Temporary Compliance Waiver Notice

At the time of initial posting on 2/25/15 the attached PDF document may not be fully accessible to readers using assistive technology. A fully accessible version of the document is in preparation and will be posted as soon as it is ready. We regret any inconvenience that this may cause our readers.

In the event you are unable to read this document or portions thereof, please contact Division of Drug Information in Office of Communications at 301-796-3634 or email druginfo@fda.hhs.gov.

Initial REMS Approval 02/2015

NDA 205353 FARYDAK (panobinostat)

histone deactylase 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) 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.

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

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 ≥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** (≥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** 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**.

NOVARTIS ONCOLOGY

Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936-1080

Reference ID: 3699607

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

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® 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**.

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** 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** or call 1-800-FDA-1088.

Sincerely,

Novartis Pharmaceuticals Corporation

NOVARTIS
ONCOLOGY

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

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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.**

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** 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** or call 1-800-FDA-1088.

Sincerely,

Novartis Pharmaceuticals Corporation

Full Prescribing Information | Medication Guide | Factsheet

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

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

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® 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**.

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** for more information.

Sincerely,

Novartis Pharmaceuticals Corporation

NOVARTIS ONCOLOGY

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

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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

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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**.

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.

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Sincerely,

Novartis Pharmaceuticals Corporation

Full Prescribing Information | Medication Guide | Factsheet

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

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

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**
  - o 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**

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
  - o Recent myocardial infarction
  - o Unstable angina
  - o QTcF >450 msec
  - o Clinically significant ST-segment or T-wave abnormalities

Indication

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.**

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** 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** for more information.

For complete safety information, please see the full Prescribing information, including Boxed Warning, available at **www.FARYDAK-REMS.com.**

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Reference ID: 3699607

Risk Evaluation and Mitigation Strategy (REMS)

What is the 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. 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 ≥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

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Letter to Health Care Providers

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Letter to Professional Societies

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/s/

RICHARD PAZDUR
02/23/2015