

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 (**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 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.