Zydelig REMS

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
FDA REQUIRED UPDATED REMS SAFETY INFORMATION

Boxed Warning includes the Risk of:

- Fatal and serious hepatotoxicity — updated
- Fatal and serious diarrhea, colitis, or ileus — updated
- Fatal and serious pneumonitis — updated
- Fatal and serious infections — updated
- Fatal and serious intestinal perforation

January 10, 2018

Dear Healthcare Provider:

The FDA has determined that the boxed warning on the Zydagel REMS (Non-Remission and Malignancy [Blood]) brochure to inform about the recent update to the prescribing information for fatal and serious toxicities and fatal and serious perforations as the Zydagel Approved Warnings of February:

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

- Fatal and serious hepatotoxicity occurred in 16% to 19% of ZYDAGEL-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue ZYDAGEL.
- Fatal and serious diarrhea or colitis occurred in 14% to 20% of ZYDAGEL-treated patients. Monitor for symptoms of increased abdominal pain, change in stool characteristics, fever, and tenderness. If symptoms persist, interrupt and then reduce or discontinue ZYDAGEL.
- Fatal and serious pneumonitis occurred in 4% of ZYDAGEL-treated patients. Monitor for pulmonary symptoms and intensified infiltrates. Interrupt or discontinue ZYDAGEL.
- Fatal and serious infections occurred in 21% to 44% of ZYDAGEL-treated patients. Monitor for signs and symptoms of infection. Interrupt ZYDAGEL if infection is suspected.
- Fatal and serious intestinal perforation can occur in ZYDAGEL-treated patients across clinical trials. Discontinue ZYDAGEL if intestinal perforation is suspected.

This updated version replaces all of our previous communications in the Zydagel REMS Updates. Please refer to this update as the preferred and most comprehensive source of information on Zydagel REMS.

Please see the Zydagel REMS Fact Sheet, a comprehensive overview of the Zydagel REMS. Zydagel REMS FACT SHEET. This fact sheet is available at www.ashp.org for more detailed information. Please refer to the Zydagel REMS Fact Sheet and fact sheet.pdf for more detailed information. Important: Zydagel REMS is a new indication not recommended for use in severe toxicities and fatal toxicities.

Thank you for your attention to this update to the Zydagel REMS. Please share this information with key stakeholders and customers.

Sincerely,

[Signature]

William Ogg, PharmD.
Boehringer Ingelheim Pharmaceuticals, Inc.

Preclinical Toxicity Studies

Survival Analysis

Importing Adverse Events

You can enter negativeelongated injuries. Second of our previous communications in the Zydagel REMS. Please refer to this update as the preferred and most comprehensive source of information on Zydagel REMS.

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Sincerely,

[Signature]

William Ogg, PharmD.
Zydex REMS

FDA REQUIRED UPDATED REMS SAFETY INFORMATION

Boxed Warning includes the Risk of:
- Fatal and serious severe side effects or deaths with use of Zydex REMS
- Boxed Warning: Risk of Hepatitis, Severe Diarrhea, Gastroenteritis, Pneumonia, Infections, and Intestinal Perforation

- Fatal and serious hepatoxicity occurred in 10% of 1,800 patients treated with Zydex REMS. Monitor hepatoxicity prior to and during treatment and stop or reduce dose of Zydex REMS if hepatoxicity occurs.
- Severe, serious, and severe diarrhea occurred in 14% to 20% of ZYDEx REMS-treated patients. Monitor for symptoms of severe, serious, and severe diarrhea or colitis. If severe, serious, and severe diarrhea or colitis occurs, reduce dose or discontinue ZYDEx REMS.
- Fatal and serious hepatoxicity occurred in 10% of patients treated with ZYDEx REMS. Monitor hepatoxicity prior to and during treatment and stop or reduce dose of ZYDEx REMS if hepatoxicity occurs. If severe, serious, and severe diarrhea or colitis occurs, reduce dose or discontinue ZYDEx REMS.
- Fatal and serious severe side effects or deaths with use of Zydex REMS.
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