NDA 205858

ZYDELG® (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:
The goal of the Zydelig REMS is to mitigate the risks of fatal and/or serious hepatotoxicity; fatal and/or serious and severe diarrhea or colitis; fatal and/or serious pneumonitis; fatal and/or serious infections, and fatal and serious intestinal perforation associated with Zydelig treatment by informing healthcare providers of the risks of

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

II. REMS ELEMENTS

A. Communication Plan

Gilead Sciences, Inc. (Gilead) must implement the following communication plan for healthcare providers who are likely to prescribe Zydelig. The communication plan must consist of the following:

1. REMS Letter Healthcare Providers - A REMS Letter to Healthcare Providers must be distributed within 30 calendar days of the approval of the REMS modification (01/26/2018). The letter must 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 must inform healthcare providers of the risks of fatal and/or serious hepatotoxicity; fatal and/or serious and severe diarrhea or colitis; fatal and/or serious pneumonitis; fatal and/or serious infections; and fatal and serious intestinal perforation associated with Zydelig treatment. The letter must be accompanied by the Prescribing Information (with Medication Guide attached) and the Zydelig REMS Fact Sheet. The REMS Letter to Healthcare Providers must be available from the Zydelig REMS Website at the time of distribution and remain on the website for 12 months after approval of the REMS modification (01/26/2018).

2. REMS Letter for Professional Societies - A REMS Letter for Professional Societies must be distributed electronically within 30 calendar days of the approval of the REMS modification (01/26/2018). If a targeted Professional Society’s email address is not available, or if an email is undeliverable, the letter must be sent through the mail. The REMS Letter for Professional Societies must 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/or serious pneumonitis; fatal and/or serious infections; and fatal and serious intestinal perforation associated with Zydelig treatment. Gilead must request the leadership of the professional societies distribute this risk information to their memberships.

The REMS Letter for Professional Societies must 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 must be distributed to Healthcare Providers. The Zydelig REMS Fact Sheet must be included in the mailings of the REMS Letter to Healthcare Providers and the REMS Letter for Professional Societies and must be available on the Zydelig REMS Website. Hard copies of the Zydelig REMS Fact Sheet must 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 REMS modification (01/26/2018). Gilead sales representatives and medical field-based personnel must orally review the risk messages contained in the Zydelig REMS Fact Sheet during the visit with the healthcare provider.

4. Journal Information Piece - Gilead must 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 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 modification (01/26/2018).

5. Dissemination of REMS information at scientific meetings – The Zydelig REMS Fact Sheet and the Prescribing Information must be prominently displayed at scientific meetings where Gilead has a presence (e.g., booth) through the end of January 2019.

6. REMS Program Website – The Zydelig REMS Program Website (www.zydeligrems.com) will continue for 12 months after the approval of this REMS modification (01/26/2018). The Zydelig REMS Program Website must include the option to print the currently approved Prescribing Information, Medication Guide, REMS Letter for Healthcare Providers, REMS Factsheet, and Patient Safety Information Card. The Zydelig product website must include a prominent REMS-specific link to the Zydelig REMS Program Website. All website information must be updated within 60 calendar days of approval of the REMS modification (01/26/2018).

7. Zydelig Patient Safety Information Card - A Patient Safety Information Card highlights the risks of Zydelig and includes information on the management of these risks. Gilead’s sales representatives or medical field based personnel must distribute the Patient Safety Information Cards to prescribers within the first 12 months of approval of the REMS modification (01/26/2018). The Patient Safety Information Card must also be available on the Zydelig REMS Program Website for 12 months after the approval of the REMS modification (01/26/2018).

The following are part of the REMS and are appended.

- REMS Letter to Healthcare Providers
- REMS Letter for Professional Societies
- REMS Fact Sheet
- Journal Information Piece
- Zydelig REMS Website
- Zydelig Patient Safety Information Card
B. Timetable for Submission of Assessments

Gilead must submit REMS assessments to the FDA 18 months, 4 years, and 7 years from the date of the initial approval of the REMS (07/23/2014). 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 calendar days before the submission date for that assessment so that it will be received by the FDA on or before the due date.
FDA REQUIRED UPDATED REMS SAFETY INFORMATION

Boxed Warning Risk of:
• Fatal and/or serious hepatotoxicity - updated
• Fatal and/or serious and severe diarrhea or colitis - updated
• Fatal and/or serious pneumonitis
• Fatal and/or serious infections - updated
• Fatal and serious intestinal perforation

January 2018

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 recent update to the incidence rates of fatal and serious toxicities in the Zydelig Boxed Warning as follows:

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

• Fatal and/or serious hepatotoxicity occurred in 16% to 18% 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% to 20% of ZYDELIG-treated patients. Monitor for the development of severe diarrhea or colitis. Interrupt and then reduce or discontinue ZYDELIG.
• Fatal and/or serious pneumonitis occurred in 4% of ZYDELIG-treated patients. Monitor for pulmonary symptoms and interstitial infiltrates. Interrupt or discontinue ZYDELIG.
• Fatal and/or serious infections occurred in 21% to 48% of ZYDELIG-treated patients. Monitor for signs and symptoms of infection. Interrupt ZYDELIG if infection is suspected.
• Fatal and serious intestinal perforation can occur in ZYDELIG-treated patients across clinical trials. Discontinue ZYDELIG if intestinal perforation is suspected.

The updated incidence rates of fatal and serious toxicities in the Zydelig Boxed Warning reflect data from patients treated with Zydelig in combination with rituximab or with unapproved combination therapies.

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

Reference ID: 4238482
Zydelig REMS

Limitation of use:
Zydelig is not indicated and is not recommended for first-line treatment of any patient. Zydelig is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of FL.

This letter does not contain the complete safety profile for Zydelig. Please review the enclosed Prescribing Information.

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,

William Guyer, Pharm.D.
Senior Vice President, Medical Affairs
Zydelig REMS

FDA REQUIRED UPDATED REMS SAFETY INFORMATION

Boxed Warning includes the Risk of:
• Fatal and/or serious hepatitis — updated
• Fatal and/or serious and severe diarrhea or colitis — updated
• Fatal and serious pneumonitis
• Fatal and serious infections — updated
• Fatal and serious intestinal perforation

January 2018

Dear Healthcare Professional,

This FDA required update systematically revises part of the Zydelig REMS (Risk Evaluation and Mitigation Strategy) to inform you about recent updates in the safety profile of Zydelig (idelalisib) tablets and fatal and serious perforations in the Zydelig Approved Warnings of February 2012.

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

• Fatal and/or serious hepatitis occurred in 16% to 19% 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% to 20% of ZYDELIG-treated patients. Monitor for symptoms of severe diarrhea or colitis. If symptoms severe, discontinue ZYDELIG.
• Fatal and/or serious and severe pneumonitis occurred in 4% of ZYDELIG-treated patients. Monitor for pulmonary symptoms and intestinal perforations. Interrupt and then reduce or discontinue ZYDELIG.

• Fatal and/or serious infections occurred in 21% to 24% of ZYDELIG-treated patients. Monitor for signs and symptoms of infection. Interrupt ZYDELIG if infection is suspected.

• Fatal and serious intestinal perforation can occur in ZYDELIG-treated patients across clinical trials. Discontinue ZYDELIG if intestinal perforation is identified.

The updated information reflects new data from recent New Safety Information and Revisions to the Zydelig V6.1 (FDA, 2016) for more detailed, relevant, and important information available on the Zydelig REMS website (https://www.zydelig.com).

The site is in English; available links for the latest available update.

is available on the Zydelig REMS website (https://www.zydelig.com) in multiple languages; in patients for whom English is a non-native language should be considered appropriate therapy due to other contraindications.

In clinical trials, 1% of patients experienced severe or more hepatic toxicity. A total of 1% of patients who received ZYDELIG were hospitalized with severe hepatic toxicity. In patients who received ZYDELIG, 1% of patients experienced severe or more skin-related events and 1% of patients experienced severe or more pulmonary-related events. In patients who received ZYDELIG, 1% of patients experienced severe or more infections.

Zydelig is indicated in countries worldwide, including the United States, with a risk evaluation and mitigation strategy (REMS) to ensure that patients receive the treatment-specific information.

Zydelig is a new drug that is not recommended for last line treatment of any patient. Zydelig is not registered and is not recommended in combination with bortezomib and/or rituximab for the treatment of FL.

The database does not contain the complete adverse effects profile for Zydelig. To review the adverse effects profile, including complete BOXED WARNING and Risk Evaluation and Mitigation Strategy, see the V6.1 label.

Providing Information

Data collection

Importing Adverse Events

You can choose to report negative clinical side effects of products across the FDA. Use Retrospective Database Analysis (RDA) to search for, report on, and analyze adverse event data in patients who have received ZYDELIG, 1% of patients experienced severe or more skin-related events and 1% of patients experienced severe or more pulmonary-related events. In patients who received ZYDELIG, 1% of patients experienced severe or more infections.

This FDA required update systematically revises part of the Zydelig REMS (Risk Evaluation and Mitigation Strategy) to inform you about recent updates in the safety profile of Zydelig (idelalisib) tablets and fatal and serious perforations in the Zydelig Approved Warnings of February 2012.

The updated information reflects new data from recent New Safety Information and Revisions to the Zydelig V6.1 (FDA, 2016) for more detailed, relevant, and important information available on the Zydelig REMS website (https://www.zydelig.com).

is available on the Zydelig REMS website (https://www.zydelig.com) in multiple languages; in patients for whom English is a non-native language should be considered appropriate therapy due to other contraindications.

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Zydelig is a new drug that is not recommended for last line treatment of any patient. Zydelig is not registered and is not recommended in combination with bortezomib and/or rituximab for the treatment of FL.

The database does not contain the complete adverse effects profile for Zydelig. To review the adverse effects profile, including complete BOXED WARNING and Risk Evaluation and Mitigation Strategy, see the V6.1 label.

Providing Information

Data collection

Importing Adverse Events

You can choose to report negative clinical side effects of products across the FDA. Use Retrospective Database Analysis (RDA) to search for, report on, and analyze adverse event data in patients who have received ZYDELIG, 1% of patients experienced severe or more skin-related events and 1% of patients experienced severe or more pulmonary-related events. In patients who received ZYDELIG, 1% of patients experienced severe or more infections.
Yazldel REMS

FDA REQUIRED UPDATED REMS SAFETY INFORMATION

Boxed Warning includes the Risk of:
• Fatal and serious seizures
• Venous and arterial thromboembolic events
• Fetal harm

Yazldel REMS

To <Healthcare Provider Name>

January 19, 2018

WILLING-ARTICULATED TOXICITIES: HEPAVIR, SEVERE DIABETES MELLITUS, MALIGNANCIES, INFECTIONS, AND GASTROINTESTINAL PROBLEMS

For more information about Yazldel, please see the Patient Medication Guide and Yazldel Full Prescribing Information.

Dear Healthcare Provider,

The U.S. FDA has required a new safety label on Yazldel (felodipine extended-release tablets) and its companion drug, Zolmitriptan (Zolmitriptan and Zolmitriptan [Zytoz]), to inform you about the risk of fetal harm and serious side effects for the use of Yazldel by pregnant women.

Yazldel is a vasodilator used to treat hypertension. It is also used to treat angina pectoris. Yazldel is not recommended for use in pregnant women because it can cause harm to the fetus. Women who are pregnant or planning to become pregnant should not take Yazldel.

Please see the Yazldel REMS Fact Sheet, a non prescription formulary that includes the following information:

1. A personal medication guide that you should keep at home or in your carry-on bag.
2. Instructions on how to request a copy of the Patient Medication Guide and Full Prescribing Information.
3. A summary of important safety information that is available only in the REMS Fact Sheet.

For more information, please see the Patient Medication Guide and Yazldel Full Prescribing Information.

Yazldel is a brand-name medication that is used to treat high blood pressure. It is a diuretic and is available in several different forms, including oral tablets, intravenous injections, and subcutaneous injections.

Limitation of Use

Yazldel is not recommended for use in patients with severe liver impairment (Child-Pugh score B). In patients with severe liver impairment (Child-Pugh score C), the dosage of Yazldel should be reduced to one-third of the usual dose.

The use of Yazldel in patients with severe liver impairment (Child-Pugh score C) is not recommended for use in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²).

Yazldel is not recommended for use in patients with severe liver impairment (Child-Pugh score C) or severe renal impairment (eGFR < 30 mL/min/1.73 m²).

Yazldel is not recommended for use in patients with severe liver impairment (Child-Pugh score C) or severe renal impairment (eGFR < 30 mL/min/1.73 m²).

Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.LovelyDrug.com or call 1-800-FDA-1088. If you are concerned about adverse effects, you may also contact your healthcare provider or pharmacist.

For more information, please see the Patient Medication Guide and Yazldel Full Prescribing Information.
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). The incidence rates of fatal and serious toxicities have been updated in the Boxed Warning for Zydelig. 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, INFECTIONS and INTESTINAL PERFORATION**

- Fatal and/or serious hepatotoxicity occurred in 16% to 18% 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% to 20% of ZYDELIG-treated patients. Monitor for the development of severe diarrhea or colitis. Interrupt and then reduce or discontinue ZYDELIG.
- Fatal and/or serious pneumonitis occurred in 4% of ZYDELIG-treated patients. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interrupt or discontinue ZYDELIG.
- Fatal and/or serious infections occurred in 21% to 48% of ZYDELIG-treated patients. Monitor for signs and symptoms of infection. Interrupt ZYDELIG if infection is suspected.
- Fatal and serious intestinal perforation can occur in ZYDELIG-treated patients across clinical trials. Discontinue ZYDELIG if intestinal perforation is suspected.

The updated incidence rates of fatal and serious toxicities in the Zydelig Boxed Warning reflect data from patients treated with Zydelig in combination with rituximab or with unapproved combination therapies.

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.
Zydelig REMS

- 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

**Limitation of use:**
Zydelig is not indicated and is not recommended for first-line treatment of any patient. Zydelig is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of FL.

This letter does not contain the complete safety profile for Zydelig. Please review the enclosed Prescribing Information.

**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,

William Guyer, Pharm.D.
Senior Vice President, Medical Affairs
FDA REQUIRED UPDATED REMS SAFETY INFORMATION

Boxed Warning includes the risk of:
- Fatal and/or serious hematopoietic — updated
- Fatal and/or serious burns or colds — updated
- Fatal and/or serious pneumonitis — updated
- Fatal and/or serious infections — updated
- Fatal and serious intestinal perforation — updated

January 2015

IMPORTANT SAFETY NOTICE

What is a Mylotarg

The Mylotarg (idelalisib) tablets are a novel treatment for relapsed or refractory chronic lymphocytic leukemia (CLL) and indolent lymphoma. Please see brief summary of prescribing information for more detailed safety information. Please request a Mylotarg HCP Handout. If you have any questions, please refer to the prescribing information for more information.

WARNING: FATAL AND SERIOUS TOXICITIES:

HEPATIC, SEVERE DIARRHEA, COLITIS, PULMONARY, INFECTIONS, AND INTESTINAL PERFORATION

- Fatal and/or serious hematopoietic occurred in 18% to 18% of ZYDELIG-treated patients. Monitor hepatic function and consider discontinuing treatment. Interrupt and then reduce or discontinue ZYDELIG.
- Fatal and/or serious burns or colds occurred in 7% to 10% of ZYDELIG-treated patients. Monitor for the development of severe diarrhea or colds and then reduce or discontinue ZYDELIG.
- Fatal and/or serious pneumonitis occurred in 4% of ZYDELIG-treated patients. Monitor for pulmonary symptoms and intrathoracic infections. Interrupt or discontinue ZYDELIG.
- Fatal and/or serious infections occurred in 21% to 48% of ZYDELIG-treated patients. Monitor for signs and symptoms of infection. Interrupt ZYDELIG if infection is suspected.
- Fatal and serious intestinal perforation can occur in patients with perforating and penetrating ulcers. Discontinue ZYDELIG if intestinal perforation is suspected.

The updated fact sheet will be faxed to all patients located in the United States. Please contact us to provide the Mylotarg Patient Safety Information Form to all patients. We have not reviewed, nor request important information. Please visit our website at:

zydelig.com

zydelig.com is a graphic symbol for the reference of zydelig.

Hepatotoxicity:

- Elevated transaminase levels (ALT and AST) in combination with elevation of bilirubin. Please review the labeling for zydelig, which states that patients with elevated transaminase levels should be considered for treatment discontinuation.

Fatal and/or serious infections:

- Elevated transaminase levels (ALT and AST) and elevated bilirubin. In patients who have received both zydelig and prior therapies.

Abnormal lipase levels:

- Elevated lipase levels (LIPASE) in patients who have received both zydelig and prior therapies.

Intervention of use:

- Elevating in a normal range and not recommended for use. Please refer to the Mylotarg Prescribing Information for more information.

- Elevating in a normal range and not recommended for use. Please contact the Hepatic Prophylaxis Program should overlap of prescribed treatment.

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This letter does not contain the complete safety profile for zydelig. For more information, please see the full prescribing information, including the Complete Boxed Warning and Mabthera (ofatumumab) Gador and, Zyrab, Zyrab

Prescribing Information

Modification guide

Reporting Adverse Events

You are encouraged to report adverse events of suspected drug reaction to the FDA. View the Medscape Drug interaction Forms. Reporting Prescribers should review for suspected adverse events with their patients. ZYDELIG to the FDU is due at 1-888-434-3226.

Report

MSDS

Zydelig (idelalisib) tablets

Zydelig REMS

Zydelig REMS Safety Information

Boxed Warning includes the risk of:
- Fatal and/or serious hematopoietic — updated
- Fatal and/or serious burns or colds — updated
- Fatal and/or serious pneumonitis — updated
- Fatal and/or serious infections — updated
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January 2015

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The Mylotarg (idelalisib) tablets are a novel treatment for relapsed or refractory chronic lymphocytic leukemia (CLL) and indolent lymphoma. Please see brief summary of prescribing information for more detailed safety information. Please request a Mylotarg HCP Handout. If you have any questions, please refer to the prescribing information for more information.

WARNING: FATAL AND SERIOUS TOXICITIES:

HEPATIC, SEVERE DIARRHEA, COLITIS, PULMONARY, INFECTIONS, AND INTESTINAL PERFORATION

- Fatal and/or serious hematopoietic occurred in 18% to 18% of ZYDELIG-treated patients. Monitor hepatic function and consider discontinuing treatment. Interrupt and then reduce or discontinue ZYDELIG.
- Fatal and/or serious burns or colds occurred in 7% to 10% of ZYDELIG-treated patients. Monitor for the development of severe diarrhea or colds and then reduce or discontinue ZYDELIG.
- Fatal and/or serious pneumonitis occurred in 4% of ZYDELIG-treated patients. Monitor for pulmonary symptoms and intrathoracic infections. Interrupt or discontinue ZYDELIG.
- Fatal and/or serious infections occurred in 21% to 48% of ZYDELIG-treated patients. Monitor for signs and symptoms of infection. Interrupt ZYDELIG if infection is suspected.
- Fatal and serious intestinal perforation can occur in patients with perforating and penetrating ulcers. Discontinue ZYDELIG if intestinal perforation is suspected.

The updated fact sheet will be faxed to all patients located in the United States. Please contact us to provide the Mylotarg Patient Safety Information Form to all patients. We have not reviewed, nor request important information. Please visit our website at:

zydelig.com

zydelig.com is a graphic symbol for the reference of zydelig.

Hepatotoxicity:

- Elevated transaminase levels (ALT and AST) in combination with elevation of bilirubin. Please review the labeling for zydelig, which states that patients with elevated transaminase levels should be considered for treatment discontinuation.

Fatal and/or serious infections:

- Elevated transaminase levels (ALT and AST) and elevated bilirubin. In patients who have received both zydelig and prior therapies.

Abnormal lipase levels:

- Elevated lipase levels (LIPASE) in patients who have received both zydelig and prior therapies.

Intervention of use:

- Elevating in a normal range and not recommended for use. Please refer to the Mylotarg Prescribing Information for more information.

- Elevating in a normal range and not recommended for use. Please contact the Hepatic Prophylaxis Program should overlap of prescribed treatment.

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MSDS

Zydelig (idelalisib) tablets

Zydelig REMS

Zydelig REMS Safety Information

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- Fatal and serious intestinal perforation can occur in patients with perforating and penetrating ulcers. Discontinue ZYDELIG if intestinal perforation is suspected.

The updated fact sheet will be faxed to all patients located in the United States. Please contact us to provide the Mylotarg Patient Safety Information Form to all patients. We have not reviewed, nor request important information. Please visit our website at:

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Hepatotoxicity:

- Elevated transaminase levels (ALT and AST) in combination with elevation of bilirubin. Please review the labeling for zydelig, which states that patients with elevated transaminase levels should be considered for treatment discontinuation.

Fatal and/or serious infections:

- Elevated transaminase levels (ALT and AST) and elevated bilirubin. In patients who have received both zydelig and prior therapies.

Abnormal lipase levels:

- Elevated lipase levels (LIPASE) in patients who have received both zydelig and prior therapies.

Intervention of use:

- Elevating in a normal range and not recommended for use. Please refer to the Mylotarg Prescribing Information for more information.

- Elevating in a normal range and not recommended for use. Please contact the Hepatic Prophylaxis Program should overlap of prescribed treatment.

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This letter does not contain the complete safety profile for zydelig. For more information, please see the full prescribing information, including the Complete Boxed Warning and Mabthera (ofatumumab) Gador and, Zyrab, Zyrab
FDA REQUIRED UPDATED REMS SAFETY INFORMATION

Zydeli REMS

Board Warning includes the Risk of:
- Fatal and/or serious hepatotoxicity
- Fatal and/or serious gastrointestinal toxicity
- Fatal and/or serious gastrointestinal perforation

IMMUNOHISTOCHEMISTRY
The Zydeli REMS has received Clinical Trials database references to the intervention, as it is not currently believed to be the same intervention. This data has been submitted to the Board Warning for Zydeli. The REMS have not been determined. Any information for these changes should be submitted to the Zydeli REMS.
FDA REQUIRED Updated Safety Information for Zydelig® (idelalisib)

Safety information updates were made to the Boxed Warning, including incidence rates of fatal and serious toxicities.

BOXED WARNING For Zydelig (Idelalisib)

<table>
<thead>
<tr>
<th>Risk of:</th>
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<tbody>
<tr>
<td>- Fatal and/or serious hepatotoxicity - updated</td>
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<tr>
<td>- Fatal and/or serious and severe diarrhea or colitis - updated</td>
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<tr>
<td>- Fatal and/or serious pneumonitis</td>
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<tr>
<td>- Fatal and/or serious infections - updated</td>
</tr>
<tr>
<td>- Fatal and serious intestinal perforation</td>
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</tbody>
</table>

Fatal and/or Serious Hepatotoxicity

- Fatal and/or serious hepatotoxicity occurred in 18% of patients treated with Zydelig monotherapy and 16% of patients treated with Zydelig in combination with rituximab or with unapproved combination therapies.
- 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 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

- Severe diarrhea or colitis (Grade 3 or higher) occurred in 14% of patients treated with Zydelig monotherapy and 20% of patients treated with Zydelig in combination with rituximab or with unapproved combination therapies. Diarrhea can occur at any time.
- Avoid concurrent use of Zydelig and other drugs that cause diarrhea. Diarrhea due to Zydelig responds poorly to antimitility 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/or Serious Pneumonitis

- Fatal and serious pneumonitis occurred in patients treated with Zydelig. Clinical manifestations included interstitial infiltrates and organizing pneumonia.
- In randomized clinical trials of combination therapies, pneumonitis occurred in 4% of patients treated with Zydelig compared to 1% on the comparator arms. Time to onset of pneumonitis ranged from <1 to 15 months. Monitor patients on Zydelig for pulmonary symptoms.
- In 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, interrupt Zydelig until the etiology has been determined.
- If symptomatic pneumonitis or organizing pneumonia is diagnosed, initiate appropriate treatment with corticosteroids and permanently discontinue Zydelig.

Reference ID: 4238482
Fatal and/or Serious Infections

- Fatal and/or serious infections occurred in 21% of patients treated with Zydelig monotherapy and 48% of patients treated with Zydelig in combination with rituximab or with unapproved combination therapies. The most common infections were pneumonia, sepsis, and febrile neutropenia. Treat infections prior to initiation of Zydelig therapy.
- Monitor patients on Zydelig for signs and symptoms of infection and interrupt Zydelig for Grade 3 or higher infection.
- Serious or fatal Pneumocystis jirovecii pneumonia (PJP) or cytomegalovirus (CMV) occurred in <1% of patients treated with Zydelig. Provide PJP prophylaxis during treatment with Zydelig. Interrupt Zydelig in patients with suspected PJP infection of any grade, and permanently discontinue Zydelig if PJP infection of any grade is confirmed. Regular clinical and laboratory monitoring for CMV infection is recommended in patients with history of CMV infection or positive CMV serology at the start of treatment with Zydelig. Interrupt Zydelig in the setting of positive CMV PCR or antigen test until the viremia has resolved. If Zydelig is subsequently resumed, patients should be monitored by PCR or antigen test for CMV reactivation at least monthly.

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.

Limitations of use:
Zydelig is not indicated and is not recommended for first-line treatment of any patient. Zydelig is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of FL.

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.
FDA REQUIRED Zydelig (idelalisib) UPDATED REMS SAFETY INFORMATION

Boxed Warning for the Risk of:
• Fatal and/or serious hepatotoxicity – updated
• Fatal and/or serious and severe diarrhea or colitis – updated
• Fatal and/or serious pneumonitis
• Fatal and/or serious infections – updated
• Fatal and serious intestinal perforation

Fatal and/or Serious Hepatotoxicity
• Fatal and/or serious hepatotoxicity occurred in 18% of patients treated with Zydelig monotherapy and 16% of patients treated with Zydelig in combination with rituximab or with unapproved combination therapies.
• 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 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
• Severe diarrhea or colitis (Grade 3 or higher) occurred in 14% of patients treated with Zydelig monotherapy and 20% of patients treated with Zydelig in combination with rituximab or with unapproved combination therapies. 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/or Serious Pneumonitis
• Fatal and serious pneumonitis occurred in patients treated with Zydelig. Clinical manifestations included interstitial infiltrates and organizing pneumonia. In randomized clinical trials of combination therapies, pneumonitis occurred in 4% of patients treated with Zydelig compared to 1% on the comparator arms. Time to onset of pneumonitis ranged from <1 to 15 months. Monitor patients on Zydelig for pulmonary symptoms.
• In 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, interrupt Zydelig until the etiology has been determined. If symptomatic pneumonitis or organizing pneumonia is diagnosed, initiate appropriate treatment with corticosteroids and permanently discontinue Zydelig.

Fatal and/or Serious Infections
• Fatal and/or serious infections occurred in 21% of patients treated with Zydelig monotherapy and 48% of patients treated with Zydelig in combination with rituximab or with unapproved combination therapies. The most common infections were pneumonia, sepsis, and febrile neutropenia. Treat infections prior to initiation of Zydelig therapy.
• Monitor patients on Zydelig for signs and symptoms of infection and interrupt Zydelig for Grade 3 or higher infection.
Fatal and/or Serious Infections (cont’d)

• Serious or fatal Pneumocystis jirovecii pneumonia (PJP) or cytomegalovirus (CMV) occurred in <1% of patients treated with Zydelig. Provide PJP prophylaxis during treatment with Zydelig. Interrupt Zydelig in patients with suspected PJP infection of any grade, and permanently discontinue Zydelig if PJP infection of any grade is confirmed. Regular clinical and laboratory monitoring for CMV infection is recommended in patients with history of CMV infection or positive CMV serology at the start of treatment with Zydelig. Interrupt Zydelig in the setting of positive CMV PCR or antigen test until the viremia has resolved. If Zydelig is subsequently resumed, patients should be monitored by PCR or antigen test for CMV reactivation at least monthly.

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.

Limitation of use:

Zydelig is not indicated and is not recommended for first-line treatment of any patient. Zydelig is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of FL.

WHAT IS THE ZYDELIG REMS?

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. FDA has determined that a REMS is necessary to ensure that the benefits of Zydelig outweigh its risks. The purpose of the Zydelig REMS is to inform Healthcare Providers of fatal and serious risks of hepatotoxicity, severe diarrhea or colitis, pneumonitis, infections, and intestinal perforation. This fact sheet is required by the FDA as part of the Zydelig REMS program.

A Patient Safety Information Card is also available for you to provide to your patients. The card reminds patients of the symptoms of the serious risks of Zydelig and should be shown to any healthcare provider involved in your patient’s care. The card and other information and resources are available at www.ZydeligREMS.com.

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.
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.

- 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)

These symptoms include:

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.
Important Safety Information for Healthcare Providers

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

Healthcare Providers:
- Evaluate urgently
- Provide all supportive care
- 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

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/or serious pneumonitis
- Fatal and/or serious infections
- Fatal and serious intestinal perforation

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 serious risks of Zydelig:

**Fatal and/or Serious Hepatotoxicity**
* Fatal and/or serious hepatotoxicity occurred in 18% of patients treated with Zydelig monotherapy and 16% of patients treated with Zydelig in combination with rituximab or with unapproved combination therapies.

**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 patients treated with Zydelig monotherapy and 20% of patients treated with Zydelig in combination with rituximab or with unapproved combination therapies. Diarrhea can occur at any time.

**Fatal and/or Serious Pneumonitis**
* Fatal and serious pneumonitis occurred in patients treated with Zydelig. Clinical manifestations included interstitial infiltrates and organizing pneumonia. In randomized clinical trials of combination therapies, pneumonitis occurred in 4% of patients treated with Zydelig compared to 1% on the comparator arms. Time to onset of pneumonitis ranged from 1 to 15 months. Monitor patients on Zydelig for pulmonary symptoms.

**Fatal and/or Serious Infections**
* Fatal and/or serious infections occurred in 21% of patients treated with Zydelig monotherapy and 46% of patients treated with Zydelig in combination with rituximab or with unapproved combination therapies. The most common infections were pneumonia, sepsis, and febrile neutropenia.

**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.

**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.
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**Limitations of use:**
Zydelig is not indicated and is not recommended for first-line treatment of any patient.
Zydelig is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of FL.

You are encouraged to report negative side effects of Zydelig to Gilead at 1-800-547-7366 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/

BARRY W MILLER
03/22/2018