ZYDELIG® is a PI3Kδ inhibitor indicated for

- Relapsed follicular lymphoma in patients who have received at least two prior systemic therapies (FL)
- Relapsed chronic lymphocytic leukemia (CLL) in combination with rituximab in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities (CLL)
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies (SLL)

Accelerated approval was granted for follicular lymphoma and SLL based on overall response rate. An improvement in patient survival or disease-related symptoms has not been established. Continued approval for these indications may be contingent upon verification of clinical benefit in confirmatory trials.

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

AE=adverse event; PI3Kδ=phosphatidylinositol 3-kinase delta.
Convenient oral dosing: 1 pill, twice daily

Recommended starting dose 150 mg PO BID

Clinical trial experience with ZYDEGLIG 100 mg BID

Dose reductions were reported in 15% of CLL patients and in 34% of patients in the trial that included follicular lymphoma.*

For patients who experienced dose interruptions, many were able to reinitiate ZYDEGLIG without AE recurrence

AMONG PATIENTS EXPERIENCING GRADE 3 HEPATOTOXICITY†:

<table>
<thead>
<tr>
<th>74%</th>
<th>who reinitiated at a lower dose did not have a recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Serious and sometimes fatal hepatotoxicity occurred in 18% of follicular lymphoma patients* and 16% of CLL patients</td>
</tr>
</tbody>
</table>

AMONG PATIENTS EXPERIENCING GRADE ≥3 DIARRHEA OR COLITIS‡:

<table>
<thead>
<tr>
<th>67%</th>
<th>were reinitiated at a lower dose</th>
<th>58% of them successfully</th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Grade ≥3 diarrhea or colitis occurred in 14% of follicular lymphoma patients* and 20% of CLL patients</td>
<td></td>
</tr>
</tbody>
</table>

Adverse reactions resulted in interruption for 42 (38%) CLL patients

Discontinuation rate due to AEs was 20% in the trial that included follicular lymphoma.* Adverse reactions resulted in interruption or discontinuation for 78 of 146 (53%) patients*.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; iNHL=indolent non-Hodgkin lymphoma.

*Follicular lymphoma dose reduction data and discontinuation rate (20%) data reflect exposure to ZYDEGLIG monotherapy in 125 patients with iNHL, including 72 patients with follicular lymphoma.

†ALP/AST elevations were generally observed within the first 12 weeks of treatment.

‡Median time to onset for mild-to-moderate diarrhea (grade 1-2) was 1.5 months (range, 0.0-15.2 months). Median time to onset for severe diarrhea (grade ≥3) was 7.1 months (range, 0.5-29.8 months).

IMPORTANT SAFETY INFORMATION

BOXED 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 ZYDEGLIG-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue ZYDEGLIG.

Please see full Prescribing Information, including BOXED WARNING regarding fatal and serious toxicities of hepatotoxicity, severe diarrhea/colitis, pneumonitis, infections, and intestinal perforation.

†ALP/AST elevations were generally observed within the first 12 weeks of treatment.

‡Median time to onset for mild-to-moderate diarrhea (grade 1-2) was 1.5 months (range, 0.0-15.2 months). Median time to onset for severe diarrhea (grade ≥3) was 7.1 months (range, 0.5-29.8 months).
### Adverse event monitoring

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First 6 months: Every 2 weeks</th>
<th>First 3 months: Every 2 weeks</th>
<th>Next 3 months: Every 4 weeks</th>
<th>Thereafter: Every 1 to 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC</td>
<td>Monitor at least weekly while neutrophil counts are $&lt;1.0 \times 10^9/\text{L}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/AST</td>
<td>ALT/AST elevations were generally observed within the first 12 weeks of treatment. Elevations were reversible with dose interruptions.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>Monitor for severe diarrhea or colitis throughout therapy. Diarrhea can occur at any time. Mild-to-moderate diarrhea: Median time to onset was 1.5 months (range, 0.0-15.2 months). Severe diarrhea: Median time to onset was 7.1 months (range, 0.5-29.8 months).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Monitor for symptomatic pneumonitis and organizing pneumonia throughout therapy. Pneumonitis: time to onset ranged from 1 to 15 months. Monitor for pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Monitor for signs and symptoms of infection throughout therapy. Serious or fatal PJP or CMV occurred in &lt;1% of patients treated with ZYDELIG. Provide PJP prophylaxis during treatment with ZYDELIG. 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.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe cutaneous reactions</td>
<td>Monitor for severe cutaneous reactions throughout therapy.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### IMPORTANT SAFETY INFORMATION

**Contraindications**
- History of serious allergic reactions, including anaphylaxis and toxic epidermal necrolysis (TEN).

**Warnings and Precautions**
- **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. 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 $>3\times$ upper limit of normal (ULN), monitor for liver toxicity weekly. If ALT/AST is $>5\times$ 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.

**Important Safety Information (continued)**
- **Severe diarrhea or colitis:** Severe diarrhea or colitis (Grade ≥3) 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. Grade 3+ diarrhea can occur at any time and responds poorly to antimotility agents. Avoid concurrent use with other drugs that cause diarrhea.

**Pneumonitis:** Fatal and serious pneumonitis occurred in 4% of patients treated with ZYDELIG compared to 1% on the comparator arms in randomized clinical trials of combination therapies. Time to onset of pneumonitis ranged from <1 to 15 months. Clinical manifestations included interstitial infiltrates and organizing pneumonia. Monitor patients on ZYDELIG for pulmonary symptoms. In patients presenting with pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on radiologic exam, or oxygen saturation decline by ≥5%, 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.

Please see full Prescribing Information, including BOXED WARNING regarding fatal and serious toxicities of hepatotoxicity, severe diarrhea/colitis, pneumonitis, infections, and intestinal perforation.
# Knowing when to interrupt or discontinue ZYDELG®

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Setting or severity</th>
<th>Management recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNEUMONITIS</td>
<td>Any symptomatic pneumonitis or organizing pneumonia</td>
<td>DISCONTINUE ZYDELG permanently in patients with any severity of symptomatic pneumonitis or organizing pneumonia and initiate appropriate treatment with corticosteroids</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>&gt;3-5 x ULN</td>
<td>MAINTAIN ZYDELG dose. Monitor at least weekly until ≤1 x ULN.</td>
</tr>
<tr>
<td></td>
<td>&gt;5-20 x ULN</td>
<td>WITHHOLD ZYDELG. Monitor at least weekly until ALT/AST are ≤1 x ULN, then may resume ZYDELG at 100 mg BID.</td>
</tr>
<tr>
<td></td>
<td>&gt;20 x ULN</td>
<td>DISCONTINUE ZYDELG permanently.</td>
</tr>
<tr>
<td>BILIRUBIN</td>
<td>&gt;1.5-3 x ULN</td>
<td>MAINTAIN ZYDELG dose. Monitor at least weekly until ≤1 x ULN.</td>
</tr>
<tr>
<td></td>
<td>&gt;3-10 x ULN</td>
<td>WITHHOLD ZYDELG. Monitor at least weekly until bilirubin is ≤1 x ULN, then may resume ZYDELG at 100 mg BID.</td>
</tr>
<tr>
<td></td>
<td>&gt;10 x ULN</td>
<td>DISCONTINUE ZYDELG permanently.</td>
</tr>
<tr>
<td>DIARRHEA*</td>
<td>Moderate diarrhea</td>
<td>MAINTAIN ZYDELG dose. Monitor at least weekly until resolved.</td>
</tr>
<tr>
<td></td>
<td>Severe diarrhea or hospitalization</td>
<td>WITHHOLD ZYDELG. May treat with corticosteroids (eg, budesonide or other oral/IV corticosteroid therapy). Monitor at least weekly until resolved, then may resume ZYDELG at 100 mg BID.</td>
</tr>
<tr>
<td></td>
<td>Life-threatening diarrhea</td>
<td>DISCONTINUE ZYDELG permanently.</td>
</tr>
<tr>
<td>NEUTROPENIA</td>
<td>ANC 1.0 to &lt;1.5 × 10⁹/L</td>
<td>MAINTAIN ZYDELG dose. Monitor ANC at least weekly.</td>
</tr>
<tr>
<td></td>
<td>ANC 0.5 to &lt;1.0 × 10⁹/L</td>
<td>INTERRUPT ZYDELG. Monitor ANC at least weekly until ANC ≥0.5 × 10⁹/L, then may resume ZYDELG at 100 mg BID.</td>
</tr>
<tr>
<td>THROMBOCYTOPENIA</td>
<td>Platelets 50 to &lt;75 × 10⁹/L</td>
<td>MAINTAIN ZYDELG dose. Monitor platelet count at least weekly.</td>
</tr>
<tr>
<td></td>
<td>Platelets 25 to &lt;50 × 10⁹/L</td>
<td>MAINTAIN ZYDELG dose. Monitor platelet counts at least weekly.</td>
</tr>
<tr>
<td></td>
<td>Platelets &lt;25 × 10⁹/L</td>
<td>INTERRUPT ZYDELG. Monitor platelet count at least weekly. May resume ZYDELG at 100 mg BID when platelets ≥25 × 10⁹/L.</td>
</tr>
<tr>
<td>INFECTIONS</td>
<td>Grade ≥3 sepsis or pneumonia</td>
<td>INTERRUPT ZYDELG until infection has resolved.</td>
</tr>
<tr>
<td></td>
<td>Evidence of CMV infection or viremia</td>
<td>INTERRUPT ZYDELG in patients with evidence of active CMV infection of any grade or viremia (positive PCR or antigen test) until the viremia has resolved. If ZYDELG is resumed, monitor patients by PCR or antigen test for CMV reactivation at least monthly.</td>
</tr>
<tr>
<td></td>
<td>Evidence of PJP infection</td>
<td>INTERRUPT ZYDELG in patients with suspected PJP infection of any grade.</td>
</tr>
<tr>
<td></td>
<td>Confirmation of PJP infection</td>
<td>DISCONTINUE ZYDELG permanently if PJP infection is confirmed.</td>
</tr>
</tbody>
</table>

**KEY:**

- **MAINTAIN**
- **WITHHOLD or INTERRUPT**
- **DISCONTINUE**

Please see full Prescribing Information, including BOXED WARNING regarding fatal and serious toxicities of hepatotoxicity, severe diarrhea/colitis, pneumonitis, infections, and intestinal perforation.

PCR=polymerase chain reaction; ULN=upper limit of normal.

*Moderate diarrhea=grade 2: increase of 4-6 stools per day over baseline; severe diarrhea=grade 3: increase of ≥7 stools per day over baseline; life-threatening diarrhea=grade 4.*

For other severe or life-threatening toxicities related to ZYDELG:

Withhold drug until toxicity is resolved. If resuming ZYDELG after interruption for other severe or life-threatening toxicities, reduce the dose to 100 mg twice daily. Discontinue ZYDELG permanently for recurrence of other severe or life-threatening ZYDELG-related toxicity upon rechallenge.
Two types of diarrhea have been observed in clinical trials

<table>
<thead>
<tr>
<th>Self-limitering diarrhea</th>
<th>Severe diarrhea (increase of ≥7 stools daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to onset</strong></td>
<td>Generally occurs within the first 8 weeks of treatment (median time to onset, 1.5 months [range, 0.0-15.2 months])⁶</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>Typically mild to moderate (grade 1-2)</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Often responsive to common antidiarrheal agents</td>
</tr>
<tr>
<td><strong>Time to onset</strong></td>
<td>Can occur at any time but tends to occur relatively late (median time to onset, 7.1 months [range, 0.5-29.8 months])⁴</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>Can be severe (grade ≥3) in its clinical course</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Responds poorly to common antidiarrheal agents Use of budesonide or systemic corticosteroids may shorten the clinical course</td>
</tr>
</tbody>
</table>

Management algorithm for grade 1-2 uncomplicated diarrhea

**Management**
- Obtain patient history and perform physical examination to rule out infection
- Maintain ZYDELIG
- Instruct patient to:
  - Stop all lactose-containing products, alcohol, and high osmolar supplements
  - Drink 8-10 large glasses of clear liquids a day (e.g., Gatorade® or broth)
  - Eat frequent, small meals (e.g., bananas, rice, applesauce, toast, plain pasta)
  - Record the number of stools and report symptoms of life-threatening sequelae (e.g., fever or dizziness upon standing)

**Treatment**
- Administer standard dose of loperamide; initial dose 4 mg, followed by 2 mg every 4 hours, or after every unformed stool

Reassess 24-48 hours later

Diarrhea resolving
- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12-hour diarrhea-free interval

Diarrhea unresolved
- Follow ZYDELIG-related diarrhea management recommendation based on severity/grade
  - Unresolved grade 1 diarrhea: maintain ZYDELIG dose. Monitor at least weekly until resolved
  - Unresolved grade 2 diarrhea: refer to management algorithm at right and ZYDELIG USPI

Diarrhea resolved to grade ≤1
- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Consider tapering off budesonide and oral steroid
- Reinitiate ZYDELIG at 100 mg BID per clinical judgment and consider concomitant budesonide

Diarrhea unresolved
- Discontinue ZYDELIG permanently

Infectious etiology is excluded
- Budesonide* or oral steroids (prednisone)† if patient can tolerate oral medications
  OR
- IV steroids if patient is being treated with IV fluid therapy or cannot tolerate oral medications

Patient can tolerate oral medication
- Switch from IV steroid to budesonide or oral steroids

Monitor weekly until resolved
Pneumonitis

- In patients taking ZYDELIG who present with pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiological exam, or a decrease >5% in oxygen saturation, interrupt ZYDELIG until the cause has been determined
- Time to onset of pneumonitis ranged from <1 to 15 months
- If symptomatic pneumonitis or organizing pneumonia is diagnosed, initiate appropriate treatment with corticosteroids and permanently discontinue ZYDELIG

Hepatotoxicity

- Patients taking ZYDELIG* may develop ALT or AST elevations
- These findings were generally observed within the first 12 weeks of treatment and were reversible with dose interruption
- In patients with ALT/AST >5-20 x ULN:
  - Withhold ZYDELIG and monitor transaminases at least weekly until resolved
  - After resolution, may resume ZYDELIG at 100 mg BID and monitor as clinically indicated
- In patients with ALT/AST >20 x ULN:
  - Permanently discontinue ZYDELIG

Additional AE management guidance

- After resolution, may resume ZYDELIG at 100 mg BID and monitor transaminases at least weekly until resolved
- Withhold ZYDELIG if ALT/AST >5 x ULN
- If ALT/AST >20 x ULN, permanently discontinue ZYDELIG

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (continued)

- Intestinal perforation: Advise patients to promptly report any new or worsening abdominal pain, chills, fever, nausea, or vomiting.
- Severe cutaneous reactions: Fatal cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have occurred. If suspected, interrupt ZYDELIG until the etiology of the reaction has been determined. If SJS or TEN is confirmed, discontinue ZYDELIG. Other severe or life-threatening (Grade ≥3) cutaneous reactions have been reported. Monitor patients for the development of severe cutaneous reactions and discontinue ZYDELIG.
- 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 25% of patients treated with monotherapy and 58% of patients treated with ZYDELIG in combination with rituximab or with unapproved combination therapies. Monitor blood counts at least every 2 weeks for the first 6 months, and at least weekly in patients while neutrophil counts are less than 1.0 Gi/L.
- 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 in patients treated with ZYDELIG in combination trials (incidence ≥30%, all grades) were diarrhea, pneumonia, pyrexia, fatigue, rash, cough, and nausea; and in the monotherapy trial (incidence ≥20%, all grades) were diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, and rash.
- Most frequent serious adverse reactions (SAR) in clinical studies in combination with rituximab were pneumonia (23%), diarrhea (10%), pyrexia (9%), sepsis (8%) and febrile neutropenia (5%); SAR were reported in 59% of patients, and 17% discontinued treatment 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% discontinued due to adverse reactions.
- Most common lab abnormalities include neutropenia, ALT elevations, and AST elevations.

Drug Interactions

- CYP3A inducers: Avoid coadministration with strong CYP3A inducers.
- CYP3A inhibitors: Avoid coadministration with strong CYP3A inhibitors. If unable to use alternative drugs, monitor patients more frequently for ZYDELIG adverse reactions.
- CYP3A substrates: Avoid coadministration with sensitive 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.
Helping patients navigate therapy and financial support offerings

Patient financial support

Patients enrolled in ZYDELIG AccessConnect will be matched with a Case Specialist who can help answer financial questions related to ZYDELIG.

Patient nurse support

Through ZYDELIG AccessConnect, patients have access to a team of Patient Support Nurses who can answer questions and provide tips to help patients adhere to ZYDELIG.

To learn more, please call ZYDELIG AccessConnect at 1-844-6ACCESS (1-844-622-2377) or visit zydeligaccessconnect.com/hcp.

IMPORTANT SAFETY INFORMATION

Dosage and Administration (continued)

• 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, thrombocytopenia, and infections. 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.


Please see full Prescribing Information, including BOXED WARNING regarding fatal and serious toxicities of hepatotoxicity, severe diarrhea/colitis, pneumonitis, infections, and intestinal perforation.