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

Reference ID: 3597801

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

Reference ID: 3597801

- 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.

Reference ID: 3597801

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™ (idelalisib) 150 mg 100 mg tablets

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

GILEAD

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

●●●○○ Applidium 11:27 AM 100 %

Back

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

View in Browser | Full Prescribing Information
Important Safety Information

Zydelig™ (idelalisib) 150 mg 100 mg tablets

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

Unsubscribe | Terms of Use | Privacy Policy | Contact Us

GILEAD

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

Zydelig (idelalisib) 150 mg 100 mg tablets

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**

July 2014

IMPORTANT SAFETY NOTICE

Dear Healthcare Provider:

The FDA has required this safety notice as part of the Zydelig REMS (**R**isk **E**valuation and **M**itigation **S**trategy) to inform you about the 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 enclosed **Zydelig REMS Fact Sheet**, a non-promotional fact sheet reviewed by the FDA, for more detailed safety information. Be sure to give the **Zydelig Patient Safety Information Card** to all patients. This card, additional copies of 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 letter does not contain the complete safety profile for Zydelig. Please review the enclosed Prescribing Information.

Zydelig™
(idelalisib) 150 mg 100 mg tablets

Zydelig REMS

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

GILEAD
© 2014 **Gilead Sciences, Inc.** 333 Lakeside Drive Foster City, CA 94404 USA REMS-ZYD-0002 07/2014
www.ZydeligREMS.com *Phone* 650 574 3000 *facsimile* 650 578 9264
Reference ID: 3597801

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

Subject: Warning: Fatalities and Serious Risks Associated with Zydelig

Zydelig® REMS

View in Browser | Full Prescribing Information | Important Safety Information

Zydelig™ (idelalisib) 150 mg 100 mg tablets

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**

July 2014

IMPORTANT SAFETY NOTICE

Dear <name>:

The FDA has required Gilead Sciences to distribute this safety notice to the [Professional Organization] as part of the Zydelig REMS (Risk Evaluation and Mitigation Strategy). We request that you distribute this information to your members 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 and then reduce 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 encourage your members to provide 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 letter 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

Unsubscribe | Terms of Use | Privacy Policy | Contact Us

GILEAD

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

●●●○○ Applidium 11:27 AM 100 %

Back

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

View in Browser | Full Prescribing Information
Important Safety Information

Zydelig™ (idelalisib) 150 mg 100 mg tablets

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**

July 2014

IMPORTANT SAFETY NOTICE

Dear <name>:

The FDA has required Gilead Sciences to distribute this safety notice to the [Professional Organization] as part of the Zydelig REMS (Risk Evaluation and Mitigation Strategy). We request that you distribute this information to your members 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 and then reduce 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 encourage your members to provide 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 letter 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

Unsubscribe | Terms of Use | Privacy Policy | Contact Us

GILEAD

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

Zydelig (idelalisib) 150 mg 100 mg tablets

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**

July 2014

IMPORTANT SAFETY NOTICE

Dear <Name>:

The FDA has required Gilead Sciences to distribute this safety notice to the [Professional Organization] as part of the Zydelig REMS (**R**isk **E**valuation and **M**itigation **S**trategy). We request that you distribute this information to your members about the following serious risks of Zydelig:

WARNING: FATAL AND SERIOUS TOXICITIES: HEPATIC, SEVERE DIARRHEA or 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 bilateral interstitial infiltrates. Interrupt and then reduce 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 enclosed **Zydelig REMS Fact Sheet**, a non-promotional fact sheet reviewed by the FDA, for more detailed safety information. Please encourage your members to provide the **Zydelig Patient Safety Information Card** to all patients. This card, additional copies of 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 letter does not contain the complete safety profile for Zydelig. Please review the enclosed Prescribing Information.

Zydelig™
(idelalisib) 150 mg 100 mg tablets

Zydelig® REMS

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

GILEAD
© 2014 **Gilead Sciences, Inc.** 333 Lakeside Drive Foster City, CA 94404 USA REMS-ZYD-0004 07/2014
www.ZydeligREMS.com *Phone* 650 574 3000 *Facsimile* 650 578 9264
Reference ID: 3597801

Z deli
(i lali i 150 mg 100 mg lets

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™
(idelalisib) 150 mg 100 mg tablets

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.

GILEAD

© 2014 Gilead Sciences, Inc. All rights reserved. REMS-ZYD-0005 07/2014
Gilead, the Gilead logo, and Zydelig are trademarks of Gilead Sciences, Inc., or one of its related companies.

Z deli
(i lali i 150 mg 100 mg lets

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.

Zydelig™
(idelalisib) 150 mg 100 mg tablets

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.

GILEAD

© 2014 Gilead Sciences, Inc. All rights reserved. REMS-ZYD-0008 07/2014
Gilead, the Gilead logo, and Zydelig are trademarks of Gilead Sciences, Inc., or one of its related companies.

Reference ID: 3597801

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. Withold 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")

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

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.

GILEAD

© 2014 Gilead Sciences, Inc. All rights reserved. REMS-ZYD-0009 July 2014
Zydelig is a registered trademark of Gilead Sciences, Inc. Gilead, the Gilead logo, and ZYDELIG are trademarks of Gilead Sciences, Inc., or one of its related companies.

Reference ID: 3597801

Close X

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 >3x upper limit of normal (ULN), monitor for liver toxicity weekly. If ALT/AST is >5x 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 ≥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 ≥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 ≥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 ≥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.

GILEAD

© 2014 Gilead Sciences, Inc. All rights reserved. REMS-ZYD-0009 July 2014
Zydelig is a registered trademark of Gilead Sciences, Inc. Gilead, the Gilead logo, and ZYDELIG are trademarks of Gilead Sciences, Inc., or one of its related companies.

Reference ID: 3597801

Zydelig™
(idelalisib) 150 mg 100 mg tablets

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.

Zydelig™

(idelalisib) 150 mg 100 mg tablets

Patient Safety Information Card

Patient Name

Zydelig Prescriber Name

Prescriber's Phone Number

© 2014 Gilead Sciences, Inc.
All rights reserved. REMS-ZYD-0007 07/2014
Gilead and Zydelig are trademarks of Gilead Sciences, Inc., or one of its related companies.

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.

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

/s/

RICHARD PAZDUR
07/23/2014