type: none"> <li>• Repeat primary induction therapy (if relapse at &gt; 6 mo)</li> <li>• Bortezomib (category 1)</li> <li>• Bortezomib/dexamethasone</li> <li>• Bortezomib/lenalidomide/dexamethasone</li> <li>• Bortezomib/ liposomal doxorubicin (category 1)</li> <li>• Bortezomib/thalidomide/dexamethasone</li> <li>• Carfilzomib<sup>8</sup></li> <li>• Cyclophosphamide/bortezomib/dexamethasone</li> <li>• Cyclophosphamide/lenalidomide/dexamethasone</li> <li>• Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)</li> <li>• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)</li> <li>• High-dose cyclophosphamide</li> <li>• Lenalidomide/dexamethasone<sup>9</sup> (category 1)</li> <li>• Pomalidomide<sup>9</sup>/dexamethasone<sup>9</sup></li> <li>• Thalidomide/dexamethasone<sup>9</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Bendamustine</li> <li>• Bortezomib/vorinostat</li> <li>• Lenalidomide/bendamustine/dexamethasone</li> </ul>

<sup>1</sup>Selected, but not inclusive of all regimens.  
<sup>2</sup>Recommend herpes zoster prophylaxis for patients treated with bortezomib and carfilzomib. Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.  
<sup>3</sup>Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.  
<sup>7</sup>Consideration for appropriate regimen is based on the context of clinical relapse.  
<sup>8</sup>Indicated for patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 90 days of completion of the last therapy.  
<sup>9</sup>Consider single-agent lenalidomide, pomalidomide, or thalidomide for steroid-intolerant individuals.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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