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RESEARCH**

APPLICATION NUMBER:

206545Orig1s000

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

**Department of Health and Human Services
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: July 22, 2014

Reviewer(s): Naomi Redd, Pharm.D., Risk Management Analyst
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H., Health Communications Analyst
DRISK

Team Leader: Doris Auth, Pharm.D.
Acting Team Leader, DRISK

Division Director: Cynthia LaCivita, Pharm.D.
Acting Director, DRISK

Subject: Final REMS review

Drug Name(s): idelalisib (Zydelig)

Therapeutic Class: phosphatidylinositol 3-kinase delta (PI3K δ) inhibitor

Dosage and Route: 150mg orally twice daily

Application Type/Number: NDA 205858 and NDA 206545

Supplement Number: eCTD 0060, Supporting Document # 64

Applicant/sponsor: Gilead Sciences, Inc.

OSE RCM #: 2013-2084

***** This document contains proprietary and confidential information that should not be released to the public. *****

1 INTRODUCTION

This review provides DRISK's evaluation and comments for Gilead's communication plan (CP) REMS, final version submitted via email on July 22, 2014 and formally to Global Submit July 22, 2014 eCTD 0060; supporting document number 64, for Zydelig® (idelalisib, NDA 205858 and NDA 206545). The Agency comments on the sponsor's proposed CP REMS were sent to the sponsor on July 21, 2014. The sponsor incorporated all of the Agency comments, therefore finalizing the review for these NDA applications.

Idelalisib is a kinase inhibitor indicated for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab and for the treatment of relapsed non-Hodgkin's lymphoma (that only includes follicular B-Cell and small lymphocytic lymphoma) in patients who have received at least two prior systemic therapies. Fatal and serious toxicities associated with Zydelig treatment include: hepatotoxicity, severe diarrhea and colitis, pneumonitis, and intestinal perforation.

2 MATERIALS REVIEWED

- Revised REMS submitted by Gilead, eCTD 0060, Supporting Document 64, July 22, 2014
- Zydelig Final label, July 18th, 2014

2.1 PREVIOUS DRISK REMS REVIEWS

- May 20th, 2014; N. Redd
- June 27th, 2014; N. Redd
- July 21st, 2014; N. Redd

3 REVIEW FINDINGS

The sponsor's submission of their revised REMS and REMS materials on July 22, 2014 was based on label negotiations with the Agency on July 18th, 2014. Revisions to the REMS and REMS materials now align with the risks outlined in the Boxed Warning and Warnings and Precautions sections which include: fatal and/or serious hepatotoxicity, fatal and/or serious and severe diarrhea or colitis, fatal and serious pneumonitis, and fatal and serious intestinal perforation. There sponsor has incorporated all of the Agency's edits, are there are no other edits or changes recommended by DRISK for these documents.

4 CONCLUSIONS AND RECOMMENDATIONS

DRISK finds the revised REMS, REMS Supporting Document, and the REMS communication materials acceptable for approval.

REMS Document
Initial Approval 07/2014

NDA 205858 and NDA 206545

ZYDELIG™ (idelalisib) tablets

Drug Class: Phosphoinositide-3 Kinase-Delta Inhibitor

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Phone: (800) 445-3235

Risk Evaluation and Mitigation Strategy (REMS)

I. GOAL(S):

The goal of the Zydelig REMS is to mitigate the risks of fatal and /or serious hepatotoxicity, fatal/or serious and severe diarrhea or colitis, fatal and serious pneumonitis, and fatal and serious intestinal perforation associated with Zydelig treatment by informing prescribers of the risks of

- fatal and/or serious hepatotoxicity
- fatal and/or serious and severe diarrhea or colitis
- fatal and serious pneumonitis
- fatal and serious intestinal perforation

II. REMS ELEMENTS

A. Communication Plan

Gilead Sciences, Inc. (Gilead) will implement the following communication plan for Healthcare Providers who are likely to prescribe Zydelig. The communication plan will consist of the following:

1. **REMS Letter** - A *REMS Letter to Healthcare Providers* will be distributed within 30 days after the REMS approval date. The letter will be distributed electronically to oncologists and hematologists who are likely to prescribe Zydelig. If a targeted Healthcare Provider's email address is not available, or if an email is undeliverable, the provider will receive the letter through the mail. The *REMS Letter to Healthcare Providers* will inform Healthcare Providers of the risks of fatal and/or serious hepatotoxicity, fatal and/or serious and severe diarrhea or colitis, fatal and serious

pneumonitis, and fatal and serious intestinal perforation associated with Zydelig treatment. The letter will be accompanied by the Prescribing Information (with Medication Guide attached) and the *Zydelig REMS Fact Sheet*. The *REMS Letter to Healthcare Providers* will be available from the *Zydelig REMS Website* at the time of distribution and will remain on the website for the duration of the REMS.

2. **REMS Letter for Professional Societies** - A *REMS Letter for Professional Societies* will be distributed electronically within 30 days after the REMS approval date. If a targeted Professional Societies' email address is not available, or if an email is undeliverable, the letter will be sent through the mail. The *REMS Letter for Professional Societies* will inform the leadership of the professional societies described below of the risks of fatal and/or serious hepatotoxicity, fatal and/or serious and severe diarrhea or colitis, fatal and serious pneumonitis, and fatal and serious intestinal perforation associated with Zydelig treatment. Gilead will request the leadership of the professional societies to distribute this risk information to their memberships.

The *REMS Letter for Professional Societies* will be distributed to the following organizations:

- 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)

3. **REMS Fact Sheet** – A *Zydelig REMS Fact Sheet* will be distributed to Healthcare Providers. The *Zydelig REMS Fact Sheet* will be included in the mailings of the *REMS Letter to Healthcare Providers* and the *REMS Letter for Professional Societies* and will be available on the *Zydelig REMS website*. Hard copies of the *Zydelig REMS Fact Sheet* will also be distributed by Gilead's sales representatives and medical field-based personnel to Healthcare Providers during follow-up details/visits with Healthcare Providers for the first 12 months after the approval of the Zydelig REMS.
4. **Journal Information Piece** - Gilead will publish in the following professional journals an information piece that includes the risks of fatal and/or serious hepatotoxicity, fatal and/or serious and severe diarrhea or colitis, fatal and serious pneumonitis and fatal and serious intestinal perforation associated with Zydelig 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.

- 5. Scientific Meetings** – The *Zydelig REMS Fact Sheet* and the Prescribing Information will be prominently displayed at scientific meetings where Gilead has a presence (e.g., booth) through the end of December 2015 following the REMS approval.
- 6. Zydelig REMS website** –The website will contain information on the Zydelig REMS and will provide access to all the REMS materials, and the Prescribing Information and Medication Guide. The website will be available for the duration of the REMS.
- 7. Zydelig Patient Safety Information Card** - A patient safety information card will highlight the risks of Zydelig and include information on the management of these risks. Gilead’s sales representatives or medical field based personnel will distribute the patient safety information cards to prescribers. The patient safety information card will also be available on the Zydelig REMS website.

The following are part of the REMS and are appended.

- The *REMS Letter to Healthcare Providers*
- The *REMS Letter for Professional Societies*
- The *REMS Fact Sheet*
- The Journal Information Piece
- The *Zydelig REMS Website* (Landing Page)
- Zydelig Patient Safety Information Card

B. Timetable for Submission of Assessments

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

From: Gilead Sciences, Inc.
To: <Healthcare Provider Name>

Subject: Warning: Fatalities and Serious Risks Associated with Zydelig

Zydelig® REMS

[View in Browser](#) | [Full Prescribing Information](#) | [Important Safety Information](#)



Zydelig REMS

FDA REQUIRED REMS SAFETY INFORMATION

Risk of:

- Fatal and/or serious hepatotoxicity
- Fatal and/or serious and severe diarrhea or colitis
- Fatal and serious pneumonitis
- Fatal and serious intestinal perforation

IMPORTANT SAFETY NOTICE

Dear Healthcare Provider:

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

- WARNING: FATAL AND SERIOUS TOXICITIES: HEPATIC, SEVERE DIARRHEA, COLITIS, PNEUMONITIS, AND INTESTINAL PERFORATION**
- Fatal and/or serious hepatotoxicity occurred in 14% of Zydelig-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue Zydelig.
 - Fatal and/or serious and severe diarrhea or colitis occurred in 14% of Zydelig-treated patients. Monitor for the development of severe diarrhea or colitis. Interrupt and then reduce or discontinue Zydelig.
 - Fatal and serious pneumonitis can occur in Zydelig-treated patients. Monitor for pulmonary symptoms and interstitial infiltrates. Interrupt or discontinue Zydelig.
 - Fatal and serious intestinal perforation occurred in Zydelig-treated patients across clinical trials. Discontinue Zydelig if intestinal perforation is suspected.

Please see the [Zydelig REMS Fact Sheet](#), a non-promotional fact sheet reviewed by the FDA, for more detailed safety information. Please give the [Zydelig Patient Safety Information Card](#) to all patients. The card, the fact sheet, and other important information are available at: www.ZydeligREMS.com.

Zydelig is a kinase inhibitor indicated for the treatment of patients with

- Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies.
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

This email does not contain the complete safety profile for Zydelig. To review the Prescribing Information, including complete **BOXED WARNING** and Medication Guide, see links below:

[Prescribing Information](#)

[Medication Guide](#)

Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. Healthcare Providers should report all suspected adverse events associated with Zydelig to the FDA or to Gilead at 1-800-445-3235.

Sincerely,

[signature]

Hans Reiser, MD
Senior Vice President, Medical Affairs

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Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
www.ZydeligREMS.com Phone 650 574 3000 Facsimile 650 578 9264 REMS-ZYD-0001

From: **Gilead Sciences, Inc.** Hide
To: **<Healthcare Provider Name>**

Warning: Fatalities and Serious Risks Associated with Zydelig

Month 30, 2014 at 5:00 PM

Zydelig® REMS

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[Important Safety Information](#)



Zydelig REMS

FDA REQUIRED REMS SAFETY INFORMATION

- Risk of:**
- **Fatal and/or serious hepatotoxicity**
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[Medication Guide](#)

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Sincerely,

[signature]

Hans Reiser, MD
Senior Vice President, Medical Affairs

Zydelig REMS

FDA REQUIRED REMS SAFETY INFORMATION

Risk of:

- **Fatal and/or serious hepatotoxicity**
- **Fatal and/or serious and severe diarrhea or colitis**
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July 2014

IMPORTANT SAFETY NOTICE

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Zydelig REMS

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Sincerely,

[signature]

Hans Reiser, MD
Senior Vice President, Medical Affairs

From: Gilead Sciences, Inc.
To: <Name, Professional Society>

Subject: Warning: Fatalities and Serious Risks Associated with Zydelig

Zydelig® REMS

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Zydelig REMS

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Risk of:

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July 2014

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Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
www.ZydeligREMS.com Phone 650 574 3000 Facsimile 650 578 9264 REMS-ZYD-0003

From: **Gilead Sciences, Inc.** Hide
To: <Name, Professional Society>

Warning: Fatalities and Serious Risks Associated with Zydelig
Month 30, 2014 at 5:00 PM

Zydelig® REMS

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Zydelig REMS

FDA REQUIRED REMS SAFETY INFORMATION

Risk of:

- **Fatal and/or serious hepatotoxicity**
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July 2014

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[Medication Guide](#)

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[signature]

Hans Reiser, MD
Senior Vice President, Medical Affairs

Zydelig[®] REMS

FDA REQUIRED REMS SAFETY INFORMATION

Risk of:

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Zydelig® REMS

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[signature]

Hans Reiser, MD
Senior Vice President, Medical Affairs

**FDA REQUIRED REMS (Risk Evaluation Mitigation Strategy)
SAFETY INFORMATION**

Zydelig[®] REMS Fact Sheet

FDA REQUIRED Zydelig (idelalisib) REMS SAFETY INFORMATION

Risk of:

- Fatal and/or serious hepatotoxicity
- Fatal and/or serious and severe diarrhea or colitis
- Fatal and serious pneumonitis
- Fatal and serious intestinal perforation

BOXED WARNING

Fatal and Serious Hepatotoxicity

- Fatal and/or serious hepatotoxicity occurred in 14% of patients treated with Zydelig.
- Elevations in ALT or AST greater than 5 times the upper limit of normal have occurred. These findings were generally observed within the first 12 weeks of treatment and were reversible with dose interruption. After resumption of treatment at a lower dose, 26% of patients had recurrence of ALT and AST elevations. Discontinue Zydelig for recurrent hepatotoxicity.
- Avoid concurrent use of Zydelig with other drugs that cause liver toxicity.
- Monitor ALT and AST in all patients every 2 weeks for the first 3 months of treatment, every 4 weeks for the next 3 months, then every 1 to 3 months thereafter. Monitor weekly for liver toxicity if the ALT or AST rises above 3 times the upper limit of normal until resolved. Withhold Zydelig if the ALT or AST is greater than 5 times the upper limit of normal, and continue to monitor AST, ALT and total bilirubin weekly until the abnormality is resolved.

Fatal, Serious, and Severe Diarrhea or Colitis

- Fatal and/or serious and severe diarrhea or colitis (Grade 3 or higher) occurred in 14% of Zydelig-treated patients across clinical trials. 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 one week and one month across trials following interruption of Zydelig therapy and in some instances, use of corticosteroids.

Fatal and Serious Pneumonitis

- Fatal and serious pneumonitis occurred in patients treated with Zydelig.
- Patients taking Zydelig who present with pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation should be evaluated for pneumonitis.

Zydelig[®] REMS Fact Sheet

- If pneumonitis is suspected, interrupt Zydelig until the etiology of the pulmonary symptoms has been determined.
- Patients with pneumonitis thought to be caused by Zydelig have been treated with discontinuation of Zydelig and administration of corticosteroids.

Fatal and Serious Intestinal Perforation

- Fatal and serious intestinal perforation occurred in Zydelig-treated patients. At the time of perforation, some patients had moderate to severe diarrhea.
- Advise patients to promptly report any new or worsening abdominal pain, chills, fever, nausea, or vomiting.
- Discontinue Zydelig permanently in patients who experience intestinal perforation.

INDICATION:

Zydelig is a kinase inhibitor indicated for the treatment of patients with

- Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies.
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

WHAT IS THE ZYDELIG 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 Zydelig outweigh its risks. The purpose of the Zydelig REMS is to inform Healthcare Providers of the serious risks of hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation. This fact sheet is required by the FDA as part of the Zydelig REMS program.

Please visit www.ZydeligREMS.com for further information and resources.

This fact sheet does not contain the complete safety profile for Zydelig. Please see the Prescribing Information, including the **BOXED WARNING** and Medication Guide.

REPORTING ADVERSE EVENTS

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. Healthcare Providers should report all suspected adverse events associated with Zydelig to the FDA or to Gilead at 1-800-445-3235.

FDA REQUIRED Safety Information for Zydelig® (idelalisib)

INDICATION:

Zydelig is a kinase inhibitor indicated for the treatment of patients with:

- Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies.
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

Risk of:

- **Fatal and/or serious hepatotoxicity**
- **Fatal and/or serious and severe diarrhea or colitis**
- **Fatal and serious pneumonitis**
- **Fatal and serious intestinal perforation**

Zydelig (idelalisib)

- **BOXED WARNING**

BOXED WARNING

Fatal and/or Serious Hepatotoxicity

- Fatal and/or serious hepatotoxicity occurred in 14% of patients treated with Zydelig.
- Elevations in ALT or AST greater than 5 times the upper limit of normal have occurred. These findings were generally observed within the first 12 weeks of treatment and were reversible with dose interruption. After resumption of treatment at a lower dose, 26% of patients had recurrence of ALT and AST elevations. Discontinue Zydelig for recurrent hepatotoxicity.
- Avoid concurrent use of Zydelig with other drugs that cause liver toxicity.
- Monitor ALT and AST in all patients every 2 weeks for the first 3 months of treatment, every 4 weeks for the next 3 months, then every 1 to 3 months thereafter. Monitor weekly for liver toxicity if the ALT or AST rises above 3 times the upper limit of normal until resolved. Withhold Zydelig if the ALT or AST is greater than 5 times the upper limit of normal, and continue to monitor AST, ALT and total bilirubin weekly until the abnormality is resolved.

FDA REQUIRED Safety Information for Zydelig[®] (idelalisib)

Fatal and/or Serious and Severe Diarrhea/Colitis

- Fatal and/or serious and severe diarrhea or colitis (Grade 3 or higher) occurred in 14% of Zydelig-treated patients across clinical trials. 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 one week and one month across trials, following interruption of Zydelig therapy and in some instances, use of corticosteroids.

Fatal and Serious Pneumonitis

- Fatal and serious pneumonitis occurred in patients treated with Zydelig.
- Patients taking Zydelig who present with pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation should be evaluated for pneumonitis.
- If pneumonitis is suspected, interrupt Zydelig until the etiology of the pulmonary symptoms has been determined.
- Patients with pneumonitis thought to be caused by Zydelig have been treated with discontinuation of Zydelig and administration of corticosteroids.

Fatal and Serious Intestinal Perforation

- Fatal and serious intestinal perforation occurred in Zydelig-treated patients.
- At the time of perforation, some patients had moderate to severe diarrhea.
- Advise patients to promptly report any new or worsening abdominal pain, chills, fever, nausea, or vomiting.
- Discontinue Zydelig permanently in patients who experience intestinal perforation.

You are encouraged to report negative side effects of Zydelig to Gilead at 1-800-445-3235 and/or the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.


This journal piece is part of the FDA-required Zydelig REMS. Visit www.ZydeligREMS.com for more information.

For complete safety information, see the Prescribing Information available at www.ZydeligREMS.com.

FRONT

INSIDE MIDDLE

FRONT RIGHT



Patient Safety Information Card

+ Important Safety Information for Patients Taking Zydelig®

There are serious risks to understand when taking Zydelig. Be certain to get regular blood tests as scheduled by your doctor. Also, if you experience any of the following symptoms, you should immediately call your doctor and seek emergency medical care.

These symptoms include:

- Stomach (abdominal) pain or swelling
- Persistent or worsening nausea or vomiting
- Severe diarrhea
- Dark urine color
- Bloody or tar-colored stool
- Shortness of breath, difficulty breathing, or wheezing
- New or worsening cough
- Persistent fever (temperature over 101°F)

⚠ Remember! Call your doctor and get emergency medical care right away if you have any of these symptoms and show this card to any doctor involved in your care.

Z-FOLD

FRONT



Patient Safety Information Card

+ Important Safety Information for Patients Taking Zydelig®

There are serious risks to understand when taking Zydelig. Be certain to get regular blood tests as scheduled by your doctor. Also, if you experience any of the following symptoms, you should immediately call your doctor and seek emergency medical care.

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- New or worsening cough
- Persistent fever (temperature over 101°F)

⚠ Remember! Call your doctor and get emergency medical care right away if you have any of these symptoms and show this card to any doctor involved in your care.

BACK

BACK MIDDLE

BACK RIGHT



Patient Safety Information Card

+ Important Safety Information for Healthcare Providers

⚠ This patient is taking Zydelig® (idelalisib) therapy for the treatment of leukemia or lymphoma.

Please evaluate urgently, provide all supportive care, and contact the prescribing physician (see contact information at left) as soon as possible to coordinate care if a patient presents with signs and symptoms of the risks noted here. For more information about Zydelig, please refer to the full Prescribing Information. In case of safety concerns, call Gilead at 1-800-445-3235.

+ Patients receiving Zydelig should carry this card at all times. Show this card to any doctor involved in your healthcare.

These are some of the serious risks associated with Zydelig:

- Fatal and/or serious hepatotoxicity
- Fatal and/or serious and severe diarrhea or colitis
- Fatal and serious pneumonitis
- Fatal and serious intestinal perforation

There are some of the serious risks associated with Zydelig:

- Fatal and/or serious and severe diarrhea or colitis
- Fatal and serious pneumonitis
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⚠ This patient is taking Zydelig® (idelalisib) therapy for the treatment of leukemia or lymphoma.

Please evaluate urgently, provide all supportive care, and contact the prescribing physician (see contact information at left) as soon as possible to coordinate care if a patient presents with signs and symptoms of the risks noted here. For more information about Zydelig, please refer to the full Prescribing Information. In case of safety concerns, call Gilead at 1-800-445-3235.

Patients receiving Zydelig should carry this card at all times. Show this card to any doctor involved in your healthcare.

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BACK



Patient Safety Information Card

+ Important Safety Information for Healthcare Providers

⚠ This patient is taking Zydelig® (idelalisib) therapy for the treatment of leukemia or lymphoma.

Please evaluate urgently, provide all supportive care, and contact the prescribing physician (see contact information at left) as soon as possible to coordinate care if a patient presents with signs and symptoms of the risks noted here. For more information about Zydelig, please refer to the full Prescribing Information. In case of safety concerns, call Gilead at 1-800-445-3235.

+ Patients receiving Zydelig should carry this card at all times. Show this card to any doctor involved in your healthcare.

These are some of the serious risks associated with Zydelig:

- Fatal and/or serious and severe diarrhea or colitis
- Fatal and serious pneumonitis
- Fatal and serious intestinal perforation

There are some of the serious risks associated with Zydelig:

- Fatal and/or serious and severe diarrhea or colitis
- Fatal and serious pneumonitis
- Fatal and serious intestinal perforation

⚠ This patient is taking Zydelig® (idelalisib) therapy for the treatment of leukemia or lymphoma.

Please evaluate urgently, provide all supportive care, and contact the prescribing physician (see contact information at left) as soon as possible to coordinate care if a patient presents with signs and symptoms of the risks noted here. For more information about Zydelig, please refer to the full Prescribing Information. In case of safety concerns, call Gilead at 1-800-445-3235.

Patients receiving Zydelig should carry this card at all times. Show this card to any doctor involved in your healthcare.

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Patient Safety Information Card

Reference ID: 3598095



Important Safety Information for Patients Taking Zydelig®

There are serious risks to understand when taking Zydelig. Be certain to get regular blood tests as scheduled by your doctor. Also, if you experience any of the following symptoms, you should immediately call your doctor and seek emergency medical care.

These symptoms include:

- Stomach (abdominal) pain or swelling
- Persistent or worsening nausea or vomiting
- Severe diarrhea
- Dark urine color
- Bloody or tar-colored stool
- Shortness of breath, difficulty breathing, or wheezing
- New or worsening cough
- Persistent fever (temperature over 101°F)



Remember! Call your doctor and get emergency medical care right away if you have any of these symptoms and **show this card** to any doctor involved in your care.



Patient Safety Information Card

Patient Name

Zydelig Prescriber Name

Prescriber's Phone Number

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Important Safety Information for Healthcare Providers



This patient is taking
Zydelig® (idelalisib) therapy
for the treatment of leukemia
or lymphoma.

These are some of the serious risks
associated with Zydelig:

- Fatal and/or serious
hepatotoxicity
- Fatal and/or serious and severe
diarrhea or colitis
- Fatal and serious pneumonitis
- Fatal and serious intestinal
perforation

Please evaluate urgently, provide
all supportive care, and contact
the prescribing physician (see
contact information at left) as
soon as possible to coordinate
care if a patient presents with
signs and symptoms of the risks
noted here. For more information
about Zydelig, please refer to the
full Prescribing Information. In
case of safety concerns, call
Gilead at 1-800-445-3235.



**Patients receiving Zydelig should carry this card at all times.
Show this card to any doctor involved in your healthcare.**

Zydelig (idelalisib) REMS (Risk Evaluation and Mitigation Strategy)

What is the Zydelig REMS?

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the Food and Drug Administration (FDA) to manage known or potential serious risks associated with a drug product.

The purpose of the Zydelig REMS is to inform healthcare providers about the following risks of Zydelig:

Fatal and/or Serious Hepatotoxicity

- Fatal and/or serious hepatotoxicity occurred in 14% of patients treated with Zydelig. Elevations in ALT and AST greater than 5 times the upper limit of normal have occurred. These findings were generally observed within the first 12 weeks of treatment and were reversible with dose interruption. After resumption of treatment at a lower dose, 26% of patients had recurrence of ALT and AST elevations. Discontinue Zydelig for recurrent hepatotoxicity.
- Avoid concurrent use of Zydelig with other drugs that may cause liver toxicity.
- Monitor ALT and AST in all patients every 2 weeks for the first 3 months of treatment, every 4 weeks for the next 3 months, then every 1 to 3 months thereafter. Monitor weekly for liver toxicity if the ALT or AST rises above 3 times the upper limit of normal until resolved. Withhold Zydelig if the ALT or AST is greater than 5 times the upper limit of normal, and continue to monitor AST, ALT and total bilirubin weekly until the abnormality is resolved.

Fatal and/or Serious and Severe Diarrhea or Colitis

- Fatal and/or serious and severe diarrhea or colitis (Grade 3 or higher) occurred in 14% of Zydelig-treated patients across clinical trials. Diarrhea can occur at any time.
- Avoid concurrent use of Zydelig and other drugs that cause diarrhea. Diarrhea due to Zydelig responds poorly to anti-motility agents. Median time to resolution ranged between one week and one month across trials following interruption of Zydelig therapy - and in some instances, use of corticosteroids.

Fatal and Serious Pneumonitis

- Fatal and serious pneumonitis occurred in patients treated with Zydelig.
- Patients taking Zydelig who present with pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation should be evaluated for pneumonitis.
- If pneumonitis is suspected, interrupt Zydelig until the etiology of the pulmonary symptoms has been determined.
- Patients with pneumonitis thought to be caused by Zydelig have been treated with discontinuation of Zydelig and administration of corticosteroids.

Fatal and Serious Intestinal Perforation

- Fatal and serious intestinal perforation occurred in Zydelig-treated patients. At the time of perforation, some patients had moderate to severe diarrhea.
- Advise patients to promptly report any new or worsening abdominal pain, chills, fever, nausea, or vomiting.
- Discontinue Zydelig permanently in patients who experience intestinal perforation.

Zydelig Fact Sheet: A non-promotional fact sheet, reviewed by the FDA, with more detailed safety information on these risks is available. (See link in the box labeled "Materials for Healthcare Providers")

Zydelig Patient Safety Information Card: This card should be given to all patients by Zydelig prescribers and should be carried by patients on Zydelig at all times. Patients should show this card to any healthcare professional that sees them in a health-related encounter. (See link in the box labeled "Materials for Patients")

INDICATION:

Zydelig is a kinase inhibitor indicated for the treatment of patients with

- Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies.
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

You are encouraged to report negative side effects of Zydelig to Gilead at 1-800-445-3235 and/or the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

This site is intended for US Healthcare Professionals.

Materials for Healthcare Providers

Zydelig REMS Letter
to Healthcare Providers

[Download PDF](#)

Zydelig REMS Fact Sheet

[Download PDF](#)

Materials for Patients

Medication Guide

[Download PDF](#)

Zydelig Patient Safety
Information Card

[Download PDF](#)

IMPORTANT SAFETY INFORMATION

WARNING: FATAL AND SERIOUS TOXICITIES: HEPATIC, SEVERE DIARRHEA, COLITIS, PNEUMONITIS, AND INTESTINAL PERFORATION

- Fatal and/or serious hepatotoxicity occurred in 14% of ZYDELIG-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue ZYDELIG as recommended
- Fatal, serious, and/or severe diarrhea or colitis occurred in 14% of ZYDELIG-treated patients. Monitor for the development of severe diarrhea or colitis. Interrupt and then reduce or discontinue ZYDELIG as recommended
- Fatal and serious pneumonitis can occur. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interrupt or discontinue ZYDELIG as recommended
- Fatal and serious intestinal perforation can occur in ZYDELIG-treated patients. Discontinue ZYDELIG for intestinal perforation

Contraindications

- History of serious allergic reactions, including anaphylaxis and toxic epidermal necrolysis (TEN)

Warnings and Precautions

- **Hepatotoxicity:** Findings were generally observed within the first 12 weeks of treatment and reversed with dose interruption. Upon rechallenge at a lower dose, ALT/AST elevations recurred in 26% of patients. In all patients, monitor ALT/AST every 2 weeks for the first 3 months, every 4 weeks for the next 3 months, and every 1 to 3 months thereafter. If ALT/AST is $>3\times$ upper limit of normal (ULN), monitor for liver toxicity weekly. If ALT/AST is $>5\times$ ULN, withhold ZYDELIG and monitor ALT/AST and total bilirubin weekly until resolved. Discontinue ZYDELIG for recurrent hepatotoxicity. Avoid concurrent use with other hepatotoxic drugs
- **Severe diarrhea or colitis:** Grade 3+ diarrhea can occur at any time and responds poorly to antimotility agents. Avoid concurrent use with other drugs that cause diarrhea
- **Pneumonitis:** Evaluate for pneumonitis in patients presenting with pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on radiologic exam, or oxygen saturation decline by $\geq 5\%$
- **Intestinal perforation:** Advise patients to promptly report any new or worsening abdominal pain, chills, fever, nausea, or vomiting
- **Severe cutaneous reactions:** One case of TEN occurred in a study of ZYDELIG in combination with rituximab and bendamustine. Other severe or life-threatening (grade ≥ 3) cutaneous reactions have been reported. Monitor patients for the development of severe cutaneous reactions and discontinue ZYDELIG if a reaction occurs
- **Anaphylaxis:** Serious allergic reactions including anaphylaxis have been reported. Discontinue ZYDELIG permanently and institute appropriate supportive measures if a reaction occurs
- **Neutropenia:** Treatment-emergent grade 3-4 neutropenia occurred in 31% of ZYDELIG-treated patients in clinical trials. In all patients, monitor blood counts \geq every 2 weeks for the first 3 months. In patients with neutrophil counts <1.0 Gi/L, monitor weekly.
- **Embryo-fetal toxicity:** ZYDELIG may cause fetal harm. Women who are or become pregnant while taking ZYDELIG should be apprised of the potential hazard to the fetus. Advise women to avoid pregnancy while taking ZYDELIG and to use effective contraception during and at least 1 month after treatment with ZYDELIG

Adverse Reactions

- **Most common adverse reactions** (incidence $\geq 20\%$; all grades) in clinical studies, when used alone or in combination with rituximab, were diarrhea, pyrexia, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash
- **Most frequent serious adverse reactions** (SAR) in clinical studies in combination with rituximab were pneumonia (17%), pyrexia (9%), sepsis (8%), febrile neutropenia (5%), and diarrhea (5%); SAR were reported in 49% of patients and 10% of patients discontinued due to adverse reactions. Most frequent SAR in clinical studies when used alone were pneumonia (15%), diarrhea (11%), and pyrexia (9%); SAR were reported in 50% of patients and 53% of patients discontinued or interrupted therapy due to adverse reactions
- **Most common lab abnormalities** (incidence $\geq 30\%$; all grades) in clinical studies were neutropenia, hypertriglyceridemia, hyperglycemia, and ALT/AST elevations

Drug Interactions

- **CYP3A inducers:** Avoid coadministration with strong CYP3A inducers
- **CYP3A inhibitors:** When coadministered with strong CYP3A inhibitors, monitor closely for ZYDELIG toxicity
- **CYP3A substrates:** Avoid coadministration with CYP3A substrates

Dosage and Administration

- **Adult starting dose:** One 150 mg tablet twice daily, swallowed whole with or without food. Continue treatment until disease progression or unacceptable toxicity. The safe dosing regimen for patients who require treatment longer than several months is unknown
- **Dose modification:** Consult the ZYDELIG full Prescribing Information for dose modification and monitoring recommendations for the following specific toxicities: pneumonitis, ALT/AST elevations, bilirubin elevations, diarrhea, neutropenia, and thrombocytopenia. For other severe or life-threatening toxicities, withhold ZYDELIG until toxicity is resolved and reduce the dose to 100 mg, twice daily, upon resuming treatment. If severe or life-threatening toxicities recur upon rechallenge, ZYDELIG should be permanently discontinued

INDICATIONS

Zydelig is a kinase inhibitor indicated for the treatment of patients with

- Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies.
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

Please see full Prescribing Information, including **BOXED WARNING**.

- Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies.
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

You are encouraged to report negative side effects of Zydelig to Gilead at 1-800-445-3235 and/or the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

This site is intended for US Healthcare Professionals.

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

/s/

NAOMI B REDD
07/23/2014

CYNTHIA L LACIVITA
07/23/2014
Concur

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:	205858 and 206545
Products:	Zydelig, Idelalisib, 100 mg and 150 mg tablets
APPLICANT:	Gilead Sciences, Inc.
FROM:	Robert C Kane, MD
DATE:	May 12, 2014

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).

The Zydelig application is under first cycle review now under two NDAs, for two indications, chronic lymphocytic leukemia (CLL) and indolent non-Hodgkin lymphoma (iNHL, including small lymphocytic lymphoma), after prior therapies. After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Zydelig to ensure that the benefits of the drug outweigh the risks of diarrhea, colitis, bowel perforation, pneumonitis, and hepatotoxicity that this REMS is intended to mitigate. In reaching this determination, we considered the following:

- A. The National Cancer Institute, NIH, estimates 15,700 new cases of CLL and 4600 deaths in 2014. No therapy is considered curative. Multiple therapies are used sequentially a single agents or as combinations. The National Cancer Institute estimates 71,000 new cases of Non-Hodgkin lymphomas and 19,000 deaths in 2014. The Leukemia and Lymphoma Society estimates that about one-third of NHL cases are indolent NHL in the U.S.
- B. Relapsed CLL and iNHL are serious and life-threatening conditions. Survival from the time of initial diagnosis is variable but may be as long as 5 – 10 years. Each is a malignancy of “B” lymphocytes, but with some differences in presentation, clinical course, and therapies.

- C. Zydelig treatment shows evidence of anti-tumor activity, mostly partial responses. However, more than half of treated patients have to dose reduce after the first cycle for toxicities. The benefit-risk relationship for chronic use (> 4-6 months) is unknown.

Idelalisib is a selective inhibitor of the delta isoform of the Class 1 phosphatidylinositol 3-kinase (PI3K) which is involved in several cellular processes necessary for cancer progression. There are no approved PI3K inhibitors. There are five currently available agents approved for the treatment of patients with follicular lymphoma (FL), low-grade non-Hodgkin lymphoma (NHL), or indolent NHL. These include chlorambucil, cyclophosphamide, rituximab, ⁹⁰Y-ibritumomab tiuxetan, and bendamustine. In addition to these drugs, fludarabine, pentostatin, ibrutinib, ofatumumab, and obinotuzumab also are approved for CLL.

- D. Zydelig may be expected to be used as monotherapy and in combination with other drugs in patients with relapsed CLL and iNHL

Zydelig safety was studied in a total of 354 patients, with various hematological malignancies and at various doses of idelalisib monotherapy. However, only 146 patients with indolent lymphoma and about 60 patients with CLL were treated with the proposed labeled dose, 150 mg BID.

In the monotherapy population:

- 2% had a fatality due to suspected drug-induced AR, including neutropenia, sudden death, tumor lysis syndrome, respiratory failure, and enteropathy
- There were 3 potential Hy's law cases by laboratory criteria, but all had confounding features

In the 146 subjects with indolent lymphoma:

- 55% interrupted or stopped idelalisib for an adverse event.
- Frequent ARs ($\geq 20\%$) included diarrhea, fatigue, cough, nausea, pyrexia, neutropenia, elevated transaminases, pneumonia, rash, and abdominal pain.
- Grade ≥ 3 ARs included neutropenia, elevated transaminases, pneumonia and diarrhea.
- Grade ≥ 3 laboratory abnormalities included neutropenia, elevated transaminases and thrombocytopenia
- 59% of patients showed transaminase elevation. 2/145 cases possibly Hy's law.
- Applicant reported 8% frequency of pneumonia. FDA determined the frequency was 16%. The actual incidence of drug-induced pneumonia is not clear, since there was a high background of infectious pneumonia. Available evidence suggests that idelalisib may be a direct cause of lung toxicity, including life-threatening and fatal cases. Applicant did not identify these cases initially.
- Treatment associated diarrhea is common and not responsive to usual agents. A generalized non-specific colitis is found on endoscopy. Two colon perforations have been identified, not reported by the applicant as possibly drug-related.

The toxicities noted are frequent, severe and serious, and fatal, and have characteristics that are atypical and not usually encountered in a community hematology-oncology practice. Events of severe diarrhea, pneumonitis, and hepatotoxicity require immediate discontinuation of Zydelig.

Therefore, recognition and management may be hindered and serious risks are increased. A REMS is appropriate to assist prescribers in recognizing and managing these events.

- E. Zydelig is a new molecular entity. Clinicians are not familiar with the toxicities expected with this drug.

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

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

/s/

MARA B MILLER
07/22/2014

ROBERT C KANE
07/22/2014

**Department of Health and Human Services
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: July 21, 2014

Reviewer(s): Naomi Redd, Pharm.D., Risk Management Analyst
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H., Health Communications Analyst
DRISK

Team Leader: Doris Auth, Pharm.D.
Acting Team Leader, DRISK

Division Director: Cynthia LaCivita, Pharm.D.
Acting Director, DRISK

Subject: Review to provide REMS comments to the sponsor

Drug Name(s): idelalisib (Zydelig)

Therapeutic Class: phosphatidylinositol 3-kinase delta (PI3K δ) inhibitor

Dosage and Route: 150mg orally twice daily

Application Type/Number: NDA 205858 and NDA 206545

Supplement Number: 56, eCTD 0054, received July 2, 2014

Applicant/sponsor: Gilead Sciences, Inc.

OSE RCM #: 2013-2084

***** This document contains proprietary and confidential information that should not be released to the public. *****

1 INTRODUCTION

This review provides DRISK's evaluation and comments for Gilead's communication plan (CP) REMS submitted on July 2, 2014 for Zydelig® (idelalisib, NDA 205858 and NDA 206545). The Agency comments on the sponsor's proposed CP REMS submitted on May 28th, 2014 were sent to the sponsor on June 27, 2014. The sponsor incorporated all of the Agency comments, in addition to providing a patient safety information wallet card that communicates the risk of Zydelig to patients and healthcare providers; also requested by the Agency. Further review of the label for Zydelig has led to additional changes in the text to communicate the risks, thereby necessitating a need to align the REMS document and REMS materials with the label dated July 18, 2014.

Zydelig is a kinase inhibitor indicated for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab and for the treatment of relapsed non-Hodgkin's lymphoma (that only includes follicular B-Cell and small lymphocytic lymphoma) in patients who have received at least two prior systemic therapies. Fatal and serious toxicities associated with Zydelig treatment include: hepatotoxicity, severe diarrhea and colitis, pneumonitis, and intestinal perforation. A detailed review of these applications has been reviewed by DRISK and submitted in DARRTS on May 20th, 2014.

2 MATERIALS REVIEWED

- Revised REMS submitted by Gilead, eCTD 0054, Supporting Document 56, July 2, 2014
- Zydelig draft label, July 14th, 2014

2.1 PREVIOUS DRISK REMS REVIEWS

- May 20th, 2014; N. Redd
- June 27th, 2014; N. Redd

3 REVIEW FINDINGS

The sponsor's submission of their revised REMS and REMS materials on July 2, 2014 was based on label negotiations with the Agency on June 17th, 2014. Since that submission, there have been revisions to the label, primarily in the Boxed Warnings and Warnings and Precautions section. Of note, the most recent label discussed with the review division on July 14th and additional revisions provided on July 18, 2014 contains updated language in the Boxed Warnings and Warnings and Precautions section. The REMS document, REMS Supporting Document, and the REMS communication plan tools which contains REMS letters to healthcare professionals and professional societies, a REMS Factsheet, a REMS journal information piece, a Zydelig Patient Safety Information Card, and a REMS website must be updated to include information found in the label received on July 18, 2014. Providing Gilead makes all the necessary changes to the REMS and all REMS related documents the REMS will be near ready for approval. DRISK will review the sponsor's final REMS submission.

4 CONCLUSIONS AND RECOMMENDATIONS

DRISK finds the outline and layout of the revised REMS, REMS Supporting Document, and most of the REMS communication materials acceptable. However, significant revisions to the language for these materials are needed based on the most recent label discussed with the review division on July 14th, 2014 and most recent changes from July 18th, 2014.

5 COMMENTS TO THE SPONSOR

1. **General comments:**

DRISK finds the outline and layout of the revised REMS, REMS Supporting Document, and the print versions of the REMS letters acceptable. The layouts of the electronic versions of the REMS Letters, the Zydelig Patient Safety Information Card, the REMS Journal Information Piece, and the Website Landing Page must be revised. Ensure that all REMS materials align with language from the final approved label and return July 22, 2014. Address all comments noted in the redlined documents of your submission and bubble comments inserted into pdf layout versions of the selected materials attached. Accept all changes and submit Word tracked changes versions and a Word clean version of each document, as well as a cover letter explaining all changes proposed in the documents. A mock up version that includes colorings and logos in Adobe pdf format of the REMS communication materials with the updated language should also be submitted. All REMS materials that contain the Zydelig logo with the 150 mg strength must be updated to also include the 100 mg strength as this is also included in the label. Note that the REMS materials are not appropriate for use in a promotional manner.

2. **REMS document:**

See the attached REMS document with the necessary changes with comments and edits in track changes. Of note, language has been included in the Patient Safety Information Card section to delineate how healthcare providers will obtain the patient safety information cards to give to patients who are prescribed Zydelig. The timetable for submission of assessments has been changed to 18 months, 3 years, and 7 years.

3. **REMS Supporting Document:**

See the attached REMS Supporting Document with the necessary changes with edits in track changes to align with labeling and the REMS document.

4. **REMS Letters (email and print):**

See the attached REMS letters with the necessary changes in track changes. The Zydelig logo with the 150 mg strength must be updated to also include the 100 mg strength.

5. **REMS Letters (email versions)**

See the attached email template for the letters Gilead will send electronically to HCPs and Professional Societies. An example with appropriate language for the subject line and body of the email has been attached for your review. The electronic version of the REMS letters should be email and handheld-device friendly. The goal is to have this

information in the body of an email, versus an attachment. The Zydelig logo with the 150 mg strength must be updated to also include the 100 mg strength.

6. **REMS Fact sheet:**

The REMS Fact sheet should be printed on thicker card stock paper with updated formatting, including logo changes for the Zydelig REMS program as stated above. See the attached REMS Fact Sheet with the necessary changes with edits in track changes.

7. **Zydelig REMS Website**

Place this text in the purple banner header copy: "Zydelig (idelalisib) REMS (Risk Evaluation and Mitigation Strategy)" and delete this text: "Zydelig (idelalisib) REMS". As a result, there will not be a subhead on the website landing page. Ensure that only the final approved Important Safety Information, Medication Guide, and Prescribing Information are available on the Zydelig REMS website.

Add the following text to the journal information piece. "You are encouraged to report negative side effects of Zydelig to Gilead at 1-800-445-3235 and/or the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088."

The Zydelig logo with the 150 mg strength must be updated to also include the 100 mg strength.

Make additional changes to the website landing page as noted in the attached MS Word document and the comments on the adobe pdf Layout document.

8. **REMS Journal Information Piece:**

Delete the title (b) (4) at the top of the journal piece. The title "FDA REQUIRED Safety Information for Zydelig (idelalisib)" should be placed in the purple banner box instead. The Zydelig logo with the 150 mg strength must be updated to also include the 100 mg strength.

Add the following text to the bottom of the journal information piece. "You are encouraged to report negative side effects of Zydelig to Gilead at 1-800-445-3235 and/or the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088."

See the attached REMS Journal Information Piece with additional edits in track changes.

9. **Zydelig Patient Safety Information Card:**

Switch the information for the patient with that for the physician, but keep the text on both purple right columns as is. In other words, the patient's name, prescriber's name, etc., should be to the right of and on the same side of the card as the information for the treating physician. This card should be printed on thicker card stock paper so that it may

be durable and easy to carry for patients. The Zydelig logo with the 150mg strength must be updated to also include the 100mg strength.

See the attached Patient Safety Information Card for additional comments and edits in track changes.

ATTACHMENTS

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

/s/

NAOMI B REDD
07/21/2014
reference to NDA 205858

CYNTHIA L LACIVITA
07/21/2014
Concur

**Department of Health and Human Services
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: June 27, 2014

Reviewer(s): Naomi Redd, PharmD, Risk Management Analyst
Division of Risk Management

Joan Blair, RN, MPH, Health Communications Analyst
Division of Risk Management

Team Leader: Doris Auth, Pharm.D.
Division of Risk Management

Division Director: Claudia Manzo, Pharm.D.
Acting OMEPRM Director

Subject: Review of proposed communication plan REMS

Drug Name(s): idelalisib (Zydelig)

Therapeutic Class: phosphatidylinositol 3-kinase delta (PI3K δ) inhibitor

Dosage and Route: 150mg orally twice daily

Application Type/Number: NDA 205858 and NDA 206545

Applicant/sponsor: Gilead

OSE RCM #: 2013-2084

***** This document contains proprietary and confidential information that should not be released to the public. *****

1 INTRODUCTION

This review provides DRISK's evaluation of the sponsor's proposed communication plan (CP) risk evaluation and mitigation strategy (REMS) for Zydelig® (idelalisib, NDA 205858 and NDA 206545) received May 21, 2014 as Supplement 46, sequence 45, and amended on May 28, 2014, Supplement 47, sequence 46. The submission on May 28th includes Adobe pdf versions of the proposed REMS communication plan tools. A detailed review of these applications to determine if a REMS is necessary has been reviewed by DRISK and submitted in DARRTS on May 20th, 2014.

2 MATERIALS REVIEWED

2.1 DRISK REVIEWS FOR THE PROPOSED REMS SUBMISSION

- Discipline Review Letter citing deficiencies outlined in the preliminary review and the need to develop a communication plan to warn healthcare providers about the risks, recommended monitoring, and dose modifications to mitigate serious or life-threatening toxicities; dated May 20, 2014
- DRISK REMS review dated May 20, 2014.

2.2 SPONSOR'S SUBMISSIONS

- Proposed REMS and REMS materials submitted May 21, 2014.
- Proposed REMS Supporting Document May 21, 2014.
- Proposed REMS amendment with mock-up versions of REMS materials submitted May 28th, 2014.

3 REVIEW FINDINGS

The sponsor's submission of their proposed REMS was based on language from the label on May 13th, 2014. Since that submission, there have been several revisions. Of note, the most recent label on June 17th, 2014 contains updated language in the boxed warnings for the risks of Zydelig which includes:

- Severe, including fatal, hepatotoxicity
- Severe diarrhea/colitis
- Pneumonitis, including fatalities
- Gastrointestinal perforation, including fatalities

These risks and the management thereof are further outlined in the Warnings and Precautions section of the label.

The REMS document, REMS Supporting Document, and the REMS communication plan tools which contain REMS letters to healthcare professionals and professional societies, REMS

Factsheet, REMS journal information piece, and REMS website must be updated to include information on the most recent submission of the label. In addition, the clinical review team and DRISK have determined that a patient safety information wallet card be included as part of the REMS communication tools to facilitate education and prompt management of the aforementioned risks of Zydelig should the patient present to an outpatient or inpatient urgent care facility for healthcare prescribers who may not be aware of the risks of Zydelig.

An OPDP consult was entered into DARRTS on May 14, 2013. Kathleen Davis served as the reviewer and completed OPDP's review on June 13, 2014. DRISK agrees with and incorporates all of OPDP's comments from their review, with the exception of the following OPDP comment:

All of the proposed REMS materials fail to communicate Zydelig's full indication, including limitations. Specifically, the proposed materials fail to include the following language from the Zydelig PI:

"Accelerated approval was granted for FL and SLL based on overall response rate. Improvement in patient survival or disease related symptoms has not been established. Continued approval for this indication may be contingent upon verification of clinical benefit."

The full FDA-approved indication, including limitations, should be communicated in the final REMS materials.

After discussing this recommendation, DRISK and DHP decided not to include text regarding "accelerated approval..." because it primarily addresses efficacy issues and not those related to the drug's safety, which is the primary focus of the REMS. Therefore, DRISK did not accept this comment.

4 CONCLUSIONS AND RECOMMENDATIONS

DRISK finds the outline and layout of the proposed REMS, REMS Supporting Document, and REMS communication materials (REMS letter to healthcare providers, REMS letter to professional societies, REMS Fact sheet, REMS journal information piece, and REMS website) acceptable. However, significant revisions to the language for these materials are needed based on the most recent label submission on June 17th, 2014. Furthermore, inclusion of a patient information wallet card, with updated language from the label submitted on June 17, 2014 should be included as part of the REMS communication tools.

5 COMMENTS TO THE SPONSOR

1. General comments:

- a. FDA finds the outline of the REMS document, REMS supporting document, and the REMS communication tools which includes the REMS letter to healthcare providers (email and print versions), REMS letter to professional societies (email and print versions), REMS Fact sheet, REMS journal information piece, and REMS website generally acceptable. However, significant revisions to the

language for these documents must align with the most recent label submission on June 17th, 2014. Please address all comments noted in the redlined documents of your submission, accept all changes, and submit both a Word tracked changes versions and a Word clean version of each document, as well as a cover letter explaining all changes proposed in the documents. A mock up version in Adobe pdf format of the REMS communication materials with the updated language should also be submitted.

- b. The REMS Journal Piece refers to www.Zydelig.com and the DHCP letters and DPS letters refer to www.gilead.com. REMS materials should only include a web address which represents a direct link to the REMS materials (such as www.ZydeligREMS.com). The web address should not represent the commercial or promotional website for the product. Establish a separate domain for the Zydelig REMS website immediately upon approval.
 - c. In addition, DRISK and DHP have concluded that inclusion of a patient safety information wallet card with updated language from the label submitted on June 17, 2014 should be included as part of the REMS communication tools. (See below).
 - d. Ensure that all materials reflect the final approved label. Incorporate all edits based on the specific track changes in each document as outlined below. The REMS materials are not appropriate for use in a promotional manner.
2. **REMS document:**
See the attached REMS document with the necessary changes with comments and edits in track changes.
 3. **REMS Supporting Document:**
See the attached REMS Supporting Document with the necessary changes with edits in track changes to align with labeling. Of note, language is included to assist with formulating your assessment plan for the REMS document.
 4. **REMS Letter to Healthcare Providers (email and print):**
See the attached REMS letters with the necessary changes with edits in track changes.
 5. **REMS letter to Professional Societies (email and print):**
See the attached REMS letters with the necessary changes with edits in track changes.
 6. **REMS Envelope:**
See the attached REMS envelope with the necessary changes with edits in track changes.

7. **REMS Fact sheet:**

See the attached REMS Fact Sheet with the necessary changes with edits in track changes.

8. **Zydelig REMS Website**

Make changes to the website landing page as noted in the attached MS Word document.

9. **REMS Journal Information Piece:**

See the attached REMS Journal Information Piece with the necessary changes with edits in track changes.

10. **Zydelig Patient Safety Information Card:**

Create a patient safety information card based on text in the attached MS Word document, formatted very similarly to that for Soliris®. This card should highlight the risks and include information on the management of these risks. It should include red and yellow colors, a white cross, and a danger symbol similar to Solaris to alert emergency personnel as to its importance. This card should be given to all patients by Zydelig prescribers and should be carried by patients on Zydelig at all times. Patients should be clearly instructed to show this card to any healthcare professional that treats them. The patient safety information card should also be available on the Zydelig REMS website as a pdf for downloading. This card may be foldable and printed on the front and back if needed - so that it may comfortably fit in a standard wallet. A pdf of the Soliris® Patient Safety Information Card is attached for your reference.

ATTACHMENTS

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

/s/

NAOMI B REDD
06/27/2014
linked to NDA 205858

CLAUDIA B MANZO
06/27/2014
concur

**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: May 20, 2014

Reviewer(s): Naomi Redd, Pharm.D.
Division of Risk Management

Team Leader: Cynthia LaCivita, Pharm.D.
Division of Risk Management

Division Director: Claudia Manzo, Pharm.D.
Division of Risk Management

Subject: Review to determine if a REMS is necessary

Drug Name(s): idelalisib (Zydelig)

Therapeutic Class: phosphatidylinositol 3-kinase delta (PI3K δ) inhibitor

Dosage and Route: 150mg orally twice daily

Application Type/Number: NDA 205858 and NDA 206545

Applicant/sponsor: Gilead

OSE RCM #: 2013-2084

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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 (NME) idelalisib. Gilead submitted a New Drug Application (NDA) 205858 for idelalisib with the proposed indications for the treatment of patients with indolent B-cell non-Hodgkin lymphoma (iNHL), and chronic lymphocytic leukemia (CLL), which has been filed under NDA 206545. The review classification for both applications is priority, and is undergoing accelerated approval for the iNHL indication.

Data for the iNHL population is based on a single-arm, multicenter trial which included 72 patients with follicular lymphoma (FL) and 28 patients with small lymphocytic lymphoma (SLL). Fifty-four percent of patients in the FL group and 58% of patients in the SLL group achieved the primary endpoint of overall response rate (ORR), with 46% of patients with FL having a partial response (PR) and 8% patients having a complete response (CR). The applicant's registrational study for CLL was a randomized, double-blind, placebo controlled trial in 220 patients to receive rituximab in combination with idelalisib or placebo. The results for both the primary and secondary endpoints were statistically significant at <0.0001 compared to placebo.

The safety data reflect exposure to idelalisib in which 146 subjects with iNHL received idelalisib 150 mg twice daily, and in 218 patients with relapsed CLL who received up to 8 doses of rituximab with or without idelalisib 150 mg twice daily. The median duration of exposure to idelalisib was 5 months. Adverse events (AE's) are reported for occurrences in $\geq 10\%$ of patients. Grade 3 and higher cases of diarrhea resulting in colitis and bowel perforations, transaminase elevations, pneumonia, and rash were noted as AEs associated with treatment interruptions, dose modifications, discontinuations, and fatalities in some patients treated with idelalisib. The applicant did not submit a proposed REMS or Risk Management Plan.

Idelalisib is a NME, and if approved will be the first in class inhibitor of phosphoinositide 3-kinase delta (PI3K δ); thus, the toxicities for this class have not been fully characterized. The risks identified in this review include hepatotoxicity, colitis, bowel perforation, and pneumonitis. These AEs are concerning for the following reasons: the serious risks reported with idelalisib differ in type and severity from the approved treatments for the aforementioned hematological malignancies, and the prescribing population initially may not be as familiar with managing these toxicities; this is an oral formulation that will be administered to patients in ambulatory/outpatient care settings and recognition of these serious AEs could be delayed; with longer treatment exposure, it is possible that the AE's reported may increase.

DRISK and Division of Hematology Products have determined that if approved, a REMS that consists of a communication plan will be necessary to ensure the benefits of idelalisib outweigh the risks of hepatotoxicity, bowel perforation, colitis, and pneumonitis.

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 (NME) idelalisib. Gilead submitted a New Drug Application (NDA) 205858 for idelalisib with the proposed indication for the treatment of patients with indolent B-cell non-Hodgkin lymphoma (iNHL), and chronic lymphocytic leukemia (CLL), which has been filed under NDA 206545. The applicant did not submit a proposed REMS or Risk Management Plan.

1.1 BACKGROUND

Indolent Non-Hodgkin's Lymphoma (iNHL):

Non-Hodgkin lymphomas encompass a heterogeneous group of cancers in which 85-90% develops from B lymphocytes.¹ These diverse groups of malignancies commonly develop in the lymph nodes, but can occur in any tissue. Indolent Non-Hodgkin's Lymphoma is commonly used to describe the clinical behavior of certain lymphomas that grow and spread slowly and have few symptoms for long periods.² Indolent non-Hodgkin's lymphomas (iNHL) encompasses several low-grade histologic subtypes of B-cell non-Hodgkin's Lymphoma such as follicular lymphoma (FL) – which accounts for approximately 20% of all NHL cases, and small lymphocytic lymphoma (SLL), a rarer form of B-cell lymphomas, accounting for approximately 5% of all NHL cases. The average age of diagnosis in patients with these lymphomas is 65, with a slightly higher incidence in men. Over 70,000 people are diagnosed with iNHL in the United States each year, resulting in nearly 19,000 deaths.³ Depending on the clinical staging of disease, treatment may include a watch and wait period for several years, with mean survival rates ranging 7-10 years. However, due to the indolent nature of these lymphomas, most patients present after they have become symptomatic with advanced disease. Current treatment options include rituximab alone or in combination with chemotherapy consisting of alkylating agents, anthracyclines, antimetabolic agents, or purine analogues.⁴

Chronic Lymphocytic Leukemia (CLL):

Chronic Lymphocytic Leukemia (CLL) is a type of cancer that originates from lymphocytes in the bone marrow before it invades other areas of the body, most commonly the blood.⁵ A common clinical observation of CLL is that in response to chemotherapy, CLL cells in the peripheral blood are effectively treated, yet the disease persists in the lymph nodes and bone marrow.⁶ CLL is the most prevalent leukemia in the

¹ Shankland K et al. Non-Hodgkin lymphoma. *Lancet* 2012; 380:848-57

² Merli M et al. Novel agents in indolent lymphomas. *Ther Adv Hematol* 2013; 4(2) 133-148

³ <http://www.cancer.org/cancer/non-hodgkinlymphoma/detailedguide/non-hodgkin-lymphoma-key-statistics> accessed 10 April 2014

⁴ Gopal A et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *NEJM* 2014; 370:1008-18

⁵ www.cancer.org/cancer/leukemia-chroniclymphocyticcll accessed 22 April 2014

⁶ Davids M et al. Targeting the B cell receptor pathway in chronic lymphocytic leukemia. *Leukemia & Lymphoma*, December 2012; 53(12):2362-2370

Western world, and is incurable by standard therapy.⁶ According to the American Cancer Society, there are approximately 15,720 new cases of CLL and 4,600 deaths each year. The average age at the time of diagnosis is 72 years, and the risk is slightly higher in men versus women.⁵ Like FL and SLL, treatment can include a watch and wait period, with mean survival rates of approximately 10 years, however, most patients present with advanced disease after they have become symptomatic. There are several treatment options, most commonly chlorambucil with combination therapy including anthracyclines, purine analogues, and monoclonal antibodies such as rituximab. Alemtuzumab (approved July 1, 2013) and ofatumumab in combination with chlorambucil (approved April 22, 2014) are monoclonal antibodies that have been recently approved for treatment of refractory CLL.

Although rituximab based therapies with or without chemotherapy have improved outcomes in iNHL and CLL, relapse is invariable, and in many, refractory disease is inevitable.⁷ These malignancies share similar demographic and pathological disease state characteristics, and of particular importance is the role of the B-cell receptor (BCR) signaling pathway in the pathogenesis of these malignancies.

Phosphoinositide 3-kinase delta (PI3K δ):

The phosphoinositide 3-kinase (PI3K) pathway is a critical signal transduction system that links oncogenes and multiple receptor classes to various cellular functions, and is the most commonly activated signaling pathway in human cancer.⁸ PI3K's have four isoforms – alpha, beta, delta, and gamma – that differ based on chemical characteristics and substrate specificity. The delta isoform of PI3K (PI3K δ) is abundantly expressed in leukocytes and activates B-cell receptor (BCR) signaling pathways.⁸ BCR hyper-activation is one of the pathologic features in B cell malignancies, in particular iNHL and CLL. Therefore, inhibiting this pathway offers a possible therapeutic option for the treatment of these diseases.

Idelalisib is a potent and highly selective inhibitor of PI3K δ , which has been demonstrated in clinical trials to inhibit proliferation, survival, and retention in the tumor microenvironment in many B-cell malignancies.⁹ The applicant is seeking approval for idelalisib (Zydelig) 150 mg oral tablets, twice daily for the treatment of iNHL as monotherapy in patients who have received at least 2 prior therapies, and for CLL to be used in combination with rituximab, in patients who have received at least one prior therapy. Idelalisib is a NME that would be the first drug in the PI3K δ inhibitor class, as well as the first oral chemotherapeutic option for the treatment of these malignancies.

1.2 REGULATORY HISTORY

The review classification for both applications is priority, and is undergoing accelerated approval for the iNHL indication. The regulatory history for this compound is extensive,

⁷ Lunning M et al. Management of indolent lymphoma: where are we now and where are we going. *Blood Reviews* 2012 (26) 279-288

⁸ Liu P et al. Targeting the phosphoinositide 3-kinase (PI3K) pathway in cancer. *Nat Rev Drug Discov*. August 200; 8(8): 627-644

⁹ Idelalisib Clinical Overview, Section 2.5

dating back to 2008 from an original IND submission for hematological malignancies, and then subsequently another IND for CLL, which has led to the regulatory history outlined below:

- Orphan drug status for CLL August 25, 2011
- Fast track designation January 30, 2012
- NDA 205858 submission for iNHL indication submitted September 11, 2013
- Breakthrough therapy designation for CLL granted November 8, 2013
- Request for Rolling Submission for CLL indication granted November 15, 2013
- Permission to cross reference NDA 205858 for iNHL indication to CLL application granted November 22, 2013
- NDA 206545 submission for CLL indication December 1, 2013

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- NDA 205858 Gilead Application Orientation Meeting October 7, 2013
- Idelalisib Section 2.4 Nonclinical Overview – submitted November 7, 2013
- Idelalisib Section 2.5 Clinical Overview for NDAs 205858 (iNHL indication) and 206545 (CLL indication) – submitted November 7, 2013
- Idelalisib Section 2.74 Clinical Safety – submitted November 7, 2013
- Idelalisib Midcycle Communication Slides – January 15, 2014
- Draft CDTL Clinical Review on Idelalisib (iNHL indication) – Dr. Angelo DeClaro
- Draft Idelalisib (Zydelig) label, May 13, 2014

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

Key Efficacy Findings for iNHL (FL and SLL)^{10,11}:

The applicant proposed that idelalisib should also be used in patients with marginal zone lymphoma (MZL) and lymphoplasmacytic lymphoma (LPL), but there were too few subjects with these diseases treated in the clinical trial to support efficacy in these populations (n = 15 and 10 patients respectively). Therefore, this analysis by the Agency for iNHL includes patients with FL and SLL. The registrational trial for iNHL, was a single-arm, multicenter, clinical trial in which the safety and efficacy of idelalisib was assessed in subjects who had relapsed within 6 months following rituximab and an alkylating agent based therapy, and had received at least two prior therapies. This included 72 patients with FL and 28 patients with SLL. The demographics were consistent to what is seen in clinical practice; largely Caucasian males, with a median age of 62 years for FL, and 65 years for SLL. The median number of prior regimens were 4 (range 2-12 for FL, and 2-9 for SLL). Patients were given idelalisib 150mg twice daily until evidence of disease progression or toxicity. The primary endpoint was overall response rate (ORR), as well as secondary endpoints, duration of response (DOR), which included those patients who had received a complete response (CR) or partial response

(PR). Median time to response was also assessed. Results are listed in the table below for both study populations.¹⁰

	FL (n = 72)	SLL (n = 26)
ORR	39 (54%)	15 (58%)
95% confidence interval	(42, 66%)	(37, 77%)
CR	6 (8%)	0
PR	33 (46%)	15 (58%)
DOR, months	Median not evaluable	11.9 (0.0+, 14,7+)

Limitations include a short exposure of treatment in patients with slow progressing lymphomas. Only 12% of patients with responses were on study drug at least one year. Median time of exposure to idelalisib was approximately 5 months.

Key Efficacy Findings for CLL^{10,11}:

At the time of this writing, the Agency's review for CLL was ongoing. The registrational study for CLL (Study 312-0116, also noted as Study 1), was a randomized, double-blind, placebo controlled trial in 220 patients with relapsed CLL who were randomized 1:1 to receive 8 doses of rituximab in combination with either idelalisib 150mg twice daily or placebo twice daily until disease progression or unacceptable toxicity. Patient demographics were similar to what is seen in the CLL population, with a median age of 71 (range 47-92), 90% were Caucasian, and 65% were male. Median number of prior therapies was 3, and 96% of patients received anti-CD20 monoclonal antibodies as prior therapies. All patients in this analysis had previously received rituximab. This study population also had significant comorbidities, which included reduced renal function (creatinine clearance <60ml/min), and grade ≥ 3 neutropenia or thrombocytopenia as a result from myelotoxic effects of prior therapies. The primary endpoint was median time to progression free survival (PFS), and secondary endpoints included ORR. Results of a second interim analysis continued to show a statistically significant improvement in patients receiving idelalisib + rituximab over the placebo group for the primary endpoint. Results are shown in the table below.

¹⁰ Draft idelalisib (Zydelig) label, May 13, 2014

	idealisib + rituximab N = 110	Placebo + rituximab N = 110
PFS median, months	NR ⁺ (10.7, NR)	5.5 (3.8, 7.1)
Hazard ratio (95% CI)	0.18 (0.10, 0.32)	
P value	<0.0001	
ORR	N = 82 (74.5%)	N = 16 (14.5%)
Odds ratio (95% CI*)	17.28 (8.66, 34.46)	
P value	<0.0001	

+ = Not reached, * = Confidence interval

3.2 SAFETY CONCERNS

The safety data reflect exposure to idelalisib in which 146 subjects with iNHL received idelalisib 150 mg twice daily, and in 218 patients with relapsed CLL who received up to 8 doses of rituximab with or without idelalisib 150 mg twice daily.¹⁰ The median duration of exposure was 5 months. Adverse events (AE's) are reported for occurrences in $\geq 10\%$ of patients. Grade 3 and higher cases of diarrhea resulting in colitis and bowel perforations, transaminase elevations, pneumonia, and rash were noted as AEs associated with treatment interruptions, dose modifications, discontinuations, and fatalities in some patients treated with idelalisib. Neither a risk management plan, nor a REMS was submitted with these applications.

3.2.1 Diarrhea/Colitis – Cases of severe diarrhea (reported as Grade 3 or 4 diarrhea and/or colitis), have been reported with idelalisib use, and occurred relatively late (median time 5 months) after the start of therapy. Some of these cases resolved within a few weeks with drug interruption and additional pharmacotherapy treatment with antidiarrheal and anti-inflammatory agents such as loperamide and enteric budesonide. For patients with iNHL in the monotherapy studies at the recommended dose, the applicant reports diarrhea as the most common adverse event; 40.5% at grade 1 or 2, and 10.5% grade 3 or higher. Cases of severe diarrhea resulting in colitis of any grade, was reported for 9 patients, with 7 of these patients diagnosed with grade 3 colitis.⁹ Three patients discontinued the study due to colitis, all grade 3. The median time to onset of diarrhea of any grade was approximately 2 months, and in those patients whose diarrhea resolved, the median time to resolution was 0.5 months. In more severe cases of diarrhea, the onset was typically later, with the median time to first onset at approximately 5 months, and median time to resolution at 0.7 months. In this same population, FDA clinical reviewers found that 45% of the subjects had diarrhea using the grouped term, and the diarrhea was grade ≥ 3 for 14%. The diarrhea was categorized as related to treatment for 48 (33%) of the subjects.¹¹ The action taken with the drug when the diarrhea occurred was withdrawal for 5 subjects, interruption for 13 subjects and reduction in dose for 7 subjects.¹¹ In addition, 8 subjects were treated with enteric

¹¹ Dr. Angelo DeClaro, CDTL Idealisib Clinical Review for iNHL

steroids, 4 subjects with octreotide, and 3 subjects with systemic steroids. The applicant reports a fatality in one patient with idelalisib-related diarrhea, and there are also at least 2 case reports, at the time of this review, of diarrhea and colitis resulting in ischemic bowel perforation. The applicant identified in their global database 44 (7%) subjects with an SAE of diarrhea for which there was no etiology found other than idelalisib use, and that these subjects “generally presented...with a history of several weeks of watery diarrhea that responded poorly to antidiarrheals or to empiric treatment with antimicrobials.”¹² In the CLL patient population for the monotherapy studies (n = 54), the applicant reports diarrhea for 16 patients (30%), in which the majority of these cases were grade 1 or 2.⁹ Grade 3 diarrhea was reported in 3 patients (6%), and colitis of any grade was reported for 4 patients (7.4%).⁹ Grade 3 colitis was reported for 2 patients, and Grade 4 was reported for 1 patient; two patients discontinued study drug due to colitis. Median time to onset and resolution of diarrhea in this population was similar to what was seen in the iNHL population. In addition, in patients with \geq grade 3 cases of diarrhea, the onset and resolution was typically much later as also seen in the iNHL patient population.

3.2.2 Hepatotoxicity – Grade 3 and 4 (more than 5 times the upper limit of normal) elevations have occurred in the clinical trials for idelalisib. Increases in ALT and AST were generally observed within the first 12 weeks of treatment, most were asymptomatic, and reversible with dose interruption.⁹ Therapy was either withheld or the dose was reduced.¹³ Eighty-four percent of these patients were re-challenged, either at 150 mg twice daily (n=3) or a lower dose (n=18).¹⁰ Of the patients re-challenged at the lower dose, 13 did not experience a recurrence, but 5 had a recurrence of ALT and AST elevations.¹⁰ The applicant reports that there were no cases of Hy’s Law; FDA clinical reviewers identified 3 cases that potentially met the criteria for Hy’s law. These cases may be confounded due to concomitant hepatotoxic medications given in these cases. Five subjects discontinued the study due to increased transaminases and undefined hepatocellular injury.⁹ There were no fatalities related to hepatotoxicity with the 150mg twice daily dose.

3.2.3 Pneumonia/pneumonitis – The applicant reports pneumonia of any grade in the iNHL population in 13% of patients, and in 11% of patients with events grade 3 or higher.⁹ For the CLL population pneumonia was reported in 22% of patients, with another 22% experiencing upper respiratory tract infection, for any grade, and 20% for events \geq grade 3.⁹ Pneumonia resulted in discontinuation of study drug in 2 patients in the CLL population. Six patients developed an AE leading to death, 3 related to pneumonia infections, 1 due to respiratory failure, 1 due to fungal sinusitis, and 1 related to infection.⁹ For the iNHL population, 2 patients died of pneumonia, 1 patient died from pneumonitis, and 1 patient died from *Pneumocystis jirovecii* pneumonia.⁹ FDA identified more subjects in the iNHL population (n=36 [25%]) with the grouped term “pneumonia.” With regard to specific preferred terms, there were a wide range of cases identified which included: 16 Pneumonia, 4 Pneumonitis, 3 Interstitial Lung Disease, 3 Pneumonia

¹² Clinical Summary of Safety section 2.7.4

¹³ Gilead Application Orientation meeting, October 7, 2013

Aspiration, 3 Respiratory Tract Infection, 2 Bronchopneumonia, 2 Lower Respiratory Tract Infection, 2 Lung Infection, 2 Lung Infiltration, and one each for Lung Infection Pseudomonal, Pneumocystis Jiroveci Pneumonia, Pneumonia Cytomegaloviral, Pneumonia Necrotizing, Pneumonia Staphylococcal, Pneumonia Streptococcal, Respiratory Syncytial Virus Infection.¹¹ Eight (5%) subjects did not have a Preferred Term listed as infection. For these 8 subjects, median time to onset of the event was 151 days (range, 93-378). Six were considered related to idelalisib, and 5 had treatment with corticosteroids. Four had idelalisib withdrawn, while treatment was unchanged or interrupted only temporarily for the other four without recurrence after resolution.

3.2.4 Rash - The association of rash was reported in a phase 1 healthy volunteer study, and was the most frequently reported AE, in another phase 1 dose escalation study; however, the sponsors report that the incidence of grade 3 and higher serious AE's are "low." Patients with grade 3 rash presented with a maculopapular rash on the trunk and extremities that was occasionally associated with fever and/or pruritus that responded to treatment with diphenhydramine and/or topical or oral steroids.⁹ In the iNHL population, idelalisib was interrupted in 4 subjects who had grade 3 rash, and recurrence of grade 1 rash occurred in 1 of these subjects upon re-challenge. The rash continued for approximately 6 months before resolving.⁹ In this same population, FDA reviewers found that 23% of the subjects had a rash using the grouped term, and the rash was grade 3 or 4.¹¹ The rash was categorized as related to idelalisib for 21 (14%) of the subjects. Median time to onset of rash was 66 days (range, 11-346 days). The action taken with the drug when the rash occurred was withdrawal for 1 subject, interruption for 3 subjects and reduction in dose for 2 subjects. In addition, 11 (8%) subjects received systemic steroids for treatment of rash.¹¹

3.2.5 Deaths¹¹ - The applicant reported that 57 subjects died on study, including 9 due to adverse events at least possibly related to idelalisib. FDA reviewed all 57 cases for root cause. The root causes of death were progressive disease for 33 (58%) subjects, infection for 16 (28%) subjects, and other adverse event for 8 (14%) subjects. For the purpose of determining relatedness, infections were considered related only when associated with drug-related neutropenia. There were seven fatal adverse events for which FDA could not exclude a possible relation to idelalisib. The fatal events included infection with neutropenia, sudden death, respiratory failure, tumor lysis syndrome, and enteropathy.

3.2.6 Pharmacology/ Toxicology Findings

Embryo-fetal toxicity – Idelalisib is embryotoxic, fetotoxic, and teratogenic in rats given 12 times the recommended human dose of 150mg twice daily.¹⁴ Idelalisib related malformation included short tail, anury, vertebral agenesis, hydrocephaly and microphthalmia/anophthalmia primarily restricted to the high dose group of 150mg/kg/day. At the mid dose of 75mg/kg/day, short tails were noted in the same litter.¹⁴ Idelalisib also showed evidence of post implantation loss, reduced fetal body weights, and teratogenicity at doses that also produced maternal toxicity. No AEs were observed at the 25mg/kg/day dose.

¹⁴ Idelalisib Section 2.4 Nonclinical Overview

Recommendations at this time will be provided in the label to advise women to avoid becoming pregnant while taking idelalisib.

Cardiac¹⁰- Cardiomyopathy, inflammation, and increased heart rate were observed in Sprague-Dawley rats in toxicology studies at exposures (AUCs) higher than those reported in patients at the recommended dose of 150mg twice daily. Cardiac inflammation was mainly seen in a 28-day study in rats; the other findings were observed in the 12 week and/or 6 month studies.

Pancreatic¹⁰- Inflammation, hemorrhage, low-incidence acinar degeneration and hyperplasia was also noted in Sprague-Dawley rats in toxicology studies at exposures higher than the recommended dose for humans.

***Reviewer comment:** None of these toxicities have been observed in the clinical trials.*

4 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

Post-marketing studies/requirements (PMR's) are in the process of being negotiated at the time of this writing. Additional studies that have been suggested involve the pharmacokinetics of idelalisib which include evaluation of idelalisib on the pharmacokinetics of drugs predominantly metabolized by CYP29 and CYP2C19, and to evaluate the effect of acid reducing agents on idelalisib pharmacokinetics.

In addition, PMR's evaluating the safety and efficacy of the dose of idelalisib for both the iNHL and CLL population are being negotiated, including 5 year safety follow-up for clinical studies in these populations, and further evaluation of pneumonitis with idelalisib.

5 DISCUSSION

FL, SLL, and CLL are part of a group of B-cell malignancies that are slow growing and have long periods between diagnosis and treatment of disease. Most patients will present at an advanced stage, after symptoms have already begin to occur, dramatically decreasing the cure rate. Many patients with B-cell malignancies will die from complications in the advanced stages of disease which commonly includes pneumonia, sepsis, or bleeding complications. There are five currently available agents approved (chlorambucil, cyclophosphamide, rituximab, 90Y-ibritumomab tiuxetan, and bendamustine) for the treatment of patients with follicular lymphoma (FL), low-grade non-Hodgkin lymphoma (NHL), or indolent NHL. The following drugs, fludarabine, pentostatin, ibrutinib, ofatumumab, and obinotuzumab are approved for CLL. These treatments are initially effective in inducing responses in most patients, however they are not curative, and show decreasing efficacy with repeated administrations, ultimately leading to refractory disease.^{4,7}

Idelalisib is a first in class, orally available, highly selective inhibitor of PI3K δ , which has been demonstrated in clinical trials to play a critical role in the pathogenesis of hyper-activation of the B-cell receptor pathway seen in hematological malignancies. Data for the iNHL indication, specifically for the FL and SLL population, is based on a single-arm, multicenter trial which included 72 patients with FL and 28 patients with SLL.

Fifty-four percent of patients in the FL group and 58% of patients in the SLL group achieved the primary endpoint of ORR, with 46% of patients with FL having a PR and 8% patients having a CR. The duration of response had not yet been reached in this group, as only 12% of patients were on therapy for at least one year. The applicant's registrational study for CLL was a randomized, double-blind, placebo controlled trial in 220 patients to receive rituximab in combination with idelalisib or placebo. The results for both the primary and secondary endpoints were statistically significant at <0.0001 as compared to placebo.

The safety of idelalisib was evaluated in an integrated safety analysis of their monotherapy and combination Phase 1 and Phase 2 studies, and also includes data from the randomized Phase 3 study for CLL. Grade 3 and higher cases of diarrhea resulting in colitis and bowel perforations, transaminase elevations, pneumonia, and rash were noted as AEs associated with treatment interruptions, dose modifications, discontinuations, and fatalities in some patients treated with idelalisib. Permanent withdrawal of idelalisib occurred in 80 (55%) subjects out of the 146 iNHL population.¹¹ Nonclinical data show that idelalisib is embryotoxic, fetotoxic, and teratogenic in rats at exposures 12 times the recommended human dose. In addition, cardiac and pancreatic toxicities were also observed in nonclinical trials with rodents.

In the iNHL population only 12% of patients were on therapy for at least one year, and in the CLL population PFS had not been reached as treatment was ongoing. The median time on idelalisib therapy is 5 months, and it is possible that the AE's reported may increase with longer treatment exposure.

Idelalisib is a NME, and if approved will be the first in class inhibitor of phosphoinositide 3-kinase delta (PI3K δ); hence, the toxicities for this class are not well characterized. The risks of hepatotoxicity, bowel perforation, colitis, and pneumonitis are concerning for the following reasons:

- the serious risks reported with idelalisib differ in type and severity from the approved treatments for the aforementioned hematological malignancies, and the prescribing population initially may not be as familiar with managing these toxicities,
- this is an oral formulation that will be administered to patients in ambulatory/outpatient care settings; recognition of these serious AEs could be delayed,
- the median time on idelalisib therapy is 5 months, and longer treatment exposure may change the risk:benefit profile.

FL, SLL, and CLL are all incurable with currently approved treatments, and patients will ultimately die as a result of their disease. Although idelalisib has demonstrated efficacy in clinical trials, and would provide an oral treatment for these diseases, the AEs observed at this time affect the benefit:risk profile for this NME. As per DHP, the toxicities noted thus far in this review are frequent, severe and serious, have characteristics that are atypical and not usually encountered in a community hematology-oncology practice, and will require early recognition and management to mitigate these risks.

6 CONCLUSION

DRISK and Division of Hematology Products have determined, if idelalisib is approved, a REMS that consists of a communication plan to address the risks of hepatotoxicity, bowel perforation, colitis, and pneumonitis will be necessary to ensure that the benefits outweigh the risks of treatment. The Agency has instructed the sponsor to submit a risk management plan that includes a proposed communication plan REMS. DRISK will review the proposed REMS upon their submission.

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05/21/2014

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