Product Monograph

PrZYDELIG®

(idelalisib) tablets
150 mg
100 mg

Antineoplastic Agent

ZYDELIG (idelalisib), indicated as monotherapy for the treatment of patients with follicular lymphoma who have received at least two prior systemic regimens and are refractory to both rituximab and an alkylating agent, has been issued marketing authorization with conditions pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ZYDELIG please refer to Health Canada's Notice of Compliance with Conditions – drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php.

ZYDELIG (idelalisib), indicated in combination with rituximab for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL), has been issued marketing authorization without conditions.

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Submission Control No.: 210648

This product has been approved under the Notice of Compliance with Conditions (NOC/c) policy for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market authorization granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating disease. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol "NOC/c". These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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PART I. HEALTH PROFESSIONAL INFORMATION

ZYDELIG (idelalisib), indicated as monotherapy for the treatment of patients with follicular lymphoma who have received at least two prior systemic regimens and are refractory to both rituximab and an alkylating agent, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.

ZYDELIG (idelalisib), indicated in combination with rituximab for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL), has been issued marketing authorization without conditions.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet Idelalisib 150 mg Idelalisib 100 mg	microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, and magnesium stearate. *For a complete listing, see the DOSAGE FORMS, COMPOSITION, AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

NOC Chronic Lymphocytic Leukemia

ZYDELIG (idelalisib) is indicated in combination with rituximab for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL).

Effectiveness of ZYDELIG in combination with rituximab is based on progression free survival benefit with limited follow up in a study of patients who were not fit to receive cytotoxic therapy.

Refer to the Rituxan Product Monograph for rituximab product information.

NOC/c

Follicular Lymphoma

ZYDELIG (idelalisib) is indicated as a monotherapy for the treatment of patients with follicular lymphoma who have received at least two prior systemic regimens and are refractory to both rituximab and an alkylating agent.

Geriatrics (≥65 years of age):

In clinical studies of ZYDELIG in patients with follicular lymphoma or CLL, no major differences in effectiveness were observed in patients 65 years of age or older compared with younger patients. Adverse events were more common and led more commonly to negative outcomes in patients over the age of 65 years (see **WARNINGS and PRECAUTIONS**).

Pediatrics (<18 years of age):

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

CONTRAINDICATIONS

Zydelig is contraindicated in first-line CLL and early-line indolent non-Hodgkin lymphoma (iNHL) outside a clinical trial. See **WARNINGS AND PRECAUTIONS**, **Serious Infections** section below.

ZYDELIG is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ZYDELIG® should only be prescribed by a qualified physician who is experienced in the use of anti-cancer agents.

Prophylaxis for *Pneumocystis carinii/jirovecii* pneumonia (PCP/PJP) and monitoring for cytomegalovirus (CMV) are required during treatment with ZYDELIG.

The following are clinically significant adverse events:

- Serious infections, including fatal cases (see **Serious Infections** below)
- Hepatotoxicity (see **Hepatic** below)
- Severe diarrhea/colitis, including fatal cases (see **Gastrointestinal** below)
- Pneumonitis, including fatal cases (see **Respiratory** below)
- Severe mucocutaneous reactions, including fatal cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (see **Skin** below)

Carcinogenesis and Mutagenesis

The carcinogenicity potential of idelalisib was evaluated in a 26-week transgenic RasH2 mouse study and a 2-year rat study. A small increase in pancreatic islet cell tumors was noted in male rats (see **TOXICOLOGY**, **Carcinogenesis**). ZYDELIG demonstrated no significant mutagenicity or genotoxicity *in vitro*, but demonstrated genotoxicity *in vivo* at a high dose (see **TOXICOLOGY, Mutagenesis**).

Drug Interactions

Cytochrome P450 (CYP) interactions

ZYDELIG is a strong CYP3A inhibitor. Coadministration of ZYDELIG with CYP3A substrates may increase their systemic exposures. Caution is recommended if ZYDELIG is coadministered with narrow therapeutic index CYP3A substrates (see **DRUG INTERACTIONS**).

Gastrointestinal

Diarrhea/Colitis:

Cases of severe diarrhea/colitis were reported commonly and occurred relatively late (months) after the start of therapy with ZYDELIG. Severe diarrhea due to ZYDELIG responds poorly to antimotility agents. Most cases resolved within a few weeks with drug interruption and additional symptomatic treatment (e.g., anti-inflammatory corticosteroid agents such as enteric budesonide) but some had a fatal outcome (see **DOSAGE AND ADMINISTRATION**, **Dose Modification**). Severe diarrhea/colitis occurring with

administration of ZYDELIG has been associated with dehydration which has responded to intravenous fluid and electrolyte replacement. Causes of diarrhea related to gastrointestinal infection should be ruled out.

For CTCAE Grade 1 diarrhea/colitis, provide anti-diarrheal (e.g., loperamide) and maintain ZYDELIG dose. For Grade 2 diarrhea/colitis, withhold ZYDELIG and monitor at least weekly until resolved to Grade ≤1.

For CTCAE Grade 3 or 4 diarrhea/colitis, withhold ZYDELIG. Consider addition of anti-inflammatory agent (e.g., sulfasalazine, budesonide). Monitor at least weekly until resolved to Grade ≤1, then may resume ZYDELIG at 100 mg BID.

Treatment of patients with ongoing inflammatory bowel disease is not recommended.

Hematologic

Neutropenia:

Treatment-emergent Grade 3 or 4 neutropenia and cases of febrile neutropenia, some which have been fatal, have occurred in patients treated with ZYDELIG. Monitor blood counts in all patients at least every 2 weeks for the first 6 months of therapy with ZYDELIG, and at least weekly in patients while absolute neutrophil counts are less than 1.0×10^9/L (see **DOSAGE AND ADMINISTRATION, Dose Modification**).

Hepatic

Hepatotoxicity:

Elevations in ALT and AST Grade 3 or 4 (greater than 5 times the upper limit of normal) have been observed in clinical trials of ZYDELIG. These laboratory findings were generally observed within the first 12 weeks of treatment, asymptomatic, and reversible within 3-4 weeks with dose interruption. While most patients resumed treatment at a lower dose, recurrence of ALT and AST elevations were common (see **DOSAGE AND ADMINISTRATION, Dose Modification**). Monitor ALT, AST, and total bilirubin in all patients every 2 weeks for the first 3 months of treatment, then every 1 to 3 months thereafter, and as clinically indicated.

For CTCAE Grade 1 (ALT/AST ≤3 x ULN) or Grade 2 (ALT/AST > 3-5 x ULN), maintain ZYDELIG dose. Monitor at least weekly until ALT/AST are ≤1 x ULN.

For CTCAE Grade 3 (ALT/AST >5-20 x ULN) or Grade 4 (ALT/AST >20 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 for recurrent hepatotoxicity.

Treatment of patients with active hepatitis or liver disease is not recommended.

Immune

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.

Serious Infections:

Treatment with ZYDELIG should not be initiated in patients with any evidence of ongoing systemic bacterial, fungal or viral infection.

Serious and fatal infections have occurred with ZYDELIG, including opportunistic infections such as *Pneumocystis carinii/jirovecii* pneumonia (PCP/PJP) and cytomegalovirus (CMV).

An increase in serious adverse events and deaths, primarily due to infections, was observed in patients receiving ZYDELIG compared with the control arms in a first-line study of CLL and two studies of relapsed early-line iNHL. Based on these findings, and the unfavourable benefit/risk assessment at interim analysis, these studies and all first-line studies in patients with CLL or iNHL were terminated. ZYDELIG is contraindicated in first-line CLL and early-line iNHL outside a clinical trial.

Administer prophylaxis for PCP/PJP to all patients throughout ZYDELIG treatment and for a period of 2 to 6 months after discontinuation. The duration of post-treatment prophylaxis should be based on clinical judgment and may take into account a patient's risk factors such as concomitant corticosteroid treatment and prolonged neutropenia.

Regular clinical and laboratory monitoring for CMV infection should be conducted. Treatment with ZYDELIG should be permanently discontinued if there is evidence of CMV infection or viremia (positive polymerase chain reaction (PCR) or antigen test).

Cases of progressive multifocal leukoencephalopathy (PML) have been reported following the use of ZYDELIG within the context of prior- or concomitant immunosuppressive therapies that have been associated with PML. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioral signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC viral DNA and repeat neurological assessments should be considered. Discontinue ZYDELIG permanently in patients with confirmed PML.

Neurologic

Effects on Ability to Drive and Use Machines

No studies of the effects of ZYDELIG on the ability to drive or use machines have been performed. A detrimental effect on such activities is not expected based on the known pharmacology and safety profile of ZYDELIG.

Respiratory

Pneumonitis:

Cases of pneumonitis, including organizing pneumonia, some with fatal outcome, have occurred with ZYDELIG. Time to occurrence of pneumonitis after the start of therapy with ZYDELIG was highly variable, ranging from a few weeks to over one year. Patients should be monitored for respiratory signs and symptoms throughout treatment and should be advised to report new respiratory symptoms promptly. In patients presenting with serious lung adverse events, ZYDELIG should be interrupted and the patient assessed for an explanatory etiology. In patients with drug-related pneumonitis or organizing pneumonia, ZYDELIG should be permanently discontinued and appropriate treatment with systemic corticosteroids should be initiated (see **DOSAGE AND ADMINISTRATION, Dose Modification**).

Skin

Cutaneous Reactions:

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with fatal outcomes have been reported in patients taking ZYDELIG when administered concomitantly with other medications associated with these syndromes. If SJS or TEN is suspected, ZYDELIG should be interrupted and the patient treated accordingly. 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. If patients develop severe cutaneous reactions, discontinue ZYDELIG (see **DOSAGE AND ADMINISTRATION, Dose Modification**).

For CTCAE Grade 1 rash, maintain ZYDELIG dose. For Grade 2 rash, withhold ZYDELIG until Grade ≤1.

For CTCAE Grade 3 or 4 rash, withhold ZYDELIG. Monitor at least weekly until resolved to Grade ≤1, then may resume ZYDELIG at 100 mg BID.

Photosensitivity:

In vitro studies have shown that idelalisib has phototoxic potential (see **TOXICOLOGY**).

Patients should be advised to avoid sun exposure or wear sufficient sun protection.

Special Populations

Pregnant Women:

There are no adequate and well-controlled studies of ZYDELIG in pregnant women.

Based on findings in animals (see **TOXICOLOGY**), idelalisib may cause fetal harm when administered to a pregnant woman. In studies of pregnant rats, idelalisib treatment was associated with increased post-implantation loss, decreased fetal weights, and skeletal malformations.

ZYDELIG should not be used during pregnancy. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving ZYDELIG. Women of child bearing potential should use highly effective contraceptive measures while taking ZYDELIG and for 1 month after stopping treatment. Idelalisib may reduce the effectiveness of hormonal contraceptives (see **DRUG INTERACTIONS**). Women who use hormonal methods of birth control should add a barrier method.

Nursing Women:

It is not known whether idelalisib or its metabolites are 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, discontinue nursing when taking ZYDELIG.

Hepatic Impairment:

Intensified monitoring of adverse events is recommended in patients with impaired hepatic function as exposure is expected to be increased in this population. 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. 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 pivotal trials.

Geriatrics:

The incidence of $\geq$ Grade 3 AEs was higher among subjects $\geq$ 65 years of age compared with subjects < 65 years of age (79.0% vs 63.2%). Subjects $\geq$ 65 years of age had a higher incidence of idelalisib discontinuation due to an AE compared with subjects < 65 years of age (24.6% vs 15.7%). A higher incidence of SAEs was observed in subjects $\geq$ 65 years of age compared with subjects < 65 years of age (59.9% vs 40.0% for all subjects).

Monitoring and Laboratory Tests

Hepatic function tests (ALT, AST, and total bilirubin) should be measured every 2 weeks for the first 3 months of treatment, then every 1 to 3 months thereafter, and as clinically indicated (see **Hepatic** section above).

Monitor blood counts at least every 2 weeks for the first 6 months of therapy, and at least weekly in patients while absolute neutrophil counts are less than 1.0×10^9/L. Monitor all patients for CMV infection during treatment with ZYDELIG.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

ZYDELIG is associated with infections. Higher frequencies of infections overall, including Grade 3 and 4 infections, were observed in the ZYDELIG arms compared to the control arms of ZYDELIG clinical studies. Most frequently observed were infections in the respiratory system and septic events. In many instances the pathogen was not identified; however, both conventional and opportunistic pathogens, including PCP/PJP and CMV, were among those identified. Nearly all PCP/PJP infections, including fatal cases, occurred in the absence of PCP/PJP prophylaxis. There have been cases of PCP/PJP after stopping idelalisib treatment.

Chronic Lymphocytic Leukemia
In the Phase 3 study in CLL, 220 previously treated patients were randomised to receive ZYDELIG (150 mg BID) + rituximab or placebo + rituximab. Serious adverse reactions were reported in 54 (49%) patients treated with ZYDELIG + rituximab. The most frequent (≥2%) serious adverse reactions reported for patients 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%) patients. The most common adverse reactions that led to treatment discontinuations were hepatotoxicity and diarrhea/colitis. A total of 39 patients (35%) had dose interruptions, 16 patients (15%) had dose reductions, and 11 patients (10%) had drug discontinuation due to adverse reactions. Patients may have had more than 1 type of dose modification. The most common reasons for dose reductions were elevated transaminases, diarrhea, and neutropenia.

Indolent Non-Hodgkin Lymphoma
In the Phase 1 and 2 studies in previously treated iNHL, 146 patients were treated with ZYDELIG monotherapy at a dose of 150 mg BID. Serious adverse reactions were reported in 73 (50%) patients treated with ZYDELIG. The most frequent serious adverse reactions were pneumonia (15%), diarrhea (11%), and pyrexia (9%). Among the 146 iNHL patients who received ZYDELIG 150 mg BID as a single agent, sixty-two (43%) had dose interruptions, thirty-four (23%) had dose reductions, and thirty-six (25%) had drug discontinuation due to adverse reactions. Patients may have had more than 1 type of dose modification. The most common reasons for dose modifications were diarrhea, elevated transaminases, and neutropenia.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 summarizes adverse events reported for ZYDELIG + rituximab and placebo + rituximab arms in 218 patients with CLL. Adverse events reflect exposure to ZYDELIG with a median duration of 5.0 months and exposure to placebo with a median duration of 3.7 months. Adverse events occurring at 5% incidence and 2% greater in the ZYDELIG arm when compared to the placebo arm are provided in Table 1.

Table 1 Adverse Events Reported in ≥5% of Patients with CLL and Occurred at ≥2% Higher Incidence in Patients Treated with ZYDELIG

	ZYDELIG + R N=110 (%)		**Placebo + R N=108 (%)**	
Adverse Event	**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)

	ZYDELIG + R N=110 (%)		**Placebo + R N=108 (%)**	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
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 2 summarizes adverse events in 146 patients with iNHL treated with ZYDELIG 150 mg BID. ZYDELIG is indicated for use in patients with follicular lymphoma. Adverse events reflect exposure to ZYDELIG with a median duration of 6.1 months.

Table 2 Adverse Events Reported in ≥ 10% Patients with Indolent Non-Hodgkin Lymphoma Treated with ZYDELIG 150 mg BID

	ZYDELIG Monotherapy N=146 (%)	
Adverse Event	**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.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Abnormalities

Table 3 summarizes the treatment-emergent laboratory abnormalities reported for ZYDELIG + rituximab and placebo + rituximab arms in patients with CLL.

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

	ZYDELIG + R N=110 (%)		**Placebo + R N=108 (%)**	
Laboratory Parameter	**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

Table 4 summarizes the treatment-emergent laboratory abnormalities in patients with iNHL treated with ZYDELIG 150 mg BID.

Table 4 Treatment-emergent Laboratory Abnormalities in Patients with Indolent Non-Hodgkin Lymphoma Treated with ZYDELIG 150 mg BID

	ZYDELIG Monotherapy N=146 (%)	
Laboratory Abnormality	**Any Grade**	**Grade 3-4**
Serum chemistry abnormalities		
ALT increased	73 (50)	27 (18)
AST increased	60 (41)	18 (12)
neutrophils decreased	78 (53)	36 (25)
hemoglobin decreased	41 (28)	3 (2)
platelets decreased	38 (26)	9 (6)

Grades were obtained per CTCAE version 4.03.

Post-Market Adverse Drug Reactions

In addition to adverse reactions from clinical studies, the following adverse reactions have been identified during post-approval use of ZYDELIG. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Skin and subcutaneous tissue disorders:	Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (see **WARNINGS and PRECAUTIONS, Skin**)
Respiratory, Thoracic and Mediastinal disorders:	Organizing pneumonia (see **WARNINGS and PRECAUTIONS, Respiratory**)
Infections and infestations:	Progressive multifocal leukoencephalopathy (see **WARNINGS and PRECAUTIONS, Serious infections**)

DRUG INTERACTIONS

Drug-Drug Interactions

Idelalisib is metabolized primarily via aldehyde oxidase, and to a lesser extent via CYP3A and glucuronidation (UGT1A4). The primary circulating metabolite (GS-563117) exceeds idelalisib human plasma levels at steady-state. GS-563117 is inactive against PI3Kδ**.**

Effects of Other Drugs on ZYDELIG

CYP3A Inducers

A clinical drug interaction study found that coadministration of ZYDELIG with rifampin (a strong CYP3A inducer) resulted in a ~75% reduction in idelalisib plasma AUC_{inf}. Coadministration of ZYDELIG with strong CYP3A inducers such as rifampin, phenytoin, St. John's Wort, or carbamazepine should be avoided.

CYP3A Inhibitors

A clinical drug interaction study found that coadministration of ZYDELIG with ketoconazole (a strong CYP3A inhibitor) resulted in a 26% increase in ZYDELIG C_{max} and a 79% increase in AUC_{inf}, indicating that ZYDELIG is not a sensitive CYP3A substrate. If patients are taking concomitant strong CYP3A inhibitors, monitor for signs of toxicity.

Other

Co-administration of drugs which are aldehyde oxidase inhibitors (e.g. raloxifene) could increase idelalisib plasma concentrations. A clinical drug interaction study has not been conducted.

Effects of ZYDELIG on Other Drugs

CYP3A Substrates

In vitro, the major circulating metabolite was shown to be an irreversible inhibitor of CYP3A. Return to normal CYP3A enzyme activity is therefore expected to take several days after stopping idelalisib administration. A clinical drug interaction study found that coadministration of ZYDELIG with midazolam (a sensitive CYP3A substrate) resulted in a ~140% increase in C_{max} and a ~440% increase in AUC_{inf} of midazolam. Accordingly, ZYDELIG is considered to be a strong CYP3A inhibitor. Coadministration of ZYDELIG with CYP3A substrates (e.g., certain antiarrhythmics, calcium channel blockers, benzodiazepines, HMG-CoA reductase inhibitors, phosphodiesterase-5 (PDE5) inhibitors, and warfarin) may increase their systemic exposures.

Caution is recommended if ZYDELIG is coadministered with narrow therapeutic index CYP3A substrates (e.g., alfentanil, cyclosporine, sirolimus, tacrolimus, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine).

CYP2C8 Substrates

In vitro, idelalisib inhibited CYP2C8. *In vivo* studies to investigate the clinical relevance have not been conducted. Caution is advised when co-administering idelalisib with narrow therapeutic index CYP2C8 substrates (e.g. repaglinide).

Substrates of CYP2B6, CYP2C9 and CYP2C19

In vitro, idelalisib demonstrated the potential to induce CYP2B6, CYP2C8 and CYP2C9, and based on these findings, is likely to induce CYP2C19. Clinical drug interaction studies have not been conducted. Caution is advised upon co-administration of idelalisib with substrates of these enzymes with narrow therapeutic indices (warfarin, phenytoin, S-mephenytoin).

Hormonal Contraceptives

In vitro, idelalisib induces CYP3A4, CYP2C9 and UGT1A1. All of these enzymes are involved in the first-pass metabolism of ethinyl estradiol in the gut wall and liver. A clinical drug interaction study has not been conducted, however idelalisib may decrease the oral bioavailability of ethinyl estradiol, decreasing the effectiveness of hormonal contraceptives.

Drug-Food Interactions

There were no clinically relevant differences in absorption when ZYDELIG was administered either with food or in a fasting state. Idelalisib can be administered without regard to food.

Drug-Herb Interactions

Coadministration with strong CYP3A inducers such as St. John's Wort should be avoided.

Drug-Laboratory Interactions

Interactions of ZYDELIG with laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ZYDELIG can be taken with or without food.

Continue treatment until disease progression or unacceptable toxicity.

Recommended Dose and Dosage Adjustment

Chronic Lymphocytic Leukemia

The recommended dose of ZYDELIG is 150 mg administered orally twice daily in combination with rituximab (8 cycles of rituximab, first cycle at 375 mg/m^2, subsequent cycles at 500 mg/m^2). See the RITUXAN Product Monograph for information on administration and dose adjustment. See Table 5 for ZYDELIG dose modifications.

Follicular Lymphoma

The recommended dose of ZYDELIG is 150 mg administered orally twice daily. See Table 5 for ZYDELIG dose modifications.

Table 5 Dose Modifications for Toxicities Due to ZYDELIG

Event	Grade 1-2	Grade 3	Grade 4
Gastrointestinal			
Diarrhea/Colitis	For Grade 1, provide anti-diarrheal (e.g., loperamide) and maintain ZYDELIG dose. For Grade 2, withhold ZYDELIG and monitor at least weekly until resolved to Grade ≤1.	Withhold ZYDELIG. Consider addition of anti-inflammatory agent (e.g., sulfasalazine, budesonide). Monitor at least weekly until resolved to Grade ≤1, then may resume ZYDELIG at 100 mg BID.	
Hematologic			
Neutropenia	Maintain ZYDELIG dose.	Maintain ZYDELIG dose. Monitor ANC at least weekly.	Interrupt ZYDELIG. Monitor ANC at least weekly until ANC ≥ 0.5 G/L, then may resume ZYDELIG at 100 mg BID.
Hepatic			
ALT/AST Elevation	Maintain ZYDELIG dose. Monitor at least weekly until ALT/AST are ≤1 x ULN.	Withhold ZYDELIG. Monitor at least weekly until ALT/AST are ≤1 x ULN, then may resume ZYDELIG at 100 mg BID.	
Infections			
Evidence of CMV infection or viremia	Discontinue ZYDELIG in patients with evidence of CMV infection or viremia (positive PCR or antigen test).		

Event	Grade 1-2	Grade 3	Grade 4
Evidence of PML	Withhold ZYDELIG at the first sign or symptom suggestive of PML. Discontinue ZYDELIG permanently in patients with confirmed PML.		
Evidence of PCP/PJP Infection	Discontinue ZYDELIG in patients with evidence of PCP/PJP infection.		
Respiratory			
Pneumonitis	Interrupt ZYDELIG and evaluate for respiratory symptoms: • If pneumonitis with non-infectious etiology or association with ZYDELIG treatment is suspected, discontinue treatment. • If pneumonitis with infectious etiology is established, monitor until resolved, then may resume ZYDELIG at 100 mg BID. • Permanently discontinue ZYDELIG in patients with evidence of organizing pneumonia.		
Skin			
Rash	For Grade 1, maintain ZYDELIG dose. For Grade 2, withhold ZYDELIG until Grade ≤1.	Withhold ZYDELIG. Monitor at least weekly until resolved to Grade ≤1, then may resume ZYDELIG at 100 mg BID.	
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CMV, cytomegalovirus; PCP/PJP, *Pneumocystis carinii/jirovecii* pneumonia ; PCR, polymerase chain reaction; ULN, upper limit of normal			

Special Patient Populations

Geriatrics (≥65 years of age)

No specific dose adjustment is required for elderly patients (aged ≥ 65 years) (see **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatrics (<18 years of age)

ZYDELIG is not indicated for use in pediatric patients < 18 years of age.

Renal Impairment

No dose adjustment is required for patients with mild, moderate, or severe renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY)**.

Hepatic Impairment

No dose adjustment is necessary when initiating treatment with ZYDELIG in patients with mild or moderate hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY**). Patients with baseline ALT or AST values greater than 2.5 x ULN or

bilirubin values greater than 1.5 x ULN were excluded from pivotal trials. There are insufficient data to make dose recommendations for patients with severe hepatic impairment**.**

Missed Dose

If a patient misses a dose of ZYDELIG within 6 hours of the time it is usually taken, the patient should take ZYDELIG as soon as possible, and then take the next dose of ZYDELIG at the regularly scheduled time.

If a patient misses a dose of ZYDELIG by more than 6 hours, the patient should not take the missed dose, but resume the usual dosing schedule.

OVERDOSAGE

If overdose occurs, the patient must be monitored for evidence of toxicity. Treatment of overdose with ZYDELIG consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Idelalisib selectively inhibits PI3Kδ kinase, which is hyperactive in B-cell malignancies and is central to multiple signaling pathways that drive proliferation, survival, homing, and retention of malignant cells in lymphoid tissues and bone marrow. Idelalisib is a selective inhibitor of adenosine-5'-triphosphate (ATP) binding to the catalytic domain of PI3Kδ, resulting in inhibition of the phosphorylation of the key lipid second messenger phosphatidylinositol (PIP) and prevention of Akt phosphorylation.

Idelalisib induces apoptosis and inhibits proliferation in cell lines derived from malignant B-cells and in primary tumor cells. Idelalisib inhibits homing and retention of malignant B-cells in the tumor microenvironment including lymphoid tissues and the bone marrow.

Pharmacodynamics

Effects on Electrocardiogram:

The effect of idelalisib at therapeutic (150 mg) and supratherapeutic (400 mg) doses on the QTc interval was evaluated in a placebo- and positive-controlled (moxifloxacin 400 mg) crossover study in 40 healthy subjects. No significant changes in the baseline-corrected QTc based on Fridericia's correction method (QTcF) (i.e., ≥10 ms) were observed.

Lymphocytosis:

Upon initiation of ZYDELIG, a temporary increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) has been observed. The onset of isolated lymphocytosis typically occurs during the first two weeks of ZYDELIG therapy. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings.

Pharmacokinetics

Absorption:

Following oral administration of a single 400 mg dose of idelalisib, peak plasma concentrations were observed 2 to 4 hours post-dose under fed conditions and 0.5 to 1.5 hours under fasted conditions.

The C_{max} and AUC of idelalisib increased in a less than dose proportional manner.

Distribution:

Idelalisib is 93% to 94% bound to human plasma proteins at concentrations observed clinically. The mean blood-to-plasma ratio was approximately 0.5.

Metabolism and Elimination:

The metabolism of idelalisib is primarily via aldehyde oxidase, and to a lesser extent via CYP3A and UGT1A4. The primary and only circulating metabolite, GS-563117, is inactive against PI3Kδ, but is a strong inhibitor of CYP3A.

The terminal elimination half-life of idelalisib is 8.2 hours following idelalisib 150 mg twice daily oral administration. Following a single 150 mg oral dose of [^{14}C]-labeled idelalisib, approximately 78% and 15% was excreted in feces and urine, respectively.

Drug-drug Interactions

In vitro, idelalisib inhibited the transport activities of BCRP, OATP1B1 and OATP1B3. A clinical drug interaction study was conducted with rosuvastatin, a sensitive substrate of these transporters. Co-administration of ZYDELIG at 150 mg BID with a single dose of rosuvastatin resulted in comparable rosuvastatin plasma exposures (AUC 90% CI: 87, 121) as observed without ZYDELIG, demonstrating that *in vitro* inhibition of BCRP or OATP1B1/1B3 is not clinically relevant.

Idelalisib inhibited the transport activity of P-gp *in vitro*. In a clinical drug interaction study, digoxin plasma exposures (AUC and C_{max}) were comparable when a single dose of digoxin was administered alone or in combination with ZYDELIG at 150 mg BID, suggesting no clinically relevant inhibition of P-gp or impact on digoxin pharmacokinetics (AUC 90% CI: 98, 111) by ZYDELIG. A risk for P-gp inhibition in the gastrointestinal tract, which could

result in increased exposure of sensitive substrates for intestinal P-gp such as dabigatran etexilate, cannot be excluded.

Idelalisib is not an inhibitor of the metabolizing enzymes CYP1A2, CYP2B6, CYP2C, CYP2D6, CYP3A, or UGT1A1, or of the transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

GS-563117 is an irreversible (mechanism-based) inhibitor of CYP3A (K_I = 0.18 μM, k_{inact} = 0.033 min^{-1}). GS-563117 is not an inhibitor of the metabolizing enzymes CYP1A2, CYP2B6, CYP2C, CYP2D6 or UGT1A1, or of the transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

Special Populations and Conditions

Pediatrics:

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

Geriatrics:

Population pharmacokinetic analyses indicated that age had no clinically relevant effect on the exposures of idelalisib or its primary metabolite GS-563117, including geriatric (65 years of age and older) compared to younger subjects.

Race:

Population pharmacokinetic analyses indicated that race had no clinically relevant effect on the exposures of idelalisib or its primary metabolite GS-563117.

Gender:

Population pharmacokinetic analyses indicated that gender had no clinically relevant effect on the exposures of idelalisib or its primary metabolite GS-563117.

Hepatic Impairment:

A study of pharmacokinetics and safety of idelalisib was performed in healthy volunteers and volunteers with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. Following a single 150 mg dose, no clinically relevant changes in plasma exposure to idelalisib or its primary metabolite, GS-563117, were observed compared to healthy control volunteers.

Renal Impairment:

A study of pharmacokinetics and safety of idelalisib was performed in healthy volunteers and volunteers with severe renal impairment (estimated creatinine clearance 15 to 29 mL per min). Following a single 150 mg dose, no clinically relevant changes in exposures to

idelalisib or its primary metabolite, GS-563117, were observed in subjects with severe renal impairment compared to healthy volunteers.

STORAGE AND STABILITY

Store below 30 °C (86 °F).

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

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ZYDELIG is available as tablets. Each tablet contains 100 or 150 mg of idelalisib. The tablets also include the following inactive ingredients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate and magnesium stearate.

The 150 mg tablets are coated with a material containing red iron oxide, polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide. ZYDELIG 150 mg tablets are pink, oval-shaped film-coated tablet debossed with “GSI” on one side and the number “150” on the other side. Each bottle contains 60 film-coated tablets and a polyester coil and is closed with a child-resistant closure.

The 100 mg tablets are coated with a material containing Sunset Yellow FCF Aluminum Lake (FD&C Yellow #6), polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide. ZYDELIG 100 mg tablets are orange, oval-shaped and film-coated, debossed with “GSI” on one side and the number “100” on the other side. Each bottle contains 60 film-coated tablets and a polyester coil and is closed with a child-resistant closure.

PART II. SCIENTIFIC INFORMATION

ZYDELIG (idelalisib), indicated as a monotherapy for the treatment of patients with follicular lymphoma who have received at least two prior systemic regimens and are refractory to both rituximab and an alkylating agent, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.

ZYDELIG (idelalisib), indicated in combination with rituximab for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL), has been issued marketing authorization without conditions.

PHARMACEUTICAL INFORMATION

ZYDELIG is the brand name for idelalisib, an isoform-selective, small-molecule inhibitor of phosphatidylinositol 3-kinase p110δ (PI3Kδ).

ZYDELIG tablets are for oral administration. Each tablet contains 150 mg of idelalisib or 100 mg of idelalisib. The tablets also include the following inactive ingredients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, and magnesium stearate. The 150 mg tablets are film-coated with a material containing polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxide red. The 100 mg tablets are film-coated with a material containing polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc and sunset yellow FCF.

Drug Substance

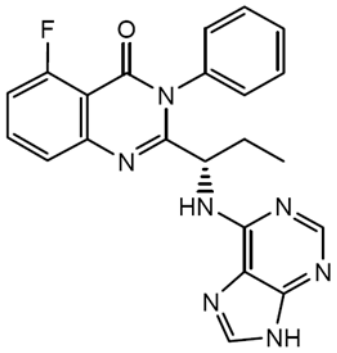
Common Name: idelalisib

Chemical Name: 5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl]quinazolin-4(3H)-one

Empirical Formula: $C_{22}H_{18}FN_7O$

Molecular Weight: 415.42

Structural Formula:



Physicochemical Properties:

Description: white to off-white solid

Solubility: <0.1 mg/mL at pH 5-7 to over 1 mg/mL at pH 2 under ambient conditions

CLINICAL TRIALS

NOC **Chronic Lymphocytic Leukemia**

The pivotal CLL study was a randomized, double-blind, placebo-controlled study in 220 patients with relapsed CLL who required treatment but were not considered suitable for cytotoxic chemotherapy based on one of the following criteria: Cumulative Illness Rating Score (CIRS)* >6; estimated CrCl <60 mL/min; 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 cycles of rituximab (first cycle at 375 mg/m^2, subsequent cycles at 500 mg/m^2) in combination with either an oral placebo twice daily or with ZYDELIG 150 mg taken twice daily until disease progression or unacceptable toxicity.

The median age was 71 (range 47, 92) with 78.2% of subjects over 65, 65.5% were male, 90.0% were white, 64.5% had a Rai stage of III or IV, and 55.9% had Binet Stage C. Subjects had a median CIRS score of 8; 81 (36.8%) had cardiac, 114 (51.8%) had respiratory, 87 (39.5%) had renal, and 93 (42.3%) had endocrine/metabolic comorbidities. Two hundred and six subjects (93.6%) had 3 or more organs with comorbidities and 82 (37.3%) had severe (score of 3 or higher in any system) comorbidities. The median number of prior therapies was 3.0 (range 1-12). Nearly all (95.9%) subjects had received prior anti-CD20 monoclonal antibodies. The most common (>15%) prior regimens were: bendamustine + rituximab (98 subjects, 44.5%), fludarabine + cyclophosphamide + rituximab (75 subjects, 34.1%), single-agent rituximab (67 subjects, 30.5%), fludarabine + rituximab (37 subjects, 16.8%), and chlorambucil (36 subjects, 16.4%). Most subjects had adverse cytogenetic prognostic factors: 43.2% had a 17p deletion and/or *TP53* mutation, and 83.6% had an unmutated *IGHV*.

The primary endpoint was progression free survival (PFS), defined as the interval from randomization to the earlier of the first documentation of definitive progressive disease (PD) or death from any cause; definitive disease progression was based on standard criteria other than lymphocytosis alone. Other efficacy outcomes included the overall response rate (ORR) and overall survival (OS). The primary analyses of PFS and ORR and were based on evaluation by an independent review committee (IRC).

* The CIRS (Refs) is an index to assess the medical burden of comorbid conditions with total scores ranging from 0 to a theoretical maximum of 56 with higher scores indicating more (or more severe) co-morbidities. Individual comorbidities are assessed in 14 organ systems; each comorbidity is rated with a score from 1-4. If there is >1 comorbidity in an organ system, only the comorbidity with the highest score counts towards the total CIRS score. Conditions that are commonly found to be related to CLL (ie, cytopenia or hypogammglobulinemia) should not be counted.

The trial was stopped for efficacy following the first pre-specified interim analysis. Results of the 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, $p < 0.0001$; see Table 6). This improvement was consistently demonstrated across all pre-specified subgroups (see Figure 2). Nineteen patients died through the cut-off date for the interim analysis; 6 in the ZYDELIG + rituximab group and 13 in the placebo + rituximab group. A statistically significant improvement in ORR was also observed. The Kaplan-Meier plot for PFS is provided in Figure 1.

Table 6. Efficacy Results from Study 312-0116

		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 †	
ORR*, n(%)		82 (74.5%)	16 (14.5%)
	Odds ratio (95% CI)	17.28 (8.66, 34.46)	
	P-value	< 0.0001 †	

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

* ORR defined as the proportion of subjects who achieved a CR or PR based on criteria described by Hallek (2008) as modified by Cheson.

† Actual p-values: for PFS, $p= 6 \times 10^{-11}$; for ORR, $p=6.3 \times 10^{-19}$

Figure 1. **Kaplan-Meier Plot of IRC Assessed PFS**

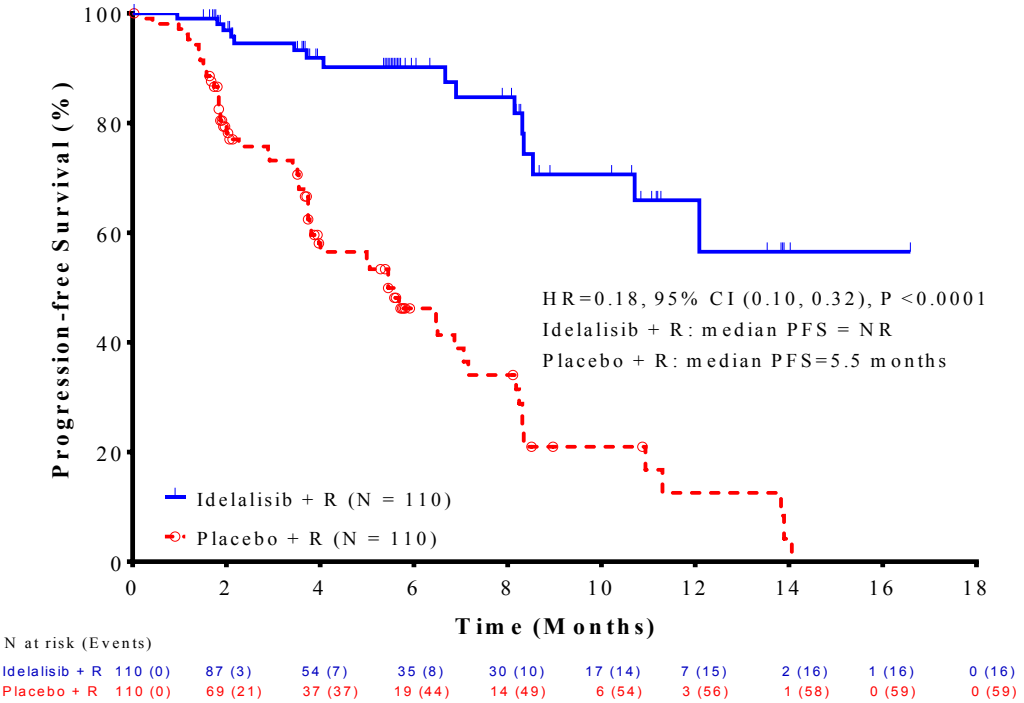
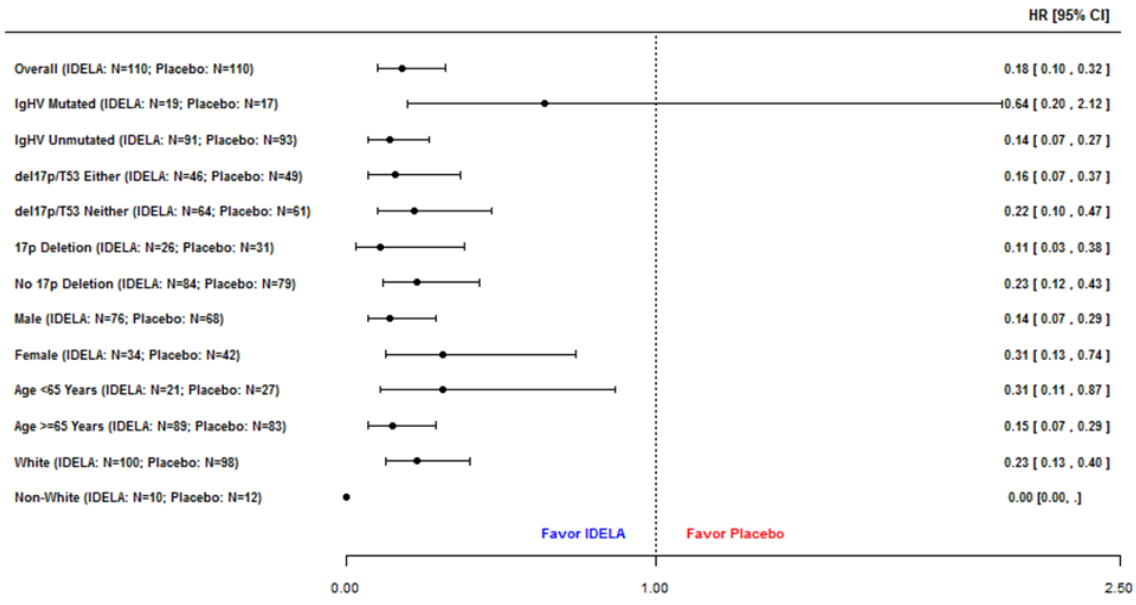


Figure 2. **Forest Plot of PFS Across Subgroups Favors ZYDELIG + Rituximab**



NOC/c

Follicular Lymphoma

The safety and efficacy of ZYDELIG was assessed in a single-arm, multicenter clinical trial that included 72 patients with follicular lymphoma who failed to respond or who had relapsed within 6 months of both rituximab therapy and an alkylating agent (separately or in combination). Subjects received ZYDELIG 150 mg taken 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 IRC-assessed overall response rate (ORR) summarized in Table 7.

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. Twenty-one patients (23.2%) had disease classified as Grade 1, 39 (54.2%) had disease classified as Grade 2, and 12 (16.7%) had disease classified as Grade 3a.

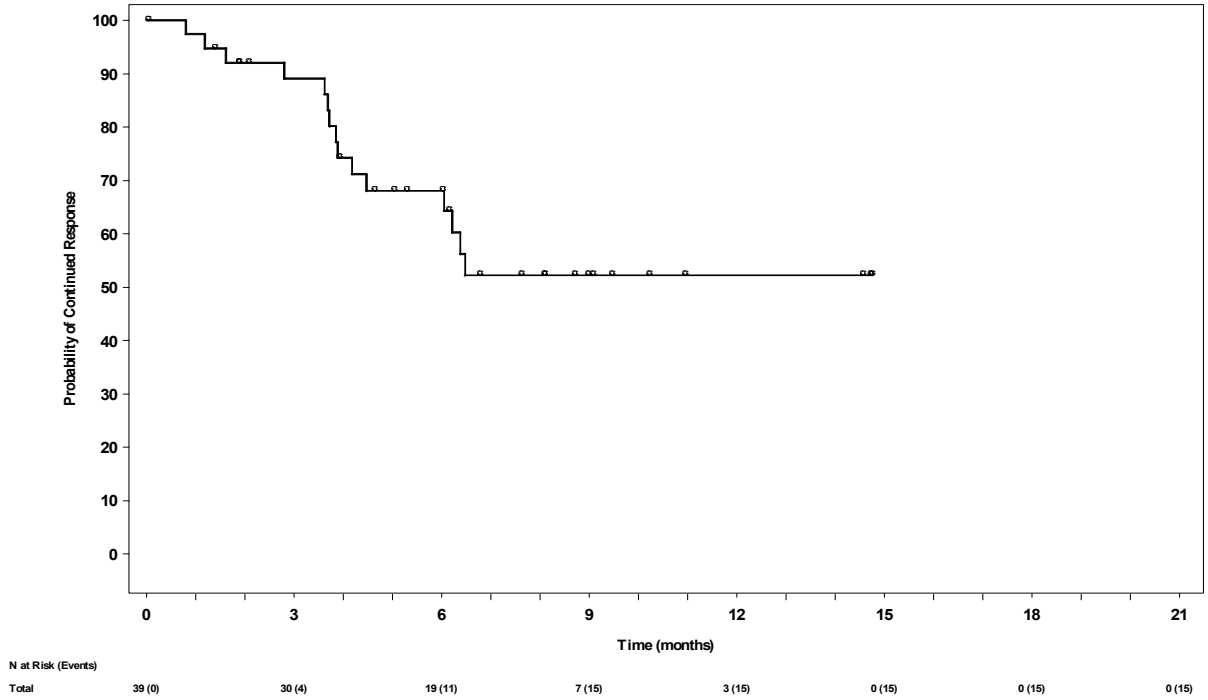
Table 7. Overall Response Rate (ORR) in Subjects with Follicular Lymphoma

	Number of Subjects (%) N=72
Overall Response (ORR)*	39 (54.2)
95% CI	(42, 66)
Response Category*	
CR	6 (8.3)
PR	33 (45.8)

* Response as determined by an independent review committee (IRC) where ORR = complete response (CR) + partial response (PR)

The median DOR could not be estimated due to the immaturity of the data (see Figure 3). Of the subjects who did not respond, 24 (33.3%) had stable disease, 8 (11.1%) had progressive disease, and 1 (1.4%) was not evaluable.

Figure 3. Kaplan-Meier Plot of IRC Assessed Duration of Response



DETAILED PHARMACOLOGY

Mechanism of Action

Idelalisib selectively inhibits PI3Kδ kinase, which is hyperactive in B-cell malignancies and is central to multiple signaling pathways that drive proliferation, survival, homing, and retention of malignant cells in lymphoid tissues and bone marrow. Idelalisib is a selective inhibitor of adenosine-5'-triphosphate (ATP) binding to the catalytic domain of PI3Kδ, resulting in inhibition of the phosphorylation of the key lipid second messenger phosphatidylinositol (PIP) and prevention of Akt phosphorylation.

Idelalisib induces apoptosis and inhibits proliferation in cell lines derived from malignant B-cells and in primary tumor cells. Idelalisib inhibits homing and retention of malignant B-cells in the tumor microenvironment including lymphoid tissues and the bone marrow.

SAFETY PHARMACOLOGY

TOXICOLOGY

Carcinogenesis

The carcinogenicity potential of idelalisib was evaluated in a 26-week transgenic RasH2 mouse study and a 2-year rat study. Idelalisib was not carcinogenic at exposures up to 1.4 and 7.9-fold (by AUC) in male and female mice, respectively compared to the exposure in patients with hematologic malignancies administered the recommended dose of 150 mg twice daily. A dose-dependent increase in pancreatic islet cell tumors was observed at low incidence in male rats at exposures up to 0.4-fold by AUC compared to the human exposure at the recommended dose; a similar finding was not observed in female rats at a 0.62-fold exposure margin.

Mutagenesis

Idelalisib did not induce mutations in the microbial mutagenesis (Ames) assay, was not clastogenic in the *in vitro* chromosome aberration assay using human peripheral blood lymphocytes. Idelalisib was genotoxic in male rats in the *in vivo* micronucleus assay at the highest dose of 2000 mg/kg.

Chronic Toxicity

In rats and dogs, the liver (hepatocellular necrosis), lymphoid tissues (lymphoid depletion) and the male reproductive system (hypospermatogenesis) were identified as target organs/tissues of toxicity in studies conducted up to 26 weeks in rats and 39 weeks in dogs. In dogs, serum transaminase elevations correlated with hepatic necrosis in studies up to 4 weeks; changes appeared to be transient and were not observed following chronic administration. Changes to lymphoid tissues (spleen, thymus, Peyer's patches) resulted from exaggerated pharmacologic activity of idelalisib.

In rats and dogs, changes in target organs/tissues were either completely or partially reversible following the non-dosing recovery period. In rats, these changes occurred at dose levels where plasma exposure to idelalisib was higher than that observed clinically in patients taking 150 mg idelalisib BID (≥ 2.5 times based on AUC). In dogs, these changes were noted at plasma levels below that observed in humans (≥ 0.25 times based on AUC).

Idelalisib's primary metabolite, GS-563117, has not been qualified in nonclinical repeat dose toxicology studies. Exposure to GS-563117 in rats and dogs in chronic toxicity studies were below that observed clinically in patients taking 150 mg BID.

Safety Pharmacology

There were no idelalisib-related acute effects on CNS function in rats at doses up to 150 mg/kg (approximately 9.2 times human exposure based on C_{max}).

Idelalisib did not produce any acute adverse effects on cardiovascular or respiratory function in dogs up to idelalisib doses of 20 mg/kg (approximately 4.1 times human exposure based on C_{max}). There was no treatment-related prolongation of QT_c interval observed at any dose level.

Reproductive Toxicology

In pregnant rats treated with idelalisib at 25, 75, or 150 mg/kg/day for 12 days (gestation day 6 to 17), postimplantation loss, lower mean fetal weights and skeletal development variations were observed at 75 and 150 mg/kg/day were observed (≥ 12 times human exposure based on AUC) .

Idelalisib was embryotoxic and teratogenic at dose levels inducing maternal toxicity in rats. Maternal toxicity was demonstrated by dose-dependent decreases in the body weight gains of the dams. Dose-dependent developmental findings included higher incidence of postimplantation loss, decrease in viable fetuses, and decreased mean fetal body weights. Dose-dependent external malformations included those of skeletal origin consistent with vertebral agenesis and short tails. Additional external malformations were single instances of hydrocephaly and microphthalmia, occurring in separate fetuses from different litters.

Fertility

The male reproductive system was a target organ of idelalisib toxicity in both rats and dogs. Idelalisib may impair fertility in humans. In male rats treated with idelalisib at 25, 50, or 100 mg/kg/day for 10 weeks, decreases in epididymides and testes weight were observed but with no adverse effects on mating or fertility parameters, and no degeneration or loss in spermatogenesis (≤ 7.8 times human exposure based on AUC).

Phototoxicity

Results in the *in vitro* 3T3 NRU phototoxicity assay were inconclusive for idelalisib due to cytotoxicity in the assay. GS-563117 may induce phototoxicity in the presence of UVA exposure.

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3. Extermann M. Measuring Comorbidity in Older Cancer Patients. Eur J of Cancer 2000, 36, 453-471.

4. Parmelee P, et al. Validation of the Cumulative Illness Rating Scale in a Geriatric Residential Population. J Amer Geriat Soc 1995, 43:130-137.

PART III. CONSUMER INFORMATION

ZYDELIG (idelalisib), indicated as monotherapy for the treatment of patients with follicular lymphoma who have received at least two prior systemic regimens and are refractory to both rituximab and an alkylating agent, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.

ZYDELIG (idelalisib), indicated in combination with rituximab for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL), has been issued marketing authorization without conditions.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

^{Pr}ZYDELIG®
(idelalisib) tablets

This leaflet is Part III of a three-part "Product Monograph" published when ZYDELIG was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about ZYDELIG. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ZYDELIG is used in adults to treat certain types of blood cancer:

- **Chronic Lymphocytic Leukemia (CLL):** ZYDELIG is used in combination with rituximab to treat CLL in patients who were previously treated for their cancer.

- **Follicular Lymphoma:** ZYDELIG is used alone to treat follicular lymphoma in patients who were previously treated at least twice for their cancer and who did not respond to both rituximab and an alkylating agent.

It is not known if ZYDELIG is safe and effective in children under the age of 18 years.

What it does:
ZYDELIG contains idelalisib, which belongs to a group of medicines called antineoplastic agents. It affects the growth of cancerous white blood cells, causing them to die.

When it should not be used:

Do not take ZYDELIG:

- as the first medicine to treat CLL or as the first or second medicine to treat follicular lymphoma.
- if you are allergic to idelalisib or to any nonmedicinal ingredient in the formulation.

What the medicinal ingredients are:
idelalisib

What the nonmedicinal ingredients are:
croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium starch glycolate, talc and titanium dioxide.

The 100 mg (orange) tablets are film-coated with a material containing: FD&C Yellow #6/Sunset Yellow

FCF Aluminum Lake, polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide.

The 150 mg (pink) tablets are film-coated with a coating material containing: red iron oxide, polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide.

What dosage forms it comes in:

Tablets: 100 mg, 150 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ZYDELIG should only be prescribed by a qualified physician who is experienced in the used of anti-cancer drugs.

Antibiotics to prevent one type of pneumonia called pneumocystis and monitoring for a viral infection called cytomegalovirus are required during your treatment with ZYDELIG and for 2 to 6 months after your treatment ends.

Serious side effects include:

- Serious infections that can lead to death.
- Liver damage.
- Severe diarrhea/colitis that can lead to death.
- Severe lung disorders that can lead to death.
- Severe skin reactions, including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, that can lead to death.

BEFORE and DURING treatment with ZYDELIG, talk to your doctor or pharmacist:

- If you have an infection.

Serious infections can happen during your treatment with ZYDELIG. Your doctor will prescribe a medicine and check your blood to reduce the risk of getting certain infections.

- If you notice or someone notices in you: trouble finding words, clumsiness of your limbs, falls or weakness, headaches, disturbance of vision, trouble remembering, confusion or changes in your personality or mood.

These symptoms may be due to a very rare but serious brain infection which can be fatal (Progressive Multifocal Leukoencephalopathy or PML).

- If you have liver problems.

Before and during treatment with ZYDELIG, you will have regular blood tests to check for the proper functioning of your liver. Your doctor may decide to stop treatment, or temporarily interrupt treatment to allow your liver to recover, before resuming treatment at a lower dose.

- If you have severe diarrhea.

Diarrhea is common with ZYDELIG and can sometimes be severe. Tell your doctor right away if the number of bowel movements you have in a day increases by four or more. Ask your doctor about medicines you can take to treat your diarrhea.

- If you have lung or breathing problems.

Your doctor may do tests to check your lungs if you have breathing problems during treatment with ZYDELIG. Tell your doctor right away if you get new or worsening cough, shortness of breath, difficulty breathing, or wheezing.

- If you have any other medical conditions.

You may become sensitive to the sun while taking ZYDELIG. Exposure to sunlight should be minimized until you know how you respond.

If you are pregnant or plan to become pregnant: ZYDELIG could harm your unborn child. Women who may become pregnant should use effective birth control (contraception) during treatment with ZYDELIG and for 1 month after stopping treatment. Talk to your healthcare provider about birth control methods that may be right for you. Tell your healthcare provider right away if you become pregnant during treatment with ZYDELIG.

***If you are breast-feeding or plan to breast-feed*:** You should not breast-feed during treatment with ZYDELIG.

Driving and using machines: Before doing tasks which require special attention, wait until you know how you respond to ZYDELIG. If you experience dizziness, trouble concentrating or drowsiness, you should not drive or operate machinery.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with ZYDELIG:

- carbamazepine, phenytoin (used to prevent seizures)
- rifampicin (used to prevent and treat tuberculosis and other infections)
- St. John's wort (*Hypericum perforatum*, a herbal remedy used for depression and anxiety)

- alfentanil, fentanyl (used for pain relief)
- cyclosporine, sirolimus, tacrolimus (used to control your body's immune response after a transplant)
- dihydroergotamine, ergotamine (used to treat migraine headache)
- pimozide (used to treat illnesses affecting the way you think, feel or behave)
- quinidine (used to correct irregular heartbeats)

PROPER USE OF THIS MEDICATION

It is very important that you see your doctor regularly while taking ZYDELIG.

Do not change your treatment or stop treatment without first talking with your doctor.

Take ZYDELIG every day exactly as your doctor prescribed it. Follow the directions from your doctor, exactly as written on the label. Set up a dosing schedule and follow it carefully.

ZYDELIG can be taken with or without food.

Only take medicine that has been prescribed specifically for you. Do not give ZYDELIG to others or take medicine prescribed for someone else.

Usual Adult Dose:

Chronic Lymphocytic Leukemia: One 150 mg tablet taken twice a day in combination with rituximab. Your doctor will decide on the dose of rituximab that is right for you.

Follicular Lymphoma: One 150 mg tablet taken twice a day.

Your doctor may reduce your dose of ZYDELIG to 100 mg twice a day if you experience side effects.

Overdosage:

If you think you may have taken too much ZYDELIG, immediately contact your doctor, hospital emergency department or regional Poison Control Centre, even if there are no symptoms.

Missed Dose:

It is important that you do not miss any doses. If you miss a dose of ZYDELIG and it is less than 6 hours from the time you usually take ZYDELIG, then take the dose right away. If more than 6 hours has passed from the time you usually take ZYDELIG, then wait until the next scheduled daily dose. Call your doctor or pharmacist if you are not sure what to do.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects of ZYDELIG may include:

- Diarrhea, nausea, vomiting
- Heartburn, stomach pain, decreased appetite
- Sores/ulcers in the mouth and/or on the lips
- Headache
- Fatigue, tiredness
- Trouble sleeping
- Stuffy nose, colds, sinus infections, bronchitis, cough
- Rash
- Fever, chills
- Night sweats
- Muscle pain

ZYDELIG can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

If you are concerned with any of the above side effects or other side effects not listed above, tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Very Common	**Liver Disorder:** yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
Very Common	**Severe diarrhea/ colitis:** increased number of bowel movements, watery or bloody stool,		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
	stomach pain and/or cramps			
Very Common	**Low levels of neutrophils in the blood:** fever, chills or sweating, or any signs of infection		√	
Very Common **<u>Serious infections may be fatal. Contact your healthcare provider immediately to report symptoms of infection.</u>**	**Serious Infections:** fever, sweats, or chills, cough or flu-like symptoms rapid breathing, shortness of breath, blood in your phlegm, muscle aches, stomach pain, burning when you urinate or urinating more often than normal		√	
Common	**Lung disorders (pneumonia, pneumonitis) :** Cough, difficult or painful breathing, wheezing, pain in chest when breathing, fever		√	
Common	**Serious skin reactions:** any combination of itchy skin rash that spreads quickly, redness, blistering and peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals			√
Uncommon	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Uncommon	**Progressive multifocal leukoence-phalopathy:** trouble finding words, clumsiness of your limbs, falls or weakness, headaches, disturbance of vision, trouble remembering, confusion or changes in your personality or mood.		√	

This is not a complete list of side effects. For any unexpected effects while taking ZYDELIG, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

- ZYDELIG should be stored below 30 °C (86 °F).
- Do not use ZYDELIG if the seal over the bottle opening is broken or missing.
- Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS
You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**

  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, can be found at: www.gilead.ca or by contacting the sponsor, Gilead Sciences Canada, Inc., at: 1-866-207-4267.

This leaflet was prepared by Gilead Sciences, Inc.

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