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 resolution of treatment at a lower dose, 20% 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 2 to 3 months thereafter. Monitor weekly for liver toxicity if the ALT or AST rises above 5 times the upper limit of normal is not resolved. Withhold Zydelig if the ALT or AST is greater than 5 times the upper limit of normal, and continue to monitor AST, ALT and total bilirubin weekly until the abnormality is resolved.

Fatal and/or Serious and Severe Diarrhea or Colitis
- Fatal and/or serious 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 two months across trials following interruption of Zydelig therapy - and in some instances, use of corticosteroids.

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

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

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

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

INDICATION:

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

You are encouraged to report negative side effects of Zydelig to Gilead at 1-866-468-3235 and/or the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

This site is intended for US Healthcare Professionals.
IMPORTANT SAFETY INFORMATION

WARNING: FATAL AND SERIOUS TOXICITIES: HEPATIC, SEVERE DIARRHEA, COLITIS, PNEUMONITIS, AND INTESTINAL PERFORATION
• Fatal and/or serious hepatoxicity 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
• Hepatoxicity: 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. ALT/AST is <3 x upper limit of normal (ULN), monitor for liver toxicity weekly. If ALT/AST is >3 x 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 or diarrhea can occur at any time and responds poorly to antimicrobial agents. Avoid concurrent use with other drugs that cause diarrhea
• Pulmonary: Evaluate for pneumonitis in patients presenting with pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on radiographic exam, or oxygen saturation decline by >20%.
• Intestinal perforation: Advise patients to promptly report any new or worsening abdominal pain, cramps, 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 3/4) cutaneous reactions have been reported. Monitor patients for the development of severe cutaneous reactions and discontinue ZYDELIG if a reaction occurs
• Anaphylaxis: Severe allergic reactions including anaphylaxis have been reported. Discontinue ZYDELIG permanently and institute appropriate supportive measures if a reaction occurs
• Neutropenia: Treatment-emergent grade 3 or neutropenia occurred in 33% 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 G/L, monitor weekly.
• Embryofetal 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, pneumonitis, abdominal pain, chills, and rash
• Most frequent serious adverse reactions (≥5%) in clinical studies in combination with rituximab were pneumonia (17%), pyrexia (9%), sepsis (6%), 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 5% of patients discontinued or interrupted therapy due to adverse reactions
• Most common lab abnormalities (incidence ≥30%; all grades) in clinical studies were neutropenia, hypoglycemia, 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 160 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, bilirubine elevations, diarrhea, neutropenia, and thrombocytopenia. For other severe or life-threatening toxicities, withhold ZYDELIG until toxicity is resolved and reduce the dose to 160 mg, twice daily, upon resuming treatment. If severe or life-threatening toxicities recur upon restarting, ZYDELIG should be permanently discontinued

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• Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

Please see full Prescribing Information, including BOXED WARNING.

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