HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZYDELIG safely and effectively. See full prescribing information for ZYDELIG.

ZYDELIG® (idelalisib) tablets, for oral use
Initial U.S. Approval: 2014

WARNING: FATAL AND SERIOUS TOXICITIES: HEPATIC, SEVERE DIARRHEA, COLITIS, PNEUMONITIS, INFECTIONS, and INTESTINAL PERFORATION
See full prescribing information for complete boxed warning.

- **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. (5.1)**
- **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. (5.2)**
- **Fatal and/or serious pneumonitis occurred in 4% of Zydelig-treated patients. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interrupt or discontinue Zydelig. (5.3)**
- **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. (5.4)**
- **Fatal and serious intestinal perforation can occur in Zydelig-treated patients across clinical trials. Discontinue Zydelig if intestinal perforation is suspected. (5.5)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	(01/2018)
Indications and Usage (1.2)	(01/2018)
Dosage and Administration (2.2)	(01/2018)
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.8, 5.9)	(01/2018)

----------INDICATIONS AND USAGE----------

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. (1.1)
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies. (1.2)
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies. (1.3)

Limitation of use:
Zydelig is not indicated and is not recommended for first-line treatment of any patient. (1.1, 1.2, 1.3)

Zydelig is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of FL. (1.2)

Accelerated approval was granted for FL and SLL based on overall response rate. 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.

----------DOSAGE AND ADMINISTRATION----------

Recommended starting dose: 150 mg orally, twice daily. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 150 mg, 100 mg. (3)

----------CONTRAINDICATIONS----------

History of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis. (4)

----------WARNINGS AND PRECAUTIONS----------

- Severe cutaneous reactions: Monitor patients for the development of severe cutaneous reactions and discontinue Zydelig. (5.6)
- Anaphylaxis: Monitor patients for anaphylaxis and discontinue Zydelig. (5.7)
- Neutropenia: monitor blood counts. (5.8)
- Embryo-fetal toxicity: Zydelig may cause fetal harm. Advise women of potential risk to a fetus and to avoid pregnancy while taking Zydelig. (5.9, 8.1, 8.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥20%) in patients treated with Zydelig in the monotherapy trial are diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, and rash. (6.1)

The most common adverse reactions (incidence ≥30%) in patients treated with Zydelig in combination trials are diarrhea, pneumonia, pyrexia, fatigue, rash, cough, and nausea. (6.1)

Common laboratory abnormalities include neutropenia, ALT elevations and AST elevations. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong CYP3A Inhibitors: Additional monitoring required if alternative therapy is not available. (7.1)
- Strong CYP3A inducers: Avoid coadministration of strong CYP3A inducers. (7.1)
- CYP3A substrates: Avoid coadministration of sensitive CYP3A substrates. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: FATAL AND SERIOUS TOXICITIES: HEPATIC, SEVERE DIARRHEA, COLITIS, PNEUMONITIS, INFECTIONS, and INTESTINAL PERFORATION
1 INDICATIONS AND USAGE
- 1.1 Relapsed Chronic Lymphocytic Leukemia
- 1.2 Relapsed Follicular B-cell non-Hodgkin Lymphoma
- 1.3 Relapsed Small Lymphocytic Lymphoma

2 DOSAGE AND ADMINISTRATION
- 2.1 Recommended Dosage
- 2.2 Dose Modification

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
- 5.1 Hepatotoxicity
- 5.2 Severe Diarrhea or Colitis
- 5.3 Pneumonitis
- 5.4 Infections
- 5.5 Intestinal Perforation
- 5.6 Severe Cutaneous Reactions
- 5.7 Anaphylaxis
- 5.8 Neutropenia
- 5.9 Embryo-fetal Toxicity

6 ADVERSE REACTIONS
- 6.1 Clinical Trial Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS
- 7.1 Effects of Other Drugs on Zydelig
- 7.2 Effects of Zydelig on Other Drugs

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
- 14.1 Relapsed Chronic Lymphocytic Leukemia
- 14.2 Relapsed Follicular B-cell non-Hodgkin Lymphoma
- 14.3 Relapsed Small Lymphocytic Lymphoma

16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 as recommended *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

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 as recommended *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Fatal and/or serious pneumonitis occurred in 4% of Zydelig-treated patients. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interrupt or discontinue Zydelig as recommended *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

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 *[see Dosage and Administration (2.2), Warnings and Precautions (5.4)].*

Fatal and serious intestinal perforation can occur in Zydelig-treated patients across clinical trials. Discontinue Zydelig for intestinal perforation *[see Warnings and Precautions (5.5)]*.

1 INDICATIONS AND USAGE

1.1 Relapsed Chronic Lymphocytic Leukemia

Zydelig is indicated, in combination with rituximab, for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL) for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

Limitation of Use

Zydelig is not indicated and is not recommended for first line treatment of patients with CLL.

1.2 Relapsed Follicular B-cell non-Hodgkin Lymphoma

Zydelig is indicated for the treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior systemic therapies.

Accelerated approval was granted for this indication based on Overall Response Rate *[see Clinical Studies (14.2)].* An improvement in patient survival or disease related

symptoms has not been established. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Limitation of Use

Zydelig is not indicated and is not recommended for first line treatment of patients with FL.

Zydelig is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of FL.

1.3 Relapsed Small Lymphocytic Lymphoma

Zydelig is indicated for the treatment of patients with relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies.

Accelerated approval was granted for this indication based on Overall Response Rate *[see Clinical Studies (14.3)].* An improvement in patient survival or disease related symptoms has not been established. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Limitation of Use

Zydelig is not indicated and is not recommended for first line treatment of patients with SLL.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended maximum starting dose of Zydelig is 150 mg administered orally twice daily.

Zydelig can be taken with or without food. Tablets should be swallowed whole.

Continue treatment until disease progression or unacceptable toxicity. The optimal and safe dosing regimen for patients who receive treatment longer than several months is unknown.

2.2 Dose Modification

See Table 1 for dose modification instructions for specific toxicities related to Zydelig. For other severe or life-threatening toxicities related to Zydelig, withhold drug until toxicity is resolved. If resuming Zydelig after interruption for other severe or life-threatening toxicities, reduce the dose to 100 mg twice daily. Discontinue Zydelig permanently for recurrence of other severe or life-threatening Zydelig-related toxicity upon rechallenge.

Table 1 Dose Modifications for Toxicities Due to Zydelig

Pneumonitis	**Any symptomatic pneumonitis**		
	Discontinue Zydelig in patients with any severity of symptomatic pneumonitis		
ALT/AST	**>3-5 × ULN**	**>5-20 × ULN**	**>20 × ULN**
	Maintain Zydelig dose. Monitor at least weekly until ≤1 x ULN.	Withhold Zydelig. Monitor at least weekly until ALT/AST are ≤1 x ULN, then may resume Zydelig at 100 mg BID.	Discontinue Zydelig permanently.
Bilirubin	**>1.5-3 × ULN**	**>3-10 × ULN**	**>10 × ULN**
	Maintain Zydelig dose. Monitor at least weekly until ≤1 x ULN.	Withhold Zydelig. Monitor at least weekly until bilirubin is ≤1 x ULN, then may resume Zydelig at 100 mg BID.	Discontinue Zydelig permanently.
Diarrhea*	**Moderate diarrhea**	**Severe diarrhea or hospitalization**	**Life-threatening diarrhea**
	Maintain Zydelig dose. Monitor at least weekly until resolved.	Withhold Zydelig. Monitor at least weekly until resolved, then may resume Zydelig at 100 mg BID.	Discontinue Zydelig permanently.
Neutropenia	**ANC 1.0 to <1.5 Gi/L**	**ANC 0.5 to <1.0 Gi/L**	**ANC <0.5 Gi/L**
	Maintain Zydelig dose.	Maintain Zydelig dose. Monitor ANC at least weekly.	Interrupt Zydelig. Monitor ANC at least weekly until ANC ≥0.5 Gi/L, then may resume Zydelig at 100 mg BID.
Thrombocytopenia	**Platelets 50 to <75 Gi/L**	**Platelets 25 to <50 Gi/L**	**Platelets <25 Gi/L**
	Maintain Zydelig dose.	Maintain Zydelig dose. Monitor platelet counts at least weekly.	Interrupt Zydelig. Monitor platelet count at least weekly. May resume Zydelig at 100 mg BID when platelets ≥25 Gi/L.
Infections	**Grade 3 or higher sepsis or pneumonia**		
	Interrupt Zydelig until infection has resolved.		
	Evidence of CMV infection or viremia		
	Interrupt Zydelig in patients with evidence of active CMV infection of any grade or viremia (positive PCR or antigen test) until the viremia has resolved. If Zydelig is resumed, monitor patients by PCR or antigen test for CMV reactivation at least monthly.		

	Evidence of PJP infection
	Interrupt Zydelig in patients with suspected PJP infection of any grade. Permanently discontinue Zydelig if PJP infection is confirmed.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; ULN, upper limit of normal; CMV, cytomegalovirus; PCR: polymerase chain reaction; PJP: *Pneumocystis jirovecii* pneumonia	

*Moderate diarrhea: increase of 4–6 stools per day over baseline; severe diarrhea: increase of ≥7 stools per day over baseline.

No dose modification is required for lymphocytosis, which has been observed in some patients taking Zydelig. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings.

3 DOSAGE FORMS AND STRENGTHS

150 mg tablets: pink, oval-shaped, film-coated tablet debossed with “GSI” on one side and “150” on the other side.

100 mg tablets: orange, oval-shaped, film-coated tablet debossed with “GSI” on one side and “100” on the other side.

4 CONTRAINDICATIONS

History of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis *[see Warnings and Precautions (5.6, 5.7)]* .

5 WARNINGS AND PRECAUTIONS

5.1 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 *[see Adverse Reactions (6.1)].* 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 *[see Dosage and Administration (2.2)].*

5.2 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 *[see Adverse Reactions (6.1)].* 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 1 week and 1 month across trials, following interruption of Zydelig therapy and in some instances, use of corticosteroids *[see Dosage and Administration (2.2)].*

5.3 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 *[see Dosage and Administration (2.2)]*.

5.4 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 *[see Adverse Reactions (6.1)]*. 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 *[see Dosage and Administration (2.2)]*.

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 *[see Dosage and Administration (2.2)]*.

5.5 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.

5.6 Severe Cutaneous Reactions

Fatal cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have occurred in patients treated with Zydelig. If SJS or TEN is suspected, interrupt Zydelig until the etiology of the reaction has been determined. If SJS or TEN is confirmed, permanently discontinue Zydelig.

Other severe or life-threatening (Grade ≥3) cutaneous reactions, including dermatitis exfoliative, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, exfoliative rash, and skin disorder, have been reported in Zydelig-treated patients. Monitor patients for the development of severe cutaneous reactions and discontinue Zydelig.

5.7 Anaphylaxis

Serious allergic reactions, including anaphylaxis, have been reported in patients on Zydelig. In patients who develop serious allergic reactions, discontinue Zydelig permanently and institute appropriate supportive measures.

5.8 Neutropenia

Treatment-emergent Grade 3 or 4 neutropenia occurred in 25% of patients treated with Zydelig 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 of therapy, and at least weekly in patients while neutrophil counts are less than 1.0 Gi/L *[see Dosage and Administration (2.2)].*

5.9 Embryo-fetal Toxicity

Based on findings in animals and its mechanism of action, Zydelig may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of idelalisib to pregnant rats during organogenesis caused decreased fetal weight and congenital malformations at systemic exposures 12 times those reported in patients at the recommended dose of 150 mg twice daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose. [*see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1), and Nonclinical Toxicology (13.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions have been associated with Zydelig in clinical trials and are discussed in greater detail in other sections of the prescribing information.

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Severe Diarrhea or Colitis *[see Warnings and Precautions (5.2)]*
- Pneumonitis *[see Warnings and Precautions (5.3)]*
- Infections *[see Warnings and Precautions (5.4)]*
- Intestinal Perforation *[see Warnings and Precautions (5.5)]*
- Severe Cutaneous Reactions *[see Warnings and Precautions (5.6)]*
- Anaphylaxis *[see Warnings and Precautions (5.7)]*
- Neutropenia *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Summary of Clinical Trials in Chronic Lymphocytic Leukemia

The safety data reflect exposure to Zydelig from two randomized, double-blind clinical trials (Studies 312-0116 and 312-0115) in 634 patients with relapsed CLL *[see Clinical Studies (14.1)]* and one randomized, open-label trial in 259 patients with relapsed CLL (Study 312-0119).

Zydelig with Rituximab (Study 312-0116; NCT01539512)

Patients with relapsed CLL received up to 8 doses of rituximab (R) with or without Zydelig 150 mg twice daily. The median duration of exposure to Zydelig was 8 months.

Serious adverse reactions were reported in 65 (59%) patients treated with Zydelig + R The most frequent serious adverse reactions reported for patients treated with Zydelig + R were pneumonia (23%), diarrhea (10%), pyrexia (9%), sepsis (8%), and febrile neutropenia (5%). Adverse reactions that led to discontinuation of Zydelig occurred in 19 (17%) patients. The most common adverse reactions that led to treatment discontinuations were hepatotoxicity and diarrhea/colitis.

Forty-two (38%) patients had dose interruptions and sixteen (15%) patients had dose reductions due to adverse reactions or laboratory abnormalities. The most common reasons for dose interruptions or reductions were pneumonia, diarrhea or colitis, rash, and elevated transaminases.

Table 2 and Table 3 summarize common adverse reactions and laboratory abnormalities reported for Zydelig + R and placebo + R arms.

Table 2 Adverse Reactions Reported in ≥5% of Patients with CLL and Occurred at ≥2% Higher Incidence in Patients Receiving Zydelig in Study 312-0116

	Zydelig + R N=110 (%)		Placebo + R N=108 (%)	
Adverse Reaction	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
General disorders and administration site conditions				
pyrexia	44 (40)	3 (3)	20 (19)	1 (1)
chills	27 (25)	2 (2)	17 (16)	0
pain	8 (7)	0	1 (1)	0
Gastrointestinal disorders				
diarrhea [(a)]	35 (32)	12 (11)	20 (19)	0
nausea	30 (27)	1 (1)	25 (23)	0
abdominal pain [(b)]	20 (18)	1 (1)	17 (16)	2 (2)
vomiting	17 (15)	0	9 (8)	0
gastroesophageal reflux disease	11 (10)	1 (1)	0	0
stomatitis	7 (6)	2 (2)	1 (1)	0
Respiratory, thoracic, and mediastinal disorders				
pneumonia [(c)]	33 (30)	23 (21)	20 (19)	14 (13)
Skin and subcutaneous tissue disorders				
rash [(d)]	27 (25)	4 (4)	7 (6)	1 (1)
Metabolism and Nutrition Disorders				
decreased appetite	18 (16)	2 (2)	12 (11)	2 (2)
dehydration	7 (6)	3 (3)	0	0
Infections and infestations				
sepsis [(e)]	10 (9)	10 (9)	4 (4)	4 (4)
sinusitis	9 (8)	0	6 (6)	0
urinary tract infection	9 (8)	1 (1)	4 (4)	2 (2)
bronchitis	8 (7)	1 (1)	5 (5)	1 (1)
oral herpes	6 (5)	1 (1)	3 (3)	0
Psychiatric disorders				
insomnia	10 (9)	0	7 (6)	0

	Zydelig + R N=110 (%)		Placebo + R N=108 (%)	
Adverse Reaction	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Musculoskeletal and connective tissue disorders				
arthralgia	9 (8)	1 (1)	4 (4)	0
Nervous system disorders				
lethargy	6 (5)	0	2 (2)	0

(a) Diarrhea includes the following preferred terms: diarrhea, colitis.
(b) Abdominal pain includes the following preferred terms: abdominal pain, abdominal pain upper, abdominal pain lower.
(c) Pneumonia includes the terms: pneumonia, pneumonitis, lung infection, lung infiltration, pneumocystis jiroveci pneumonia, pneumonia legionella, lung infection pseudomonal, pneumonia fungal, respiratory tract infection, lower respiratory tract infection, and lower respiratory tract infection bacterial.
(d) Rash includes the following preferred terms: dermatitis exfoliative, drug eruption, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash morbilliform, and exfoliative rash.
(e) Sepsis includes the terms: sepsis, septic shock, neutropenic sepsis, and sepsis syndrome

Table 3 Hematologic and Hepatic Laboratory Abnormalities Reported in ≥10% of Patients with CLL and Occurred at ≥5% Higher Incidence in Patients Receiving Zydelig in Study 312-0116

	Zydelig + R N=110 (%)		Placebo + R N=108 (%)	
Laboratory Parameter	**Any Grade**	**Grade 3–4**	**Any Grade**	**Grade 3–4**
Hematology abnormalities				
neutropenia	71 (65)	46 (42)	61 (56)	33 (31)
leukopenia	34 (31)	9 (8)	25 (23)	9 (8)
lymphocytopenia	23 (21)	11 (10)	13 (12)	4 (4)
Serum chemistry abnormalities				
ALT increased	43 (39)	10 (9)	13 (12)	1 (1)
AST increased	31 (28)	6 (5)	16 (15)	0

After closure of Study 312-0116, 71 patients continued treatment with Zydelig on an extension study (Study 312-0117; NCT01539291). The median duration of exposure was 18 months. Serious adverse reactions occurred in 48 (68%) patients. The most frequent serious adverse reactions reported were pneumonia (30%), diarrhea (15%), and pyrexia (11%).

The most frequent adverse reactions were pneumonia (51%), pyrexia (46%), and cough (45%). The most frequent Grade 3 or greater adverse reactions were pneumonia (30%), diarrhea (15%), and sepsis (10%).

Zydelig with Ofatumumab (Study 312-0119; NCT01659021)

In Study 312-0119, 259 patients with relapsed CLL received up to 12 doses of ofatumumab with or without Zydelig 150 mg twice daily. The median duration of exposure to Zydelig was 13.9 months.

Serious adverse reactions were reported in 133 (77%) patients treated with Zydelig + ofatumumab. The most frequent serious adverse reactions reported were pneumonia (14%), pyrexia (13%), and diarrhea (12%).

Adverse reactions that led to discontinuation of Zydelig occurred in 71 (41%) patients. One hundred and ten (64%) patients had dose interruptions and 42 (24%) patients had dose reductions due to adverse reactions or laboratory abnormalities. The most common reasons for dose discontinuations, reductions, or interruptions were diarrhea and colitis. The most common adverse reactions were diarrhea (55%), pyrexia (38%), nausea (34%), and fatigue (34%).

Zydelig with Bendamustine and Rituximab (Study 312-0115; NCT01569295)

In Study 312-0115, patients with relapsed CLL received up to 6 cycles of bendamustine and rituximab (BR) with or without Zydelig 150 mg twice daily. The median duration of exposure to Zydelig was 18.2 months.

Serious adverse reactions were reported in 147 (71%) patients treated with Zydelig + BR. The most frequent serious adverse reactions reported for patients treated with Zydelig + BR were febrile neutropenia (21%), pneumonia (17%), pyrexia (12%), and diarrhea (6%).

Adverse reactions that led to discontinuation of Zydelig occurred in 68 (33%) patients. The most common adverse reactions that led to treatment discontinuations were pneumonia, diarrhea, and pyrexia.

One hundred twenty-two (59%) patients treated with Zydelig + BR had dose interruptions and 34 (16%) patients had dose reductions due to adverse reactions. The most common reasons for dose interruptions or reductions were increased ALT and diarrhea. The most common adverse reactions were neutropenia (64%), pyrexia (43%), and diarrhea (41%).

Summary of Clinical Trials in Indolent Non-Hodgkin Lymphoma

The safety data reflect exposure to Zydelig from three open-label clinical trials (Studies 101-09 (NCT01282424), 101-02 (NCT00710528), and 101-10 (NCT01306643) in 146 patients with indolent non-Hodgkin lymphoma (iNHL) treated with Zydelig 150 mg twice daily *[see Clinical Studies (14.2, 14.3)]*. The median duration of exposure was 6.1 months (range 0.3 to 26.4 months).

Serious adverse reactions were reported in 73 (50%) patients. The most frequent serious adverse reactions that occurred were pneumonia (15%), diarrhea (11%), and pyrexia (9%).

Adverse reactions resulted in interruption or discontinuation for 78 (53%) patients. The most common reasons for interruption or discontinuations were diarrhea (11%), pneumonia (11%), and elevated transaminases (10%).

Table 4 provides the adverse reactions occurring in at least 10% of patients receiving Zydelig monotherapy, and Table 5 provides the hematologic and hepatic laboratory abnormalities.

Table 4 Adverse Reactions Reported in ≥ 10% of Patients with Indolent NHL Treated with Zydelig 150 mg BID

	Zydelig Monotherapy N=146 (%)	
Adverse Reaction	**Any Grade**	**Grade ≥3**
Gastrointestinal disorders		
diarrhea [(a)]	68 (47)	20 (14)
nausea	42 (29)	2 (1)
abdominal pain [(b)]	38 (26)	3 (2)
vomiting	22 (15)	2 (1)
General disorders and administration site conditions		
fatigue	44 (30)	2 (1)
pyrexia	41 (28)	3 (2)
asthenia	17 (12)	3 (2)
peripheral edema	15 (10)	3 (2)
Respiratory, thoracic, and mediastinal disorders		
cough	42 (29)	1 (1)
pneumonia [(c)]	37 (25)	23 (16)
dyspnea	25 (17)	6 (4)
Skin and subcutaneous disorders		
rash [(d)]	31 (21)	4 (3)
night sweats	18 (12)	0
Metabolism and nutrition disorders		
decreased appetite	24 (16)	1 (1)
Infections and infestations		
upper respiratory tract infection	18 (12)	0
Psychiatric disorders		
insomnia	17 (12)	0
Nervous system disorders		
headache	16 (11)	1 (1)

(a) Diarrhea includes the following preferred terms: diarrhea, colitis, enterocolitis, and gastrointestinal inflammation.

(b) Abdominal pain includes the following preferred terms: abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.
(c) Pneumonia includes the terms: pneumonia, pneumonitis, interstitial lung disease, lung infiltration, pneumonia aspiration, respiratory tract infection, atypical pneumonia, lung infection, pneumocystis jiroveci pneumonia, bronchopneumonia, pneumonia necrotizing, lower respiratory tract infection, pneumonia pneumococcal, pneumonia staphylococcal, pneumonia streptococcal, pneumonia cytomegaloviral, and respiratory syncytial virus infection.
(d) Rash includes the following preferred terms: dermatitis exfoliative, rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, and exfoliative rash.

Table 5 Hematologic and Hepatic Laboratory Abnormalities in Patients with Indolent non-Hodgkin Lymphoma Treated with Zydelig 150 mg BID

	Zydelig Monotherapy N=146 (%)		
Laboratory Abnormality	**Any Grade**	**Grade 3**	**Grade 4**
Serum chemistry abnormalities			
ALT increased	73 (50)	20 (14)	7 (5)
AST increased	60 (41)	12 (8)	6 (4)
Hematology abnormalities			
neutrophils decreased	78 (53)	20 (14)	16 (11)
hemoglobin decreased	41 (28)	3 (2)	0
platelets decreased	38 (26)	4 (3)	5 (3)

Grades were obtained per CTCAE version 4.03.

Summary of Discontinued Clinical Trials in First-Line CLL and Early Line iNHL

Safety data described below reflect exposure to Zydelig in three randomized, double-blind clinical trials (Studies 312-0123, 313-0124, and 313-0125) in patients with CLL and iNHL.

In Study 312-0123 (NCT01980888), 311 patients with previously untreated CLL received up to 6 cycles of BR with or without Zydelig 150 mg twice daily.

In Study 313-0124 (NCT01732913), 295 patients with previously treated iNHL received 8 doses of R with or without Zydelig 150 mg twice daily. Patients had a median of one prior therapy.

In Study 313-0125 (NCT01732926), 475 patients with previously treated iNHL received up to 6 cycles of BR with or without Zydelig 150 mg twice daily. Patients had a median of two prior therapies.

These three studies were terminated early due to a higher incidence of fatal and/or serious adverse reactions observed in patients treated with Zydelig in combination with R or BR. The most frequent serious adverse reactions were in the system organ classes of infections and infestations, blood and lymphatic system disorders, and gastrointestinal disorders.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Zydelig. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Disorders - Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Zydelig

Table 6 lists the potential effects of the coadministration of strong CYP3A modulators on Zydelig.

Table 6 Drug Interactions with Zydelig that affect Idelalisib Concentrations

Strong CYP3A Inhibitors	
Clinical Impact	• Coadministration with strong CYP3A inhibitors may increase idelalisib concentrations *[see Clinical Pharmacology (12.3)]*. • Increased idelalisib concentrations may increase the risk of exposure related adverse reactions.
Prevention or Management	• Use other drugs that are not strong CYP3A inhibitors. • If unable to use alternative drugs, monitor patients more frequently for Zydelig adverse reactions *[see Adverse Reactions (6.1)]*.
Strong CYP3A Inducers	
Clinical Impact	• Coadministration with strong CYP3A inducers may decrease idelalisib concentrations *[see Clinical Pharmacology (12.3)]*. • Decreased idelalisib concentrations may reduce efficacy.
Prevention or Management	Avoid coadministration of Zydelig with strong CYP3A4 inducers.

7.2 Effects of Zydelig on Other Drugs

The coadministration of Zydelig with a CYP3A substrate may increase the concentrations of this CYP3A substrate. Avoid coadministration of Zydelig with sensitive CYP3A substrates *[see Clinical Pharmacology (12.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies *(see Data)* and the mechanism of action *[see Clinical Pharmacology (12.1)]*, Zydelig may cause fetal harm when administered to a pregnant woman.

There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of idelalisib to pregnant rats during organogenesis resulted in decreased fetal weight and congenital malformations in rats at maternal exposures (AUC) 12 times those reported in patients at the recommended dose of 150 mg twice daily *(see Data)*.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies in the U.S. general population.

Data

Animal Data

In an embryo-fetal development study in rats, pregnant animals receiving oral doses of idelalisib during the period of organogenesis (implantation to closure of the hard palate), embryo-fetal toxicities were observed at the mid- and high-doses that also resulted in maternal toxicity, based on reductions in maternal body weight gain. Adverse findings at idelalisib doses ≥ 75 mg/kg/day included decreased fetal weights, external malformations (short tail), and skeletal variations (delayed ossification and/or unossification of the skull, vertebrae, and sternebrae). Additional findings were observed at 150 mg/kg/day dose of idelalisib and included urogenital blood loss, complete resorption, increased post-implantation loss, and malformations (vertebral agenesis with anury, hydrocephaly, and microphthalmia/anophthalmia). The dose of 75 and 150 mg/kg/day of idelalisib in rats resulted in exposures (AUC) of approximately 12 and 30 times, respectively, the human exposure at the recommended dose of 150 mg twice daily.

8.2 Lactation

Risk Summary

No data are available regarding the presence of idelalisib or its metabolites in human milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions from Zydelig in a breastfed child, advise lactating women not to breastfeed while taking Zydelig and for at least 1 month after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy

Based on animal studies, Zydelig may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Females of reproductive potential should have a pregnancy test prior to starting treatment with Zydelig.

Contraception

Females

Based on animal studies, Zydelig can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Zydelig and for at least 1 month after the last dose.

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of Zydelig *[see Use in Specific Populations (8.1)]*.

8.4 Pediatric Use

Safety and effectiveness of Zydelig in children less than 18 years of age have not been established.

8.5 Geriatric Use

In clinical trials of Zydelig in 615 patients with FL, SLL, and CLL, 327 (53%) patients were age 65 and older. No major differences in effectiveness were observed. When comparing patients 65 years of age or older to younger patients with indolent non-Hodgkin lymphoma, older patients had a higher incidence of discontinuation due to an adverse reaction (28% vs 20%), higher incidence of serious adverse reactions (64% vs 37%), and higher incidence of death (11% vs 5%). When comparing patients 65 years of age or older to younger patients with CLL, older patients had a higher incidence of discontinuation due to an adverse reaction (36% vs 28%), higher incidence of serious adverse reactions (73% vs 67%), and higher incidence of death (13% vs 9%).

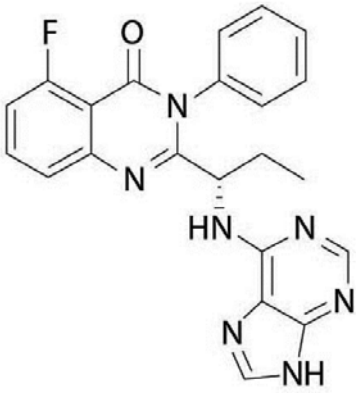
8.6 Hepatic Impairment

Dose adjustment is not recommended for patients with ALT or AST or bilirubin > upper limit of normal (ULN); however, limited safety and efficacy data are available for patients with baseline AST or ALT > 2.5 x ULN or bilirubin > 1.5 x ULN. Monitor patients with baseline hepatic impairment for signs of Zydelig toxicity *[see Warnings and Precautions (5)].* Follow dose modifications for adverse reactions *[see Dosage and Administration (2.2)].*

11 DESCRIPTION

Idelalisib is an inhibitor of phosphatidylinositol 3-kinase, PI3Kδ.

The chemical name for idelalisib is 5-fluoro-3-phenyl-2-[(1S)-1-(*9H*-purin-6-ylamino)propyl]quinazolin-4(*3H*)-one. It has a molecular formula of $C_{22}H_{18}FN_7O$ and a molecular weight of 415.42 g/mol. Idelalisib has the following structural formula:



Idelalisib is a white to off-white solid with a pH-dependent aqueous solubility ranging from <0.1 mg/mL at pH 5-7 to over 1 mg/mL at pH 2 under ambient conditions.

Zydelig (idelalisib) tablets are for oral administration. Each tablet contains either 100 mg or 150 mg of idelalisib with the following inactive ingredients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate and a tablet coating. The tablet coating consists of polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide and of FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake (for the 100 mg tablet) and red iron oxide (for the 150 mg tablet).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Idelalisib is an inhibitor of PI3Kδ kinase, which is expressed in normal and malignant B-cells. Idelalisib induced apoptosis and inhibited proliferation in cell lines derived from malignant B-cells and in primary tumor cells. Idelalisib inhibits several cell signaling pathways, including B-cell receptor (BCR) signaling and the CXCR4 and CXCR5 signaling, which are involved in trafficking and homing of B-cells to the lymph nodes and bone marrow. Treatment of lymphoma cells with idelalisib resulted in inhibition of chemotaxis and adhesion, and reduced cell viability.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose 2.7 times the maximum recommended dose, Zydelig did not prolong the QT/QTc interval (i.e., ≤10 ms).

12.3 Pharmacokinetics

Idelalisib exposure increased in a less than dose-proportional manner over a dose range of 50 mg to 350 mg twice daily (0.3 to 2.3 times the approved recommended dosage).

Following 150 mg twice daily administration of idelalisib, average (% coefficient of variation) maximum concentrations (C_{max}) and area under the curve (AUC) at steady-state were 1861 (43%) ng/mL and 10598 (41%) ng•h/mL for idelalisib.

Absorption

The median time to peak concentration (T_{max}) was observed at 1.5 hours.

Food Effect

The administration of a single dose of Zydelig with a high-fat meal (900 calories: 525 calories fat, 250 calories carboydrates, and 125 calories protein) increased idelalisib AUC 1.4-fold relative to fasting conditions. Zydelig can be administered without regard to food.

Distribution

Protein binding of idelalisib is ≥ 84% with no concentration dependence.

The mean blood-to-plasma ratio was 0.7.

The apparent central volume of distribution at steady state is 23 L (%CV ~85%).

Idelalisib is a substrate of P-glycoprotein (P-gp) and BCRP in vitro.

Elimination

The population apparent systemic clearance at steady-state is 14.9 L/hr (%CV ~ 38%). The population terminal elimination half-life of idelalisib is 8.2 hours.

Metabolism

Idelalisib is metabolized via aldehyde oxidase and CYP3A with additional minor metabolism by UGT1A4.

Excretion

Following a single 150 mg dose of radiolabeled idelalisib, 78% of the radioactivity was excreted in feces and 14% was excreted in the urine. Idelalisib is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

Specific Populations

Age (18 to 91 years), sex, race (White, and non-Whites), renal impairment (creatinine clearance ≥ 15 mL/min) and weight (38 to 148 kg) had no effect on idelalisib exposure.

Pediatric Patients

The pharmacokinetics of idelalisib in pediatric patients is unknown.

Patients with Hepatic Impairment

The mean AUC increased up to 1.7-fold in patients with hepatic impairment (defined as ALT or AST or bilirubin values ≥ ULN) compared to patients with normal hepatic function. There is limited information on idelalisib exposure in patients with baseline AST or ALT > 2.5 × ULN or bilirubin > 1.5 × ULN *[see Specific Populations (8.6)].*

Drug Interaction Studies

Effect of Other Drugs on Idelalisib

The coadministration of rifampin (strong CYP3A inducer and P-gp inducer) to healthy subjects decreased the mean idelalisib AUC by 75% and the mean C_{max} by 58% *[see Drug Interactions (7.1)].*

The coadministration of ketoconazole (strong CYP3A inhibitor and P-gp inhibitor) to healthy subjects increased the mean idelalisib AUC by 1.8-fold. No changes in the mean C_{max} were observed *[see Drug Interactions (7.1)].*

In vitro studies suggest that idelalisib inhibits CYP2C8, CYP2C19, and UGT1A1 and induces CYP2B6.

Effect of Idelalisib on Other Drugs

The mean C_{max} of midazolam increased by 2.4-fold and the mean AUC of midazolam increased by 5.4-fold when midazolam (sensitive CYP3A substrate) was coadministered with Zydelig [*see Drug Interactions (7.2)].*

No changes in exposure to rosuvastatin (OATP1B1 and OATP1B3 substrate) or digoxin (P-glycoprotein substrate) were observed when coadministered with Zydelig.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Idelalisib was not carcinogenic in a 26-week study in transgenic mice when administered daily by oral gavage at doses up to 500 mg/kg/day in males and 1000 mg/kg/day in females. Idelalisib was not carcinogenic in a 2-year study in rats when administered daily by oral gavage at exposures 0.40/0.62-fold (male/female), compared to the exposure in patients with hematologic malignancies administered the recommended dose of 150 mg twice daily.

Idelalisib did not induce mutations in the bacterial mutagenesis (Ames) assay and was not clastogenic in the in vitro chromosome aberration assay using human peripheral blood lymphocytes. Idelalisib was genotoxic in males in the in vivo rat micronucleus study at a high dose of 2000 mg/kg.

Idelalisib may impair fertility in humans. In a fertility study, treated male rats (25, 50, or 100 mg/kg/day of idelalisib) were mated with untreated females. Decreased epididymidal and testicular weights were observed at all dose levels and reduced sperm concentration at the mid- and high doses; however, there were no adverse effects on fertility parameters. The low dose in males resulted in an exposure (AUC) that is

approximately 50% of the exposure in patients at the recommended dose of 150 mg twice daily.

In a separate fertility study, treated female rats (25, 50, or 100 mg/kg/day of idelalisib) were mated with untreated males. There were no adverse effects on fertility parameters; however, there was a decrease in the number of live embryos at the high dose. The high dose in females resulted in an exposure (AUC) that is approximately 17-fold the exposure in patients at the recommended dose of 150 mg twice daily.

13.2 Animal Toxicology and/or Pharmacology

Toxicities observed in animals and not reported in patients include cardiac toxicity (cardiomyopathy, inflammation, and increased heart weight) and pancreatic findings (inflammation, hemorrhage, and low-incidence acinar degeneration and hyperplasia). These findings were observed in Sprague-Dawley rats in toxicology studies at exposures (AUCs) higher than those reported in patients at the recommended dose of 150 mg twice daily. Cardiac inflammation was mainly seen in a 28-day study in rats, the other findings were observed in the 13-week and/or 6-month studies.

14 CLINICAL STUDIES

14.1 Relapsed Chronic Lymphocytic Leukemia

Study 312-0116

Zydelig was evaluated in a randomized, double-blind, placebo-controlled study GS-US-312-0116 (referred to as 312-0116) (NCT01539512) in 220 patients with relapsed CLL who required treatment and were unable to tolerate standard chemoimmunotherapy due to coexisting medical conditions, reduced renal function as measured by creatinine clearance < 60 mL/min, or NCI CTCAE Grade ≥ 3 neutropenia or Grade ≥ 3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents. Patients were randomized 1:1 to receive 8 doses of rituximab (first dose at 375 mg/m^2, subsequent doses at 500 mg/m^2 every 2 weeks for 4 infusions and every 4 weeks for an additional 4 infusions) in combination with either an oral placebo twice daily or with Zydelig 150 mg taken twice daily until disease progression or unacceptable toxicity.

In Study 312-0116, the median age was 71 years (range 47, 92) with 78% over 65, 66% were male, and 90% were Caucasian. The median time since diagnosis was 8.5 years. The median number of prior therapies was 3. Nearly all (96%) patients had received prior anti-CD20 monoclonal antibodies. The most common (>15%) prior regimens were: bendamustine + rituximab (BR) (98 patients, 45%), fludarabine + cyclophosphamide + rituximab (75 patients, 34%), single-agent rituximab (67 patients, 31%), fludarabine + rituximab (37 patients, 17%), and chlorambucil (36 patients, 16%). The median CIRS (Cumulative Illness Rating Scale) score was 8 (range 0-17), and 85% of patients had a score of >6. Median Karnofsky score was 80. Median estimated Creatinine Clearance (eCrCl) was 63.6 mL/min, with 41% of patients having an eCrCl of <60 mL/min. At

screening, 19.5% of patients had a platelet count of <50 × 10^9/L, and 13.2% had an absolute neutrophil count (ANC) of <1 × 10^9/L.

The efficacy of Zydelig was evaluated by progression free survival (PFS), as assessed by an independent review committee (IRC). The trial was stopped for efficacy following the first pre-specified interim analysis. Results of a second interim analysis continued to show a statistically significant improvement for Zydelig + R over placebo + R for the primary endpoint of PFS (HR: 0.18, 95% CI [0.10, 0.32], p < 0.0001).

At the final analysis, with a median follow-up of 8.3 months for the Zydelig + R group, and 5.6 months for the placebo + R group, the median PFS for the Zydelig + R group was 19.4 months (95% CI: 12.3, Not Reached) versus 6.5 months (95% CI: 4.0, 7.3) for the placebo + R group (HR: 0.15, 95% CI [0.09, 0.24], p < 0.0001).

Updated efficacy results are shown in Table 7, and the Kaplan-Meier curve for PFS is shown in Figure 1.

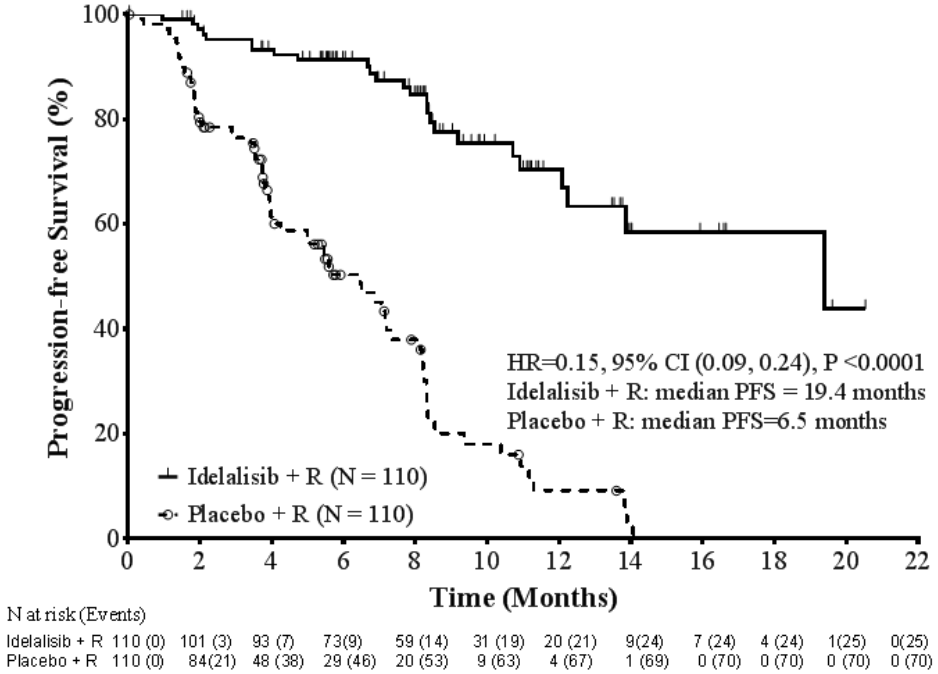
Table 7 Efficacy Results from Study 312-0116

		Zydelig + R N=110	**Placebo + R N=110**
PFS	Median (months) (95% CI)	19.4 (12.3, NR)	6.5 (4.0, 7.3)
	Hazard ratio (95% CI)	0.15 (0.09, 0.24)	
	P-value	< 0.0001 †	
ORR*	(All PRs)	92 (83.6%)	17 (15.5%)
	95% CI	75.4, 90.0	9.3, 23.6
	Odds Ratio (95% CI)	27.8 (13.4, 57.5)	
	P-value	<0.0001	
DOR	Median (months) (95% CI)	NR (12, NR)	6.2 (2.8, 6.5)

PFS: progression-free survival; NR: not reached; ORR: overall response rate; PR: partial response; DOR: duration of response

† The p value for PFS was based on stratified log-rank test.
* ORR defined as the proportion of patients who achieved a complete response (CR) or PR. All PRs achieved; none of the patients achieved a CR.

Figure 1 Kaplan-Meier Plot of IRC-Assessed PFS for Study 312-0116



14.2 Relapsed Follicular B-cell non-Hodgkin Lymphoma

Study 101-09

The safety and efficacy of Zydelig in patients with FL was evaluated in a single-arm, multicenter study 101-09 (NCT01282424) which included 72 patients with follicular B-cell non-Hodgkin lymphoma who had relapsed within 6 months following rituximab and an alkylating agent and had received at least 2 prior treatments. The median age was 62 years (range 33 to 84), 54% were male, and 90% were Caucasian. At enrollment, 92% of patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 4.7 years and the median number of prior treatments was 4 (range 2 to 12). The most common prior combination regimens were R-CHOP (49%), BR (50%), and R-CVP (28%). At baseline, 33% of patients had extranodal involvement and 26% had bone marrow involvement.

Patients received 150 mg of Zydelig orally twice daily until evidence of disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group response criteria for malignant lymphoma. The primary endpoint was Independent Review Committee-assessed overall response rate (ORR). Efficacy results are summarized in Table 8.

Table 8 Overall Response Rate (ORR) and Duration of Response (DOR) in Patients with Relapsed Follicular Lymphoma

	N=72
ORR 95% CI	39 (54%) (42, 66%)
CR PR	6 (8%) 33 (46%)
Median* DOR, months (range)	median not evaluable (0.0+, 14.8+)

CI = confidence interval; CR = complete response; PR = partial response
* Kaplan-Meier estimate

The median time to response was 1.9 months (range 1.6–8.3).

14.3 Relapsed Small Lymphocytic Lymphoma

Study 101-09

The safety and efficacy of Zydelig in patients with SLL was evaluated in a single-arm, multicenter study 101-09 (NCT01282424) which included 26 patients with small lymphocytic lymphoma who had relapsed within 6 months following rituximab and an alkylating agent and had received at least 2 prior treatments. The median age was 65 years (range 50 to 87), 73% were male, and 81% were Caucasian. At enrollment, 96% of patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 6.7 years and the median number of prior treatments was 4 (range 2 to 9). The most common prior combination regimens were BR (81%), FCR (62%) and R-CHOP (35%). At baseline, 27% of patients had extranodal involvement.

Patients received 150 mg of Zydelig orally twice daily until evidence of disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group response criteria for malignant lymphoma. The primary endpoint was Independent Review Committee-assessed overall response rate (ORR). Efficacy results are summarized in Table 9.

Table 9 Overall Response Rate (ORR) and Duration of Response (DOR) in Patients with Relapsed Small Lymphocytic Lymphoma

	N=26
ORR 95% CI	15 (58%) (37, 77%)
CR PR	0 15 (58%)
Median* DOR, months (range)	11.9 (0.0+, 14.7+)

CI = confidence interval; CR = complete response; PR = partial response
* Kaplan-Meier estimate

The median time to response was 1.9 months (range 1.6–8.3).

16 HOW SUPPLIED/STORAGE AND HANDLING

Zydelig tablets supplied as follows:

Tablet Strength	Package Configuration	NDC No.	Description of Tablet; Debossed on Tablet
150 mg	High density polyethylene (HDPE) bottle with a polyester fiber coil, capped with a child-resistant closure. Each bottle contains 60 film-coated tablets.	61958-1702-1	Oval shaped; pink; “150” on one side and "GSI" on the other side
100 mg		61958-1701-1	Oval-shaped; orange; “100” on one side and “GSI” on the other side

Store between 20–30 °C (68–86 °F) with excursions permitted 15–30 ºC (59–86 ºF).

- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Physicians and health care professionals are advised to discuss the following with patients prior to treatment with Zydelig:

- **Hepatotoxicity**

Advise patients that Zydelig can cause significant elevations in liver enzymes, and that serial testing of serum liver tests (ALT, AST, and bilirubin) are recommended while taking Zydelig *[see Warnings and Precautions (5.1)].* Advise patients to report symptoms of liver dysfunction including jaundice, bruising, abdominal pain, or bleeding.

- **Severe Diarrhea or Colitis**

Advise patients that Zydelig may cause severe diarrhea or colitis and to notify their healthcare provider immediately if the number of bowel movements in a day increases by six or more *[see Warnings and Precautions (5.2)].*

- **Pneumonitis**

Advise patients of the possibility of pneumonitis, and to report any new or worsening respiratory symptoms including cough or dyspnea *[see Warnings and Precautions (5.3)].*

- **Infections**

Advise patients that Zydelig can cause serious infections that may be fatal. Advise patients to immediately report symptoms of infection (e.g. pyrexia) *[see Warnings and Precautions (5.4)]*.

- **Intestinal Perforation**

Advise patients of the possibility for intestinal perforation and to notify their healthcare provider immediately if they experience severe abdominal pain *[see Warnings and Precautions (5.5)].*

- **Severe Cutaneous Reactions**

Advise patients that Zydelig may cause severe cutaneous reactions and to notify their healthcare provider immediately if they develop a severe skin reaction *[see Warnings and Precautions (5.6)].*

- **Anaphylaxis**

Advise patients that anaphylaxis can occur during treatment with Zydelig and to notify their healthcare provider immediately if they experience symptoms of anaphylaxis *[see Warnings and Precautions (5.7)].*

- **Neutropenia**

Advise patients of the need for periodic monitoring of blood counts. Advise patients to notify their healthcare provider immediately if they develop a fever or any signs of infection *[see Warnings and Precautions (5.8)]*.

- **Embryo-Fetal Toxicity**

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment and for 1 month after receiving the last dose of Zydelig *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3)]*.

Advise lactating women not to breastfeed during treatment with Zydelig and for at least 1 month after the last dose *[see Use in Specific Populations (8.2)]*.

- **Instructions for Taking Zydelig**

Advise patients to take Zydelig exactly as prescribed and not to change their dose or to stop taking Zydelig unless they are told to do so by their healthcare provider. Zydelig may be taken with or without food. Zydelig tablets should be swallowed whole. Advise

patients that if a dose of Zydelig is missed by less than 6 hours, to take the missed dose right away and take the next dose as usual. If a dose of Zydelig is missed by more than 6 hours, advise patients to wait and take the next dose at the usual time.

Manufactured and distributed by:

Gilead Sciences, Inc.

Foster City, CA 94404

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