Product Information

ZYDELIG® (100 mg and 150 mg idelalisib) tablets

NAME OF THE MEDICINE

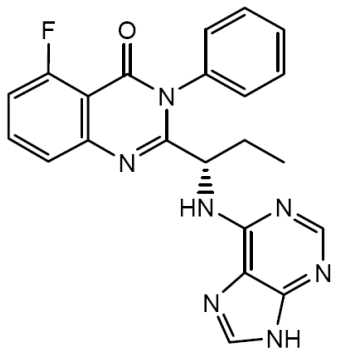
ZYDELIG (100 mg and 150 mg idelalisib) tablets.

The active substance in ZYDELIG tablets is idelalisib.

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

DESCRIPTION

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



CAS registry number: 870281-82-6

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. The partition coefficient (*log p*) for idelalisib is 2.0 and the pKa is 1.6, 3.4 and 9.8.

ZYDELIG 100 mg tablets are for oral administration. Each tablet contains 100 mg of idelalisib and the following ingredients as excipients:
Tablet core; microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, sodium starch glycolate, and magnesium stearate.
Film-coating: sunset yellow FCF aluminium lake (E110), macrogol 3350 (E1521), talc (E553B), polyvinyl alcohol (E1203), and titanium dioxide (E171).

ZYDELIG 150 mg tablets are for oral administration. Each tablet contains 150 mg of idelalisib and the following ingredients as excipients:
*Tablet core:*cellulose-microcrystalline, hydroxypropylcellulose, croscarmellose sodium, sodium starch glycolate, and magnesium stearate.
Film-coating: iron oxide red (E172), macrogol 3350 (E1521), talc (E553B), polyvinyl alcohol (E1203), and titanium dioxide (E171).

The tablets are supplied in bottles with child resistant closures.

PHARMACOLOGY

Pharmacotherapeutic group: antineoplastic agents, ATC code: L01XX47.

Mechanism of action

Idelalisib inhibits PI3Kδ kinase, which is hyperactive in B-cell malignancies and is central to multiple signalling 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 tumour cells. Idelalisib inhibits homing and retention of malignant B-cells in the tumour 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 patients. No significant changes in the baseline-corrected QTc based on Friderica's correction method (QTcF) (i.e., ≥10 ms) were observed.

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 and the binding is independent of concentrations observed clinically. The mean blood-to-plasma ratio was approximately 0.5.

Metabolism
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. GS-563117 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]-labelled idelalisib, approximately 78% and 15% was excreted in faeces and urine, respectively.

Effect of food
Relative to fasting conditions, administration of a single idelalisib dose with a high-fat meal resulted in no change in C_{max} and a 36% increase in mean $AUC_{inf.}$ Idelalisib can be administered without regard to food.

Age, Gender and Ethnicity
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.

Paediatric Population: The pharmacokinetics of idelalisib has not been studied in paediatric patients.

Elderly: 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 patients.

Patients with Impaired Renal Function
A study of pharmacokinetics and safety of idelalisib was performed in healthy patients and patients 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 patients with severe renal impairment compared to healthy patients. Therefore, no dose adjustment is necessary in patients with mild, moderate, or severe renal impairment.

Patients with Hepatic Impairment
A study of pharmacokinetics and safety of idelalisib was performed in healthy patients and patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. Following a single 150 mg dose, idelalisib AUC was ~60% (1.6 fold) higher in patients with moderate and severe hepatic

impairment compared to matched controls.As chronic use of ZYDELIG has not been studied in cancer patients with severe hepatic impairment, caution is recommended when administering ZYDELIG in this population. Patients with baseline hepatic impairment should be monitored for signs of ZYDELIG toxicity.

CLINICAL TRIALS

Chronic lymphocytic leukaemia (CLL)

ZYDELIG in combination with chemotherapy and immunotherapy

Study 312-0116

Study 312-0116 was a randomised, 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. Patients were randomised 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 ZYDELIG 150 mg taken twice daily until disease progression or unacceptable toxicity.

The median age was 71 (range 47, 92) with 78.2% 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. Patients 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 (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. Nearly all (95.9%) patients had received prior anti-CD20 monoclonal antibodies. The most common (>15%) prior regimens were: bendamustine + rituximab (98 patients, 44.5%), fludarabine + cyclophosphamide + rituximab (75 patients, 34.1%), single-agent rituximab (67 patients, 30.5%), fludarabine + rituximab (37 patients, 16.8%), and chlorambucil (36 patients, 16.4%). Most patients had adverse cytogenetic prognostic factors: 43.6% 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), lymph node response rate (LNR), and overall survival (OS). The primary analyses of PFS, ORR and LNR were based on assessment by an independent review committee (IRC) which included board-certified radiologists and oncologist/hematologists operating under an independent review charter.

The trial was stopped for overwhelming efficacy following the first pre-specified interim analysis. Results of the second interim analysis continued to show statistically significant improvement for ZYDELIG + rituximab over placebo + rituximab for the primary endpoint of PFS (HR: 0.18, p < 0.0001; see Table 1). This statistically significant improvement in PFS was consistently present in all pre-specified subgroups including patients with 17p deletion. ZYDELIG + rituximab also demonstrated a statistically significant improvement in overall survival over placebo + rituximab (HR: 0.28, p-value from stratified log-rank test = 0.003; see Table 1), in addition to a statistically significant improvement in ORR and LNR. Table 2 presents a summary of response rates (PFS and ORR) across pre-specified subgroups.

Table 1: Efficacy Results from Study 312-0116

		ZYDELIG + R n=110	**R + placebo n=110**
PFS	Median (months) (95% CI)	NR (10.7, NR)	5.5 (3.8, 7.1)
	Hazard ratio[1] (95% CI)	0.18 (0.10, 0.32)	
	P-value	< 0.0001 †	
ORR*		82 (74.5%)	16 (14.5%)
	(95% CI)	(65.4, 82.4)	(8.5, 22.5)
	Odds ratio	17.28 (8.66, 34.46)	
	P-value	< 0.0001 †	
Lymph Node Response **		94/102 (92.2%)	6/101 (5.9%)
	(95% CI)	(85.1, 96.6)	(2.2, 12.5)
	Odds ratio (95% CI)	165.5 (52.17, 524.98)	
	P-value	< 0.0001 †	
OS^	Median (months)	NR	NR
	(95% CI)	(NR, NR)	(12.8, NR)
	Hazard ratio (95% CI)	0.28 (0.11, 0.69)	
	P-value	0.003	

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

* ORR defined as the proportion of patients who achieved a CR or PR based on the 2013 NCCN response criteria and Cheson (2012). .

** Lymph node response defined as the proportion of patients who achieve a ≥50% decrease in the sum of products of the greatest perpendicular diameter (SPD) of index lesions. Only patients that had both baseline and ≥1 evaluable post-baseline SPD were included in this analysis

^ Overall survival (OS) analysis includes data from subjects who received placebo + R on study 312-0116 and subsequently received idelalisib in an extension study, based on intent-to-treat analysis

† Actual p-values: for PFS, $p= 6 \times 10^{-11}$; for ORR, $p=6.3 \times 10^{-19}$; for LNR, $p=4.1 \times 10^{-34}$

[1] Hazard ratio estimate is based on a Cox model adjusted for stratification factors 17p deletion/TP53 mutation and IgHV mutation status.

Table 2: Summary of PFS and ORR in Pre-specified Subgroups from Study 312-0116

		ZYDELIG + R	R + placebo
17p deletion/TP53 Mutation		**n=46**	**n=49**
	Median PFS (95% CI)	NR (8.3, NR)	4.0 (3.5, 5.7)
	Hazard Ratio (95% CI)	0.16 (0.07, 0.37)	
	ORR	78.3%	12.2%
	95% CI	63.6, 89.1	4.6, 24.8
unmutated *IGHV*		**n=91**	**n=93**
	Median PFS (95% CI)	NR (NR, NR)	5.5 (3.8, 6.9)
	Hazard Ratio (95% CI)	0.14 (0.07, 0.27)	
	ORR	73.6%	15.1%
	95% CI	63.3, 82.3	8.5, 24.0
Age ≥ 65 years		**n=89**	**n=83**
	Median PFS (95% CI)	NR (12.1, NR)	5.5 (3.7, 7.1)
	Hazard Ratio (95% CI)	0.15 (0.07, 0.29)	
	ORR	74.2%	15.7%
	95% CI	63.8, 82.9	8.6, 25.3

R: rituximab; NR: not reached

Study 101-07

Study 101-07 was an open-label study that enrolled 114 patients with relapsed or refractory CLL and 80 patients with iNHL. Patients received ZYDELIG in combination with chemotherapy and/or immunotherapy. The ORR (CR+PR) for the 114 CLL patients across all treatment arms was 82.5%, with 7 CRs and 87 PRs and a median duration of response (DOR) of 23.9 months. For patients receiving ZYDELIG in combination with an anti-CD20 monoclonal antibody, the ORR was 82.5%, with a median DOR of 23.9 months. For patients receiving ZYDELIG in combination with chemotherapy (bendamustine, chlorambucil, or fludarabine) and/or an anti-CD20 monoclonal antibody, the ORR was 82.4%, with a median DOR of 26.6 months.

Study 101-08

Study 101-08 enrolled 64 patients with previously untreated CLL, including 5 with SLL. The median age was 71 (range 65, 90), 62.5% were male, 95.3% were white. Of the 64 patients, 9 (14.1%) had 17p deletion and/or *TP53* mutation, and 37 (57.8%) had an unmutated IGHV. Patients received ZYDELIG 150 mg twice daily and rituximab 375 mg/m^2 weekly. The ORR was 96.9%, with 12 CRs (18.8%) and 50 PRs (78.1%); the 2 patients who didn't respond were not evaluable. The median DOR has not been reached. Of the 9 patients with a 17p deletion and/or *TP53* mutation, 3 had a CR and 6 had a PR. Of the 37 patients with unmutated IGHV, 2 had a CR and 34 had a PR. For the 5 patients with SLL, the ORR was 100%.

ZYDELIG as a single agent

The safety and efficacy of ZYDELIG as a single agent were evaluated in 54 patients with chronic lymphocytic leukaemia (CLL) in Study 101-02 .

Study 101-02 enrolled 54 patients with CLL and 11 patients with SLL. The median age was 62.5 years (range 37, 82); 83.3% were male, and 88.9% were white. Of the 54 patients, 13 (24.1%) had 17p deletion and/or *TP53* mutation, and 49 (90.7%) patients had unmutated IGHV, all of which are established markers for poor prognosis. Patients were heavily pre-treated with a median of 5 regimens, and all had previously received anti-CD20 monoclonal antibodies. Patients received ZYDELIG at doses ranging from 50 mg to 350 mg, once or twice daily. Eleven patients with CLL and 2 with SLL received the recommended dosage of 150 mg twice daily.

The ORR for Study 101-02 was 72.2% (95% CI 58.4, 83.5) with a median DOR of 16.2 months (95% CI 4.6, 40.9). In the 13 patients who received 150 mg twice daily, the ORR was 81.8% (95% CI 48.2, 97.7) and the median DOR was 8.1 months (95% CI 2.6, 39.8). The ORR for SLL patients in Study 101-02 was 54.5% (95% CI 23.4, 83.3) and the median DOR was 2.3 months (95% CI 1, NR).

Fifteen patients did not respond; of these, 12 (22.2%) had stable disease and 3 (5.6%) were not evaluable. For the 13 patients with a 17p deletion and/or *TP53* mutation, the ORR was 38.5% (95% CI 13.9, 68.4) and the DOR was 9.2 months.

Follicular Lymphoma

Study 101-09

The safety and efficacy of ZYDELIG were assessed in a single-arm, multicentre clinical trial (study 101-09) conducted in 125 patients with indolent B-cell non-Hodgkin lymphoma who had a history of failing to respond or having relapsed within 6 months of both rituximab therapy and an alkylating agent (separately or in combination). Patients received 150 mg of ZYDELIG orally twice daily until evidence of disease progression or unacceptable toxicity.

Of the 125 patients enrolled, 80 (64%) were male, the median age was 64 (range 33 to 87), and 110 (89%) were white. Table 3 presents details of disease characteristics at time of study entry.

Table 3. Disease Characteristics at Study Entry

Diagnosis	Number of Patients (%)
Follicular Lymphoma	72 (57.6)
Grade: Grade 1	21 (29.2)
Grade 2	39 (54.2)
Grade 3a	12 (16.7)
FLIPI: Low (≤ 1)	15 (20.8)
Intermediate (2)	18 (25.0)
High (≥ 3)	39 (54.2)
Small Lymphocytic Lymphoma	28 (22.4)
Lymphoplasmacytic Lymphoma/Waldenström macroglobulinemia	10 (8.0)
Marginal Zone Lymphoma	15 (12.0)

All patients had received rituximab and an alkylating agent. Most patients had received cyclophosphamide (89%) and/or bendamustine (65%). The most common prior regimens (>20%) were BR (48%), R-CHOP (45%), and R-CVP (29%). All patients were refractory to rituximab and 124 of 125 patients were refractory to at least one alkylating agent. One hundred and twelve (89.6%) patients were refractory to their last regimen prior to study entry.

The primary endpoint was the overall response rate (ORR) defined as the proportion of patients who achieved a complete response (CR) or partial response (PR) based on the Revised Response Criteria for Malignant Lymphoma (Cheson). Duration of response (DOR) was a secondary endpoint and was defined as the time from the first documented response (CR, PR, or MR) to the first documentation of disease progression or death from any cause. Efficacy results on ORRare summarised in Table 4.

Table 4. Summary of response in patients with Follicular Lymphoma treated with ZYDELIG (IRC assessment)

Characteristic	Study Patients n (%)
ORR*(follicular lymphoma) 95% CI	39 (54.2) 42.0 – 66.0
ORR*(all patients)* 95% CI	71 (56.8) 47.6 – 65.6
Response Category*(follicular lymphoma)	
CR	6 (8.3)
PR	33 (45.8)

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

The median DOR was 12.5 months as estimated using the Kaplan-Meier method. Of the patients who did not respond, 42 (33.6%) had stable disease, 10 (8.0%) had progressive disease, and 2 (1.6%) were not evaluable.

INDICATIONS

ZYDELIG in combination with rituximab is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) for whom chemo-immunotherapy is not considered suitable, either:

- upon relapse after at least one prior therapy, or
- as first-line treatment in the presence of 17p deletion or TP53 mutation.

ZYDELIG is indicated as monotherapy for the treatment of patients with refractory follicular lymphoma who have received at least two prior systemic therapies.

CONTRAINDICATIONS

ZYDELIG tablets are contraindicated in patients with known hypersensitivity to the active substance or to any other component of the tablets.

PRECAUTIONS

Hepatotoxicity

Elevations in ALT and AST Grade 3 and 4 (greater than 5 times the upper limit of normal) have occurred with ZYDELIG. These laboratory findings were generally observed within the first 12 weeks of treatment, were generally asymptomatic, and were reversible with dose interruption. Most patients resumed treatment at a lower dose without recurrence (see DOSAGE AND ADMINISTRATION). Monitor ALT, AST, and total bilirubin in all patients every 2 weeks for the first 3 months of treatment, then as clinically indicated. If Grade 2 or higher elevations in ALT and/or AST are observed, monitor weekly until resolved to Grade 1 or below.

Intensified monitoring of side effects is recommended in patients with impaired hepatic function as exposure is expected to be increased in this population, in particular in patients with severe hepatic impairment (see PHARMACOLOGY). No patients with severe hepatic impairment were included in clinical studies of idelalisib. Caution is recommended when administering ZYDELIG in this population.

Hepatitis Infection and Reactivation

Idelalisib has not been studied in patients with chronic active hepatitis including viral hepatitis. Caution should be exercised when administering ZYDELIG in patients with active hepatitis.

All patients should be screened for hepatitis B viruses (HBV) and hepatitis C viruses (HCV) in accordance with local guidelines prior to starting treatment with ZYDELIG. Such screening should at least include determination of HBsAg and anti-HBc, and be expanded to cover other appropriate markers. A single case of treatment-emergent hepatitis B reactivation occurred in a patient with iNHL who was receiving ZYDELIG with concomitant bendamustine and rituximab.

Diarrhoea/Colitis

Severe diarrhoea or colitis (Grade 3 or higher) occurred in 14% of ZYDELIG-treated patients across clinical studies (see ADVERSE EVENTS). Diarrhoea occurred relatively late (months) after the start of therapy and resolved between one week and one month following drug interruption and additional symptomatic treatment (e.g., corticosteroids, antidiarrhoeal and anti-inflammatory agents such as enteric budesonide) (see DOSAGE AND ADMINISTRATION). Of these patients, 58% resumed treatment without any recurrence of diarrhoea. Infectious causes (e.g., *Clostridum difficile*) should be excluded when assessing patients with colitis. Assessment of hydration status should be considered for all patients with diarrhoea, especially in those with increased risk for dehydration, such as pre-existing renal failure.

Pneumonitis

Cases of pneumonitis, some with a fatal outcome have occurred with ZYDELIG. Patients presenting with pulmonary symptoms or radiographic appearances consistent with drug-induced pneumonitis should be assessed. If pneumonitis is suspected, idelalisib should be interrupted and the patient treated accordingly. Where moderate-severe symptomatic pneumonitis occurs, ZYDELIG should not be reinstituted (see DOSAGE and ADMINISTRATION).

Immunisation

The safety of immunisation with live or inactivated live vaccines in association with idelalisib therapy has not been studied, and vaccination with live vaccines is not recommended. For patients who are at substantial risk of an infection (e.g., influenza or pneumococcal sepsis), consideration should be given to providing the vaccine prior to idelalisib treatment.

Neutropenia, Anaemia, Lymphopenia and Thrombocytopenia

Treatment-emergent neutropenia, anaemia, lymphopenia and thrombocytopenia have occurred in ZYDELIG-treated patients across clinical trials. Severe cases should be managed through temporary dose interruptions until resolved (see DOSAGE AND ADMINISTRATION).

Severe Cutaneous Reactions

Severe mucocutaneous reactions can occur in the setting of haematological malignancies and have been reported in association with idelalisib use. In the case of such an event, treatment should be discontinued.

Intestinal Perforation

Fatal and serious intestinal perforation occurred in ZYDELIG-treated patients. At the time of perforation, some patients had moderate to severe diarrhoea. 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.

Progressive Multifocal Leukoencephalopathy (PML)

PML has been reported in patients with CLL receiving cytotoxic pharmacotherapy. A single case of PML occurred in one study of ZYDELIG in a patient with CLL who had previously received rituximab. A diagnosis of PML should be considered in any patient receiving ZYDELIG who reports the new onset of, or changes in pre-existing neurologic signs and symptoms.

Transient Lymphocytosis

Transient lymphocytosis has occurred in ZYDELIG-treated patients across clinical trials. Lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings.

Infections

Infections have occurred in ZYDELIG-treated patients across clinical trials; however a causal relationship to ZYDELIG has not been established. Patients with fever and other signs of infection should be evaluated promptly and treated accordingly.

Effects on Fertility

Idelalisib did not affect male or female fertility in conventional rat fertility and early embryonic development studies at doses ≤100 mg/kg/day (resulting in exposures [AUC] 8 and 15 times the clinical AUC in males and females, respectively). However, embryolethality was observed. Idelalisib caused seminiferous tubular atrophy/degeneration and hypospermatogenesis in rats and dogs treated chronically with idelalisib. A NOEL was not established. Exposures (AUC) at the LOEL were subclinical.

Females of reproductive potential should be advised to use highly-effective contraception while taking ZYDELIG and for 1 month after stopping treatment. The effect of idelalisib on oral contraceptives is unknown.

Use in Children:
The safety and efficacy of ZYDELIG in children under the age of 18 years have not been established. No data are available (see DOSAGE AND ADMINISTRATION).

Use in Pregnancy

Pregnancy Category D

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

Based on findings in animals (see below), idelalisib may cause fetal harm when administered to a pregnant woman. 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 use highly-effective contraception methods while receiving idelalisib.

Embryofetal lethality (increased post-implantation loss), embryofetal toxicity (reduced fetal weights and incomplete ossification) and teratogenicity (short tail, anury, vertebral agenesis, micropthalmia/anophthalmia and hydrocephaly) were seen in rats that received oral doses of idelalisib (≥75 mg/kg/day) during the period of organogenesis. Exposure (AUC) at the NOAEL for embryofetal effects was approximately equivalent to the clinical AUC.

Use in Lactation

It is not known whether idelalisib is excreted in human milk.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ZYDELIG therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Due to the effects of idelalisib on fertility, its use is not recommended during pregnancy or lactation.

Genotoxicity

Idelalisib did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in the *in vitro* chromosome aberration assay using human peripheral blood lymphocytes. An in vivo rat micronucleus study gave equivocal results. The risk of genotoxicity is considered low.

Carcinogenicity

Carcinogenicity studies with idelalisib have not been conducted.

Malignancies: There is an increased incidence of second malignancies in patients with CLL. Data from the pivotal study in patients with CLL does not demonstrate an increased risk of second malignancies following ZYDELIG therapy.

INTERACTIONS WITH OTHER MEDICINES

Established and Other Potentially Significant Interactions

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.

CYP3A Inhibitors

Co-administration of ZYDELIG with a strong CYP3A inhibitor (ketoconazole) resulted in a 26% increase in ZYDELIG C_{max} and a 79% increase in $AUC_{inf.}$ While no initial dose adjustment of ZYDELIG is considered necessary when administered with a CYP3A inhibitor, intensified monitoring of side effects is recommended.

Effects of ZYDELIG on Other Drugs

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

ZYDELIG is a strong CYP3A inhibitor; plasma AUC of sensitive CYP3A substrate, midazolam increased 440% with ZYDELIG. 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.

Effects on ability to drive and use machines

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

ADVERSE EFFECTS

Experience from Clinical Trials

Assessment of adverse reactions is based on 1 Phase 3 study and 7 Phase 1 and 2 studies. Phase 3 Study 312-0116 was a randomized, double-blind, placebo-controlled study in which 220 relapsed CLL patients were randomized 1:1 to receive ZYDELIG + rituximab or placebo + rituximab. The Phase 1 and 2 studies assessed the safety of ZYDELIG in 490 patients with haematologic malignancies, including 354 patients who received ZYDELIG (any dose) as a single agent and 136 patients who received ZYDELIG in combination with other therapies.

The frequencies of adverse drug reactions reported with ZYDELIG alone or in combination with chemotherapy (including monoclonal antibodies) are summarised in Table 5.

Table 5: Adverse Drug Reactions Reported in Clinical Trials in Patients with Haematologic Malignancies Receiving ZYDELIG

Reaction	Any Grade	Grade ≥ 3
Blood and lymphatic system disorders:		
Neutropenia	298 (49.7%)	165 (27.5%)
Respiratory, thoracic and mediastinal disorders		
Pneumonitis	20 (3.3%)	13 (2.2%)
Gastrointestinal disorders		
Diarrhoea/colitis	229 (38.2%)	84 (14.0%)
Hepatobiliary disorders		
Transaminase increased	293 (48.8%)	89 (14.8%)
Skin and subcutaneous tissue disorders		
Rash*	146 (24.3%)	27 (4.5%)
General disorders and administration site conditions		
Pyrexia	189 (31.5%)	13 (2.2 %)

* Includes the preferred terms dermatitis exfoliative, drug eruption, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash morbilliform, and exfoliative rash.

DOSAGE AND ADMINISTRATION

The recommended dose of ZYDELIG for adults is 150 mg, taken orally, twice daily.

Continue treatment until disease progression or unacceptable toxicity.

ZYDELIG can be taken with or without food.

Dose Modification

See Table 6 for dose modification instructions for specific toxicities related to ZYDELIG.

Table 6: Dose Modifications for Toxicities Due to ZYDELIG

Hepatotoxicity (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.
	If the event does not recur, the dose can be escalated to 150 mg twice daily at the discretion of the treating physician. If the event recurs, withhold until return to Grade 1 or below, after which re-initiation may be considered at the discretion of the physician.		
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.
Diarrhoea	**Grade 2**	**Grade 3**	**Grade 4**
	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.
	If diarrhea does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician (see ADVERSE EFFECTS).		
Neutropenia	**ANC 1.0 to <1.5 $x10^9$/L**	**ANC 0.5 to <1.0 $x10^9$/L**	**ANC <0.5 $x10^9$/L**
	Maintain ZYDELIG g dose.	Maintain ZYDELIG dose. Monitor ANC at least weekly.	Interrupt ZYDELIG. Monitor ANC at least weekly until ANC ≥0.5 $x10^9$/L, then may resume ZYDELIG at 100 mg BID.
Thrombocytopenia	**Platelets 50 to <75 $x10^9$/L**	**Platelets 25 to <50 $x10^9$/L**	**Platelets <25 $x10^9$/L**
	Maintain ZYDELIG dose.	Maintain ZYDELIG dose. Monitor platelet counts at least weekly.	Interrupt ZYDELIG. Monitor platelet count at least weekly. May resume ZYDELIG at 100 mg BID when platelets ≥25 $x10^9$/L.
Rash	**Moderate Rash**	**Severe Rash**	**Comment**

	Maintain ZYDELIG dose. Monitor until resolved.	Withhold ZYDELIG for rash of Grade 3 or 4. Once rash has returned to Grade 1 or below, resume ZYDELIG at 100 mg BID.	If rash does not recur, the dose can be re-escalated to 150 mg BID at the discretion of the treating physician.
Pneumonitis	**Any symptomatic pneumonitis**		**Comment**
	Discontinue ZYDELIG in patients with any severity of symptomatic pneumonitis		Once pneumonitis has resolved and if re-treatment is appropriate, resumption of treatment at 100 mg BID can be considered.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; ULN, upper limit of normal			

Special patient populations

Elderly
No specific dose adjustment is required for elderly patients (aged ≥ 65 years) (see PHARMACOLOGY).

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

Hepatic impairment
No dose adjustment is required when initiating treatment with ZYDELIG in patients with mild or moderate hepatic impairment, but an intensified monitoring of side effects is recommended (see PRECAUTIONS). There is insufficient data to make dose recommendations for patients with severe hepatic impairment. Therefore, caution is recommended when administering ZYDELIG in this population and intensified monitoring of side effects is recommended (see PRECAUTIONS).

Paediatric population
The safety and efficacy of ZYDELIG in children under the age of 18 years have not been established. No data are available (see PRECAUTIONS).

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 information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) and 0800 764 766 (New Zealand).

PRESENTATION AND STORAGE CONDITIONS

ZYDELIG is available as tablets. Each tablet contains 100 mg or 150 mg of idelalisib.

Each 100 mg ZYDELIG tablet is oval-shaped, film-coated and orange in colour. Each tablet is debossed with 'GSI' on one side and '100' on the other side. Each 150 mg ZYDELIG tablet is oval-shaped, film-coated and pink in colour. Each tablet is debossed with 'GSI' on one side and '150' on the other side.

ZYDELIG is supplied in high density polyethylene (HDPE) bottles containing 60 tablets and a polyester coil and is closed with a child resistant closure.

ZYDELIG should be stored below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Gilead Sciences Pty Ltd
Level 6, 417 St Kilda Road
Melbourne, Victoria 3004

POISON SCHEDULE OF THE DRUG

S4

DATE OF FIRST INCLUSION ON ARTG

9 February 2015