

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, and INTESTINAL PERFORATION

See full prescribing information for complete boxed warning.

- Fatal and/or serious hepatotoxicity occurred in 14% 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% of Zydelig-treated patients. Monitor for the development of severe diarrhea or colitis. Interrupt and then reduce or discontinue Zydelig. (5.2)
- Fatal and serious pneumonitis can occur in Zydelig-treated patients. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interrupt or discontinue Zydelig. (5.3)
- Fatal and serious intestinal perforation can occur in Zydelig-treated patients across clinical trials. Discontinue Zydelig if intestinal perforation is suspected. (5.4)

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)

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)

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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. (5.5)
- Anaphylaxis: Monitor patients for anaphylaxis and discontinue Zydelig. (5.6)
- Neutropenia: monitor blood counts. (5.7)
- Embryo-fetal toxicity: may cause fetal harm. Advise women of potential risk to a fetus and to avoid pregnancy while taking Zydelig. (5.8)

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 20\%$) are diarrhea, pyrexia, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash (6.1).

The most common laboratory abnormalities (incidence $\geq 30\%$) are neutropenia, hypertriglyceridemia, hyperglycemia, 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

- CYP3A inducers: Avoid coadministration of strong CYP3A inducers with Zydelig. (7.1)
- CYP3A substrates: Avoid coadministration of CYP3A substrates with Zydelig. (7.2)

USE IN SPECIFIC POPULATIONS

Nursing mothers: Discontinue drug or nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2014

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FULL PRESCRIBING INFORMATION

WARNING: FATAL AND SERIOUS TOXICITIES: HEPATIC, SEVERE DIARRHEA, COLITIS, PNEUMONITIS, and INTESTINAL PERFORATION

- **Fatal and/or serious hepatotoxicity occurred in 14% 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% 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 serious pneumonitis can occur in 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 serious intestinal perforation can occur in Zydelig-treated patients across clinical trials. Discontinue Zydelig for intestinal perforation [see *Warnings and Precautions (5.4)*].**

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.

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.

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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

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 the table below 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. Recurrence of other severe or life-threatening Zydelig-related toxicity upon rechallenge should result in permanent discontinuation of Zydelig.

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 x ULN	>5-20 x ULN	>20 x 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 x ULN	>3-10 x ULN	>10 x 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*	<u>Moderate diarrhea</u>	<u>Severe diarrhea or hospitalization</u>	<u>Life-threatening diarrhea</u>
	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	<u>ANC 1.0 to <1.5 Gi/L</u>	<u>ANC 0.5 to <1.0 Gi/L</u>	<u>ANC <0.5 Gi/L</u>
	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	<u>Platelets 50 to <75 Gi/L</u>	<u>Platelets 25 to <50 Gi/L</u>	<u>Platelets <25 Gi/L</u>
	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.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; ULN, upper limit of normal			

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

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.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Fatal and/or serious hepatotoxicity occurred in 14% of patients treated with Zydelig. 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 Zydelig-treated patients across clinical trials [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. 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.

5.4 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.

5.5 Severe Cutaneous Reactions

One case of toxic epidermal necrolysis (TEN) occurred in a study of Zydelig in combination with rituximab and bendamustine. 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.

5.6 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.

5.7 Neutropenia

Treatment-emergent Grade 3 or 4 neutropenia occurred in 31% of Zydelig-treated patients across clinical trials [see *Adverse Reactions (6.1)*]. Monitor blood counts at least every two weeks for the first 3 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)*].

5.8 Embryo-fetal Toxicity

Based on findings in animals, Zydelig may cause fetal harm when administered to a pregnant woman. Idelalisib is teratogenic in rats, at systemic exposures 12 times those reported in patients at the recommended dose of 150 mg twice daily. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see *Use in Specific Populations (8.1)*].

Advise females of reproductive potential to avoid becoming pregnant while taking Zydelig. If contraceptive methods are being considered, use effective contraception

during treatment, and for at least 1 month after the last dose of Zydelig [see *Use in Specific Populations (8.6)*].

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)*]
- Intestinal Perforation [see *Warnings and Precautions (5.4)*]
- Severe Cutaneous Reactions [see *Warnings and Precautions (5.5)*]
- Anaphylaxis [see *Warnings and Precautions (5.6)*]
- Neutropenia [see *Warnings and Precautions (5.7)*]

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 subject exposure to Zydelig from Study 1, in which 218 subjects with relapsed CLL received up to 8 doses of rituximab with or without Zydelig 150 mg twice daily. The median duration of exposure to Zydelig was 5 months.

Serious adverse reactions were reported in 54 (49%) subjects treated with Zydelig + rituximab. The most frequent ($\geq 2\%$) serious adverse reactions reported for subjects treated with Zydelig were pneumonia (17%), pyrexia (9%), sepsis (8%), febrile neutropenia (5%) and diarrhea (5%). Adverse reactions that led to discontinuation of Zydelig occurred in 11 (10%) subjects. The most common adverse reactions that led to treatment discontinuations were hepatotoxicity and diarrhea/colitis.

Thirty-nine subjects (35%) had dose interruptions and sixteen subjects (15%) had dose reductions due to adverse reactions or laboratory abnormalities. The most common reasons for dose reductions were elevated transaminases, diarrhea or colitis, and rash.

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

Table 2 Adverse Reactions Reported in ≥5% of CLL Patients and Occurred at ≥2% Higher Incidence in Subjects Receiving Zydelig

Adverse Reaction	Zydelig + R N=110 (%)		Placebo + R N=108 (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Gastrointestinal disorders				
nausea	28 (25)	0	23 (21)	0
vomiting	14 (13)	0	9 (8)	0
diarrhea ^(a)	23 (21)	6 (5)	17 (16)	0
gastroesophageal reflux disease	7 (6)	0	1 (1)	0
stomatitis	7 (6)	2 (2)	2 (2)	0
Nervous system disorders				
headache	11 (10)	1 (1)	5 (5)	0
General disorders and administration site conditions				
pyrexia	38 (35)	3 (3)	18 (17)	1 (1)
chills	23 (21)	2 (2)	17 (16)	0
pain	8 (7)	0	2 (2)	0
Skin and subcutaneous tissue disorders				
rash ^(b)	20 (18)	4 (4)	7 (6)	1 (1)
Respiratory, thoracic, and mediastinal disorders				
pneumonia ^(c)	25 (23)	18 (16)	19 (18)	14 (13)
nasal congestion	6 (5)	0	2 (2)	0
Infections and infestations				
sepsis ^(d)	9 (8)	8 (7)	4 (4)	4 (4)
bronchitis	7 (6)	1 (1)	3 (3)	1 (1)
sinusitis	9 (8)	0	4 (4)	0
urinary tract infection	6 (5)	0	3 (3)	2 (2)
Musculoskeletal and connective tissue disorders				
arthralgia	8 (7)	1 (1)	4 (4)	1 (1)

(a) Diarrhea includes the following preferred terms: diarrhea, colitis.

(b) Rash includes the following preferred terms: dermatitis exfoliative, rash, rash macular, rash maculo-papular, rash papular, rash pruritic, and skin disorder.

(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) Sepsis includes the terms: sepsis, septic shock, neutropenic sepsis, and sepsis syndrome.

R: rituximab

Table 3 Treatment-emergent Laboratory Abnormalities Reported in ≥10% of CLL Patients Occurring at a ≥5% Higher Incidence in Subjects Receiving Zydelig

Laboratory Parameter	Zydelig + R N=110 (%)		Placebo + R N=108 (%)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Hematology abnormalities				
neutrophil count decreased	66 (60)	41 (37)	55 (51)	29 (27)
lymphocyte count decreased	22 (20)	10 (9)	13 (12)	4 (4)
lymphocyte count increased	27 (25)	20 (18)	10 (9)	5 (5)
Serum chemistry abnormalities				
ALT increased	38 (35)	9 (8)	11 (10)	1 (1)
AST increased	27 (25)	6 (5)	15 (14)	0
GGT increased	29 (26)	2 (2)	15 (14)	3 (3)
triglycerides (hypertriglyceridemia)	62 (56)	3 (3)	37 (34)	0
hyperglycemia	59 (54)	8 (7)	50 (46)	2 (2)
hypoglycemia	12 (11)	0	5 (5)	0
hyponatremia	22 (20)	2 (2)	16 (15)	7 (6)

Grades were obtained per CTCAE version 4.03.
R: rituximab

Summary of Clinical Trials in Indolent Non-Hodgkin Lymphoma

The safety data reflect exposure to Zydelig in 146 adults with indolent non-Hodgkin lymphoma treated with Zydelig 150 mg twice daily in clinical trials. The median duration of exposure was 6.1 months (range 0.3 to 26.4 months).

Serious adverse reactions were reported in 73 (50%) subjects. 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%) subjects. 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 subjects receiving Zydelig monotherapy, and Table 5 provides the treatment-emergent laboratory abnormalities.

Table 4 Adverse Reactions (≥ 10% of Subjects) in Patients with Indolent non-Hodgkin Lymphoma Treated with Zydelig 150 mg BID

Adverse Reaction	Zydelig Monotherapy N=146 (%)	
	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)
Infections and infestations		
upper respiratory tract infection	18 (12)	0
Respiratory, thoracic, and mediastinal disorders		
pneumonia ^(c)	37 (25)	23 (16)
cough	42 (29)	1 (1)
dyspnea	25 (17)	6 (4)
Skin and subcutaneous disorders		
rash ^(d)	31 (21)	4 (3)
night sweats	18 (12)	0
Nervous system disorders		
headache	16 (11)	1 (1)
Metabolism and nutrition disorders		
decreased appetite	24 (16)	1 (1)
Psychiatric disorders		
insomnia	17 (12)	0

(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 Treatment-emergent Laboratory Abnormalities in Patients with Indolent non-Hodgkin Lymphoma Treated with Zydelig 150 mg BID

Laboratory Abnormality	Zydelig Monotherapy N=146 (%)		
	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.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Zydelig

CYP3A Inducers

The AUC of idelalisib was reduced by 75% when Zydelig was coadministered with a strong CYP3A inducer. Avoid coadministration of Zydelig with strong CYP3A inducers, such as rifampin, phenytoin, St. John's wort, or carbamazepine [see *Clinical Pharmacology (12.3)*].

CYP3A Inhibitors

The AUC of idelalisib was increased 1.8-fold when Zydelig was coadministered with a strong CYP3A inhibitor [see *Clinical Pharmacology (12.3)*]. If patients are taking concomitant strong CYP3A inhibitors, monitor for signs of Zydelig toxicity [see *Warnings and Precautions (5)*]. Follow dose modifications for adverse reactions [see *Dosage and Administration (2.2)*].

7.2 Effects of Zydelig on Other Drugs

CYP3A Substrates

Zydelig is a strong CYP3A inhibitor. The AUC of a sensitive CYP3A substrate was increased 5.4-fold when Zydelig was coadministered with a sensitive CYP3A substrate. Avoid coadministration of Zydelig with CYP3A substrates [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see *Warnings and Precautions (5.8)*]

Risk Summary

Based on findings in animals, Zydelig may cause fetal harm when administered to a pregnant woman. Idelalisib was teratogenic in animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Animal Data

In an embryo-fetal development study, pregnant rats were administered oral doses of idelalisib during the period of organogenesis at 25, 75, and 150 mg/kg/day. 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 \geq 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 sternbrae). 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.

8.3 Nursing Mothers

It is not known whether idelalisib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Zydelig, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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 patients with FL, SLL, and CLL, 131/208 (63%) patients were age 65 and older. No major differences in effectiveness were observed. In patients 65 years of age or older with indolent non-Hodgkin lymphoma in comparison to younger patients, 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%). In patients 65 years of age or older with CLL in comparison to younger patients, older patients had a higher incidence of

discontinuation due to an adverse reaction (11% vs 5%), higher incidence of serious adverse reactions (51% vs 43%), and higher incidence of death (3% vs 0%).

8.6 Females of Reproductive Potential

Contraception

Zydelig may cause fetal harm when administered during pregnancy. Advise females of reproductive potential to avoid becoming pregnant while taking Zydelig. If contraceptive methods are being considered, use effective contraception while taking Zydelig and for at least one month after taking the last dose of Zydelig. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking Zydelig [see *Use in Specific Populations (8.1)*].

8.7 Renal Impairment

No dose adjustment of Zydelig is necessary for patients with creatinine clearance (CL_{cr}) ≥ 15 mL/min [see *Clinical Pharmacology (12.3)*].

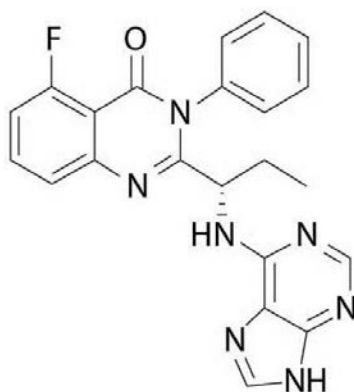
8.8 Hepatic Impairment

The AUC of idelalisib increased up to 1.7-fold in subjects with ALT or AST or bilirubin greater than the upper limit of normal (ULN) compared to healthy subjects with normal ALT or AST or bilirubin values [see *Clinical Pharmacology (12.3)*]. Safety and efficacy data are not available in patients with baseline ALT or AST values greater than 2.5 x ULN or bilirubin values greater than 1.5 x ULN, as these patients were excluded from Studies 1 and 2. Patients with baseline hepatic impairment should be monitored 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 C₂₂H₁₈N₇O 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 PI3K δ 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

Electrocardiographic Effects

The effect of Zydelig (150 mg and 400 mg) on the QT/QTc interval was evaluated in a placebo- and positive-controlled (moxifloxacin 400 mg) crossover study in 46 healthy subjects. At a dose 2.7 times the maximum recommended dose, Zydelig did not prolong the QT/QTc interval (i.e., not greater than or equal to 10 ms).

12.3 Pharmacokinetics

Absorption

Following oral administration of a single dose of Zydelig in the fasted state, the median T_{max} was observed at 1.5 hours.

Idelalisib exposure increased in a less than dose-proportional manner over a dose range of 50 mg to 350 mg twice daily in the fasted state.

Relative to fasting conditions, the administration of a single dose of Zydelig with a high-fat meal increased idelalisib AUC 1.4-fold. Zydelig can be administered without regard to food.

Distribution

Idelalisib is greater than 84% bound to human plasma proteins with no concentration dependence. The mean blood-to-plasma ratio was 0.7. The population apparent central volume of distribution at steady state is 23 L.

Metabolism and Elimination

Idelalisib is metabolized to its major metabolite GS-563117 via aldehyde oxidase and CYP3A. GS-563117 is inactive against PI3K δ in vitro. Idelalisib undergoes minor metabolism by UGT1A4.

The population apparent systemic clearance at steady-state is 14.9 L/hr. The population terminal elimination half-life of idelalisib is 8.2 hours. Following a single dose of 150 mg of [14 C] idelalisib, 78% and 14% of the radioactivity was excreted in feces and urine, respectively. GS-563117 accounted for 49% of the radioactivity in the urine and 44% in the feces.

Specific Populations

Age, Gender, Race, and Weight

Population pharmacokinetic analyses indicated that age, gender, race, and weight had no effect on idelalisib exposure.

Pediatric Patients

The pharmacokinetics of idelalisib has not been studied in pediatric patients.

Patients with Renal Impairment

A pharmacokinetic study following a single dose of 150 mg of Zydelig was performed in healthy subjects and subjects with severe renal impairment (CLcr 15 to 29 mL/min). Creatinine clearance had no effect on idelalisib exposure. No dose adjustment is needed for patients with CLcr \geq 15 mL/min.

Patients with Hepatic Impairment

A pharmacokinetic study of Zydelig was performed in healthy subjects and subjects with hepatic impairment. The geometric mean AUC increased up to 1.7-fold in subjects with ALT or AST or bilirubin values greater than the upper limit of normal (ULN) compared to subjects with normal AST or ALT or bilirubin values. Limited safety and efficacy data are available for patients with baseline AST or ALT greater than 2.5 x ULN or bilirubin greater than 1.5 x ULN, as these patients were excluded from Studies 1 and 2. Patients with baseline hepatic impairment should be monitored for signs of Zydelig toxicity [see *Boxed Warning and Warnings and Precautions (5.1)*]. Follow dose modifications for adverse reactions [see *Dosage and Administration (2.2)*].

Drug Interactions

In Vitro Studies

Idelalisib is a substrate for aldehyde oxidase, CYP3A, and UGT1A4 in vitro.

Idelalisib inhibits CYP2C8, CYP2C9, CYP3A, and UGT1A1 and GS-563117 inhibits CYP2C8, CYP2C9, CYP2C19, CYP3A and UGT1A1 in vitro. Idelalisib and GS-563117 are not likely to inhibit CYP1A, CYP2B6, and CYP2D6.

Idelalisib induces CYP2B6 and CYP3A4, but does not induce CYP1A2 in vitro. GS-563117 does not induce these enzymes.

Idelalisib and GS-563117 are substrates of P-glycoprotein (P-gp) and BCRP in vitro. Idelalisib is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. GS-563117 is not a substrate of OATP1B1 or OATP1B3.

Idelalisib inhibits P-gp, OATP1B1, and OATP1B3, and GS-563117 inhibits OATP1B1, OATP1B3 in vitro. Idelalisib is not likely to inhibit BCRP, OCT2, OAT1, or OAT3, and GS-563117 is not likely to inhibit P-gp, BCRP, OCT2, OAT1, or OAT3.

Effect of Other Drugs on Idelalisib

A single dose of 150 mg of Zydelig was administered alone and after rifampin (a strong CYP3A and P-gp inducer) 600 mg once daily for 8 days in healthy subjects. Rifampin decreased the geometric mean idelalisib AUC by 75% and the geometric mean C_{max} by 58%. Avoid coadministration of Zydelig with strong CYP3A and P-gp inducers.

A single dose of 400 mg of Zydelig was administered alone and after ketoconazole (a strong CYP3A and P-gp inhibitor) 400 mg daily for 4 days in healthy subjects. Ketoconazole increased the geometric mean idelalisib AUC by 1.8-fold. No changes in the geometric mean C_{max} were observed. Patients taking concomitant CYP3A inhibitors should be monitored for signs of Zydelig toxicity [see *Warnings and Precautions (5)*]. Follow dose modifications for adverse reactions [see *Dosage and Administration (2.2)*].

Effect of Idelalisib on Other Drugs

A single oral dose of midazolam 5 mg was administered alone and after Zydelig 150 mg for 15 doses in healthy subjects. The geometric mean midazolam C_{max} increased by 2.4-fold and the geometric mean midazolam AUC increased by 5.4-fold. Avoid coadministration of Zydelig with CYP3A substrates, as Zydelig is a strong CYP3A inhibitor.

A single dose of 10 mg of rosuvastatin (OATP1B1 and OATP1B3 substrate) was administered alone and after Zydelig 150 mg for 12 doses in healthy subjects. No changes in exposure to rosuvastatin were observed.

A single dose of 0.5 mg of digoxin (P-gp substrate) was administered alone and after Zydelig 150 mg for 19 doses in healthy subjects. No changes in exposure to digoxin were observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with idelalisib have not been conducted.

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 Pharmacology and/or Toxicology

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

Zydelig was evaluated in a randomized, double-blind, placebo-controlled study (Study 1) in 220 subjects 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. Subjects were randomized 1:1 to receive 8 doses of rituximab (first dose at 375 mg/m², subsequent doses at 500 mg/m² 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 1, the median age was 71 (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%) subjects had received prior anti-CD20 monoclonal antibodies. The most common (>15%) prior regimens were: bendamustine + rituximab (98 subjects, 45%), fludarabine + cyclophosphamide + rituximab (75 subjects, 34%), single-agent rituximab (67 subjects, 31%), fludarabine + rituximab (37 subjects, 17%), and chlorambucil (36 subjects, 16%).

The primary endpoint was 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 + rituximab over placebo + rituximab for the primary endpoint of PFS (HR: 0.18, 95% CI [0.10, 0.32], p < 0.0001). The efficacy results are shown in Table 6 and the Kaplan-Meier curve for PFS is shown in Figure 1.

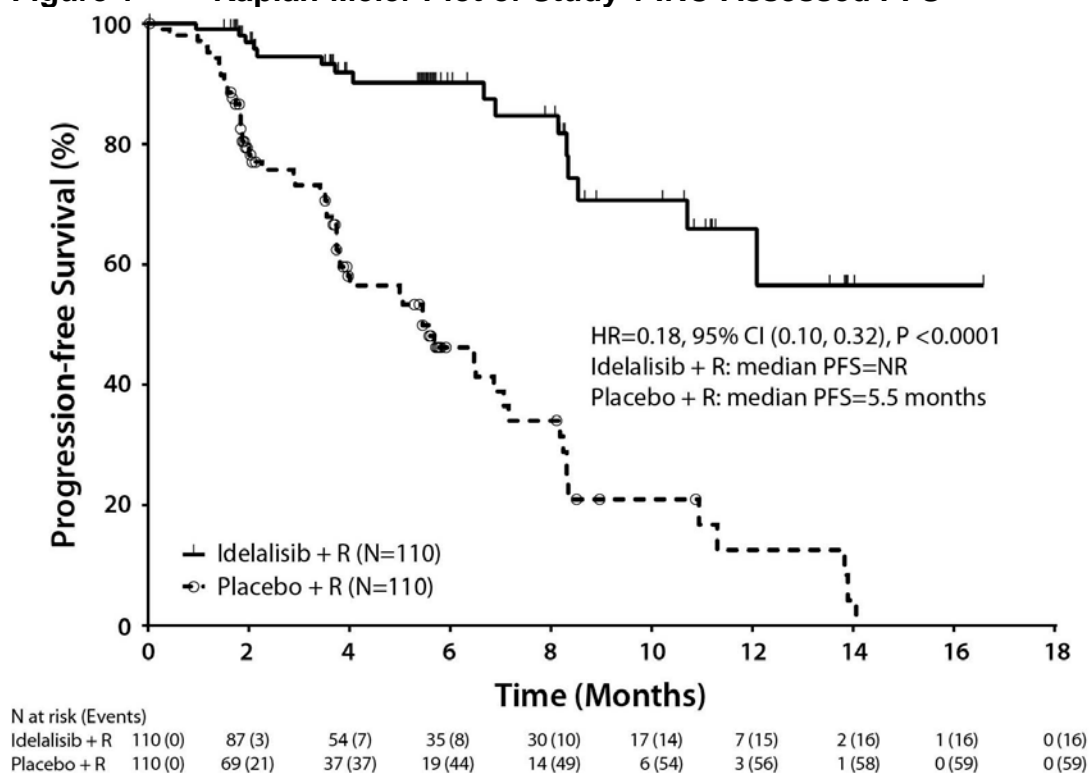
Table 6 Efficacy Results from Study 1

	Zydelig + R n=110	Placebo + R n=110
PFS Median (months) (95% CI)	NR (10.7, NR)	5.5 (3.8, 7.1)
Hazard ratio (95% CI)	0.18 (0.10, 0.32)	
P-value	< 0.0001 †	

R: rituximab; PFS: progression-free survival; NR: not reached

† The p value for PFS was based on stratified log-rank test.

Figure 1 Kaplan-Meier Plot of Study 1 IRC-Assessed PFS



14.2 Relapsed Follicular B-cell non-Hodgkin Lymphoma

The safety and efficacy of Zydelig in patients with FL was evaluated in a single-arm, multicenter clinical trial 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 7.

Table 7 Overall Response Rate (ORR) and Duration of Response (DOR) in Patients with Relapsed Follicular Lymphoma

	N=72
ORR	39 (54%)
95% CI	(42, 66%)
CR	6 (8%)
PR	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

The safety and efficacy of Zydelig in patients with SLL was evaluated in a single-arm, multicenter clinical trial 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.

Subjects 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 Small Lymphocytic Lymphoma

	N=26
ORR	15 (58%)
95% CI	(37, 77%)
CR	0
PR	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 °C (59–86 °F).

- 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)*].

- **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 (5.4)*].

- **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 (5.5)*].

- **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 (5.6)*].

- **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 (5.7)*].

- **Pregnancy and Nursing**

Advise women of the potential hazard to the fetus and to avoid pregnancy during treatment with Zydelig. If contraceptive methods are being considered, advise to use adequate contraception during therapy and for at least one month after completing therapy. Also advise patients not to breastfeed while taking Zydelig [see *Warnings and Precautions (5.8)* and *Use in Specific Populations (8.1, 8.3, and 8.6)*].

- **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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205858-GS-000-PI