Product Information

ZYDELIG® (100 mg and 150 mg idelalisib) tablets

Idelalisib can cause serious infections. The increased risk of infection may be due to immunomodulatory effects of the drug.

In three large randomised studies in relapsed early-line iNHL and first-line CLL patients, more patients died in idelalisib-containing arms than in placebo-containing arms (7.4% vs 3.5%). Death often occurred within 180 days of treatment starting (4.4% vs 1.0% respectively) and was often due to infection (e.g. sepsis and pneumonia). These studies were stopped early.

In approved uses of idelalisib, the risk of serious infection is also considered present, therefore:

- Do not start idelalisib treatment in patients with active infection.
- Use antibiotic prophylaxis against *Pneumocystis jirovecii* throughout idelalisib treatment and for a period of time after treatment is stopped.
- Monitor closely for laboratory and clinical evidence of CMV infection. Use of idelalisib may need to be interrupted or stopped.

See PRECAUTIONS – Serious Infection.

Idelalisib can cause fatal pneumonitis. Some of the imbalance in deaths noted above may have been due to idelalisib-induced pneumonitis. See PRECAUTIONS – Pneumonitis.

NAME OF THE MEDICINE

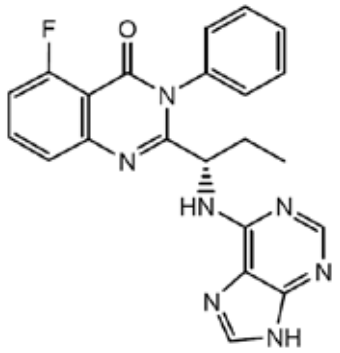
ZYDELIG (100 mg and 150 mg idelalisib) tablets.

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, hyprolose, 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, hyprolose, 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 years (range 47, 92 years) with 78.2% over 65, 65.5% were male, 90.0% were white, 64.1% 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 92 (41.8%) had endocrine/metabolic comorbidities. Two hundred and eight (94.5%) 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 (38 patients, 17.3%), and chlorambucil (36 patients, 16.4%).

Most patients 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), 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 final analysis continued to show statistically significant improvement for ZYDELIG + rituximab over placebo + rituximab for the primary endpoint of PFS (HR: 0.15, $p < 0.0001$; see Table 1). This statistically significant improvement in PFS was consistently present in all pre-specified subgroups including patients with 17p deletion/TP53 mutation. ZYDELIG + rituximab also demonstrated a statistically significant improvement in overall survival over placebo + rituximab (HR: 0.34, p-value from stratified log-rank test = 0.0001; see Table 1), in addition to a statistically significant improvement in ORR and LNR. No CRs were observed in either arm. Table 2 presents a summary of response rates (PFS and ORR) across pre-specified subgroups. The Kaplan-Meier curve for PFS is provided in Figure 1.

Table 1: Efficacy Results from Study 312-0116

		ZYDELIG + R n=110	R + placebo n=110
PFS	Median (months) (95% CI)	19.4 (12.3, NR)	6.5 (4.0, 7.3)
	Hazard ratio[1] (95% CI)	0.15 (0.09, 0.24)	
	P-value	< 0.0001 †	
ORR*		92 (83.6%)	17 (15.5%)
	(95% CI)	(75.4, 90.0)	(9.3, 23.6)
	Odds ratio	27.76 (13.40, 57.49)	
	P-value	< 0.0001 †	
Lymph Node Response **		102/106 (96.2%)	7/104 (6.7%)
	(95% CI)	(90.6, 99.0)	(2.7, 13.4)
	Odds ratio (95% CI)	225.83 (65.56, 777.94)	
	P-value	< 0.0001 †	
OS^	Median (months)	NR	20.8
	(95% CI)	(NR, NR)	(14.8, NR)
	Hazard ratio (95% CI)	0.34 (0.19, 0.60)	
	P-value	0.0001	

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). No CRs were observed.

** 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 patients 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, $p= 1.6 \times 10^{-16}$; for ORR, $p=1.3 \times 10^{-23}$; for LNR, $p= 8.5 \times 10^{-38}$

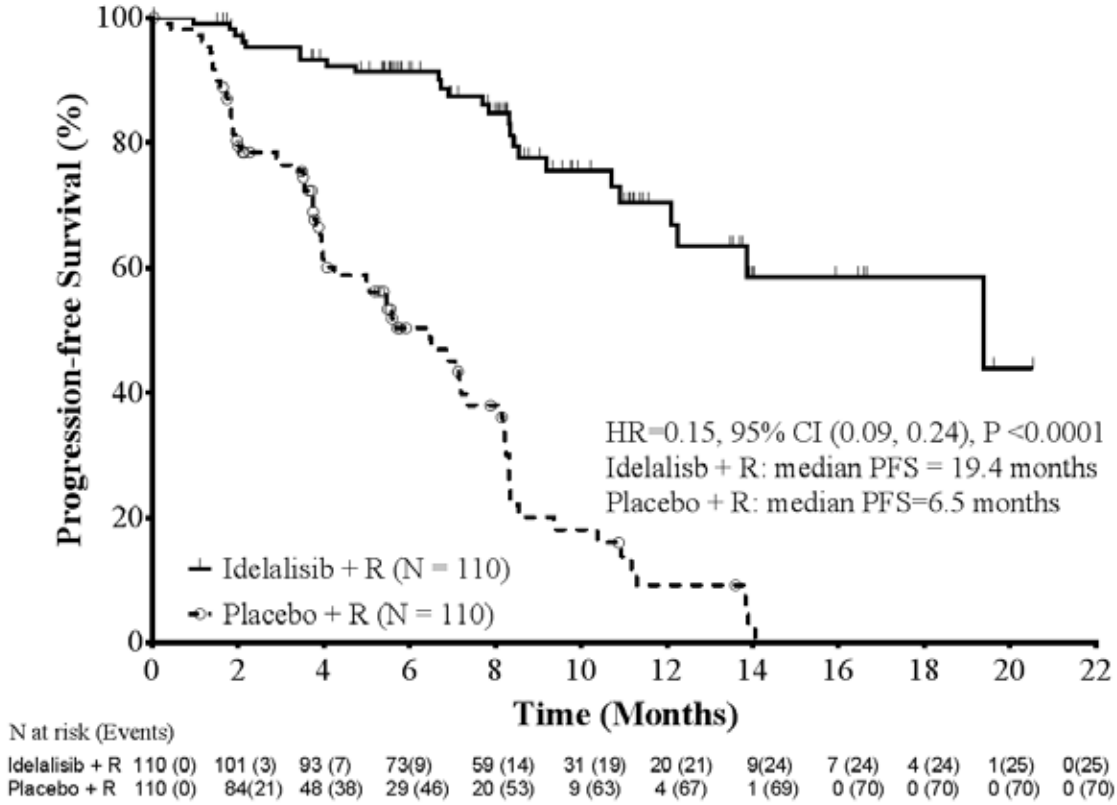
[1] Hazard ratio estimate is based on a Cox model adjusted for stratification factors 17p deletion/TP53 mutation and IgHV mutation status.

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 (12.3, NR)	4.0 (3.7, 5.7)
	Hazard Ratio (95% CI)	0.13 (0.07, 0.27)	
	ORR	84.8%	12.2%
	95% CI	71.1, 93.7	4.6, 24.8
unmutated *IGHV*		**n=91**	**n=93**
	Median PFS (95% CI)	19.4 (13.9, NR)	5.6 (4.0, 7.2)
	Hazard Ratio (95% CI)	0.14 (0.08, 0.23)	
	ORR	82.4%	15.1%
	95% CI	73.0, 89.6	8.5, 24.0
Age ≥ 65 years		**n=89**	**n=83**
	Median PFS (95% CI)	19.4 (12.3, NR)	5.7 (4.0, 7.3)
	Hazard Ratio (95% CI)	0.14 (0.08, 0.25)	
	ORR	84.3%	16.9%
	95% CI	75.0, 91.1	9.5, 26.7

R: rituximab; NR: not reached

Figure 1: Kaplan-Meier curve of PFS from study 312-0116 (intent-to-treat population)



The analysis of PFS was based on evaluation by an IRC. For patients in the placebo + R group, the summary includes data up to the first dosing of idelalisib in an extenstion study.

Study 312-0119

ZYDELIG was evaluated in a randomised, open-label, multicenter, controlled, parallel-group study in 261 patients with relapsed CLL who had measurable lymphadenopathy, required treatment, and experienced CLL progression <24 months since the completion of the last prior treatment. Patients were randomised 2:1 to receive ZYDELIG 150 mg taken twice daily with 12 infusions of ofatumumab over 24 weeks (ZYD + O), or 12 infusions of ofatumumab only over 24 weeks (O). The first infusion of ofatumumab was administered at a dose of 300 mg and was continued with a dose of either 1000 mg (ZYDELIG + O) or 2000 mg (O) weekly for 7 doses, and then every 4 weeks for 4 doses. ZYDELIG was taken until disease progression or unacceptable toxicity.

The median age was 68 (range 36 to 85) with 64.0% over 65 years of age, 71.3% were male, 84.3% were white, 63.6% had a Rai stage of III or IV, and 58.2% had Binet Stage C. Patients had a median CIRS score of 4. The median time since diagnosis was 7.7 years and the median number of prior therapies was 3. The most common last prior regimens were: bendamustine + rituximab (28.7%), fludarabine + cyclophosphamide + rituximab (21.5%), fludarabine + rituximab (5.4%), and single-agent rituximab (5.0%).

The primary endpoint was PFS, as assessed by an IRC. Results of the final analysis showed a statistically significant improvement for ZYDELIG + ofatumumab over ofatumumab alone for PFS (HR: 0.27, 95% CI [0.19, 0.39], p < .0001).

ZYDELIG + ofatumumab also demonstrated a statistically significant improvement in ORR and LNR.

A statistically significant difference OS between treatment groups was not achieved. Overall, a total of 64 patients died on study (42 patients in the ZYDELIG + ofatumumab group and 22 patients in the ofatumumab alone group) with an adjusted HR (95% CI) of 0.74 (0.44, 1.25); p=0.27.

The efficacy results are shown in Table 3 and the Kaplan-Meier curve for PFS is shown in Figure 1.

Table 3: Summary of PFS and Response Rates from Study 312-0119

		ZYDELIG + O n= 174	**Ofatumumab n= 87**
PFS	Number (%) of Patients with Events	76 (43.7%)	54 (62.1%)
	Disease Progression	54 (31.0%)	48 (55.2%)
	Death	22 (12.6%)	6 (6.9%)
	Median (months) (95% CI)	16.3 (13.6, 17.8)	8.0 (5.7, 8.2)
	Hazard ratio[1] (95% CI)	0.27 (0.19, 0.39)	
	P-value	<0.0001	
ORR*		131 (75.3%)	16 (18.4%)
	(95% CI)	(68.2, 81.5)	(10.9, 28.1)
	CR (%)	1 (0.6)	0
	PR (%)	130 (74.7)	16 (18.4)
	Odds Ratio (95% CI)	15.94 (7.8, 32.58)	
	P-value	<0.0001	
Lymph Node Response**		153/164 (93.3%)	4/81 (4.9%)
	Odds ratio (95% CI)	486.96 (97.91, 2421.85)	
	P-value	<0.0001	

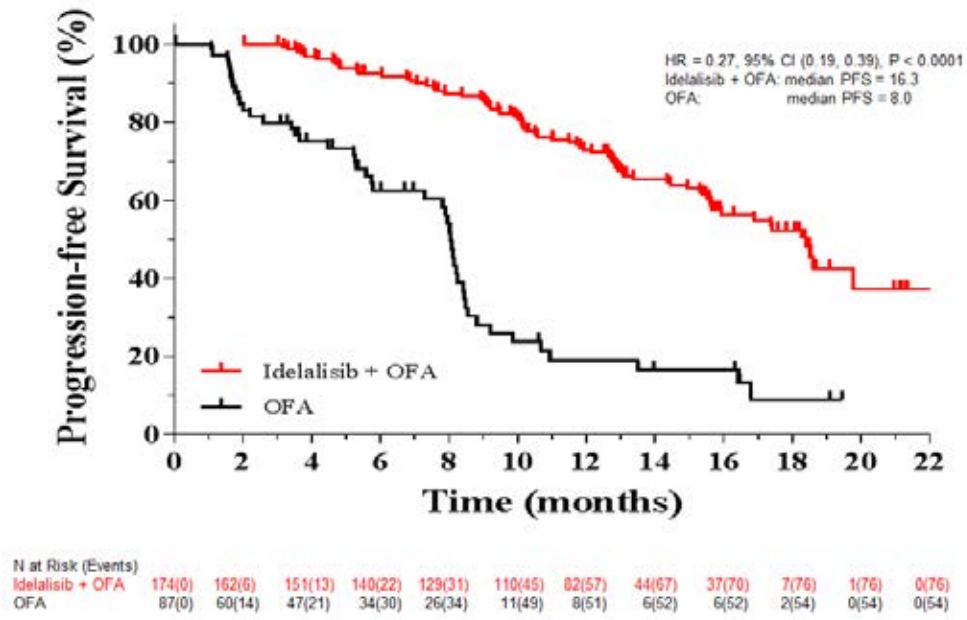
O: ofatumumab; PFS: progression-free survival; ORR: overall response rate

* ORR defined as the proportion of patients who achieved a CR or PR and maintained response for at least 8 weeks.

** 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 lesion.

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

Figure 1: Kaplan-Meier Plot of PFS for Study 312-0119



Study 312-0116 and 312-0119 Patients with 17p deletion and/or TP53 mutation

Study 312-0116 included 95 patients with the presence of 17p deletion and/or TP53 mutation. The median age was 69 years (range, 48 to 90 years), 63% were male, and 89% were white. Study 312-0119 included 103 patients with the presence of either 17p deletion and/or TP53 mutation. The median age was 68 years (range, 49 to 84 years), 66% were male, and 81% were white. In both studies, analysis of PFS and ORR were assessed by an IRC. The efficacy results are shown in Table 4.

Table 4: **Efficacy Results in CLL Patients with 17p deletion and/or TP53 mutation**

	312-0116		312-0119		Pooled	
	ZYD + R n=46	**Placebo + R n=49**	**ZYD + O n=70**	**O n=33**	**ZYD + anti-CD20 n=116**	**Anti-CD20 alone n=82**
PFS Median (months) (95% CI)	NR (12.3, NR)	4.0 (3. 7, 5.7)	13.7 (11, 17.8)	5.8 (4.5, 8.4)	15.4 (13.3, 17.8)	5.5 (3.8, 6.5)
Hazard ratio (95% CI)	0.13 (0.07, 0. 27)		0.32 (0.18, 0.57)		0.18 (0.11 0.27)	
ORR*	39 (84.8%)	6 (12.2%)	51 (72.9)	5 (15.2)	90 (77.6%)	11 (13.4%)
95% CI	71.1, 93.7	4.6, 24.8	60.9, 82.8	5.1, 31.9	68.9, 84.8	6.9, 22.7
Odds ratio (95% CI)	39.93 (12.35, 129.09)		15.03 (5.07, 44.6)		26.59 (11.37, 62.19)	

ZYD: ZYDELIG; R: rituximab O: ofatumumab; PFS: progression-free survival; ORR: overall response rate
* ORR defined as the proportion of patients who achieved a CR or PR; in Study 312-0119 improvements were requireed to be maintained for at least 8 weeks to meet the definition of response.

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%.

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 5 presents details of disease characteristics at time of study entry.

Table 5. 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 ORR are summarised in Table 6.

Table 6. Summary of response in patients with Follicular Lymphoma treated with ZYDELIG (IRC assessment)

Characteristic	Study Patients n (%)
ORR*(follicular lymphoma) 95% CI	40 (55.6) 43.4 – 67.3
ORR*(all patients)* 95% CI	72 (57.6) 48.4 – 66.4
Response Category*(follicular lymphoma, n = 72) CR PR	 10 (13.9) 30 (41.7)

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

The median DOR was 14.7 months as estimated using the Kaplan-Meier method. Of the patients who did not respond, 41 (32.8%) had stable disease, 10 (8.0%) had progressive disease, and 2 (1.6%) were not evaluable. The median OS, including long-term follow-up for all 125 patients, was 38.1 months.

INDICATIONS

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

ZYDELIG in combination with ofatumumab is indicated for the treatment of adult patients with CLL/SLL upon relapse in patients for whom chemo-immunotherapy is not considered suitable.

ZYDELIG is indicated as monotherapy for the treatment of patients with follicular lymphoma which is refractory to at least two prior systemic therapies. The disease must be refractory to both rituximab and an alkylating agent.

CONTRAINDICATIONS

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

PRECAUTIONS

Serious Infections

Treatment with ZYDELIG should not be initiated in patients with any evidence of ongoing systemic bacterial, fungal, or viral infection (see also IMMUNISATION). Serious and fatal infections have occurred with ZYDELIG, including opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP) and cytomegalovirus (CMV). 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 PJP and CMV, were among those identified.
Administer prophylaxis for 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 (see ADVERSE EFFECTS, Dose Modification Table 13).

Before commencing ZYDELIG, all patients should have CMV status assessed. At least monthly clinical and laboratory monitoring for CMV infection is recommended in patients with positive CMV serology at baseline or other evidence of a history of CMV infection or disease. Patients with CMV viraemia without attributable symptoms or signs should be monitored for evidence of high or rising viral load. For asymptomatic patients with evidence of high or rising viral load, consideration should be given to interruption of ZYDELIG and commencement of antiviral therapy to prevent invasive disease. For patients with evidence of CMV viraemia and attributable symptoms or signs, initiate antiviral therapy; and strong consideration should be given to interrupting ZYDELIG until CMV disease has resolved. If the benefits of resuming ZYDELIG are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy. Patients with fever and / or other signs of infection should be evaluated promptly and treated accordingly (see ADVERSE EFFECTS, Dose Modification Table 13).

Hepatotoxicity

Elevations in ALT and AST Grade 3 and 4 (greater than 5 times the upper limit of normal) have occurred with ZYDELIG. Transaminitis was sometimes accompanied by elevated bilirubin. Grade 3-4 transaminitis was reported in 9-11% of patients in ZYDELIG-containing arms of CLL studies 312-0116 and 312-0119 (versus 0-1% of control arm patients), and in 13% of patients in the iNHL study 101-09. A higher rate has been reported in other ZYDELIG studies. 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 18% of ZYDELIG-treated patients across clinical studies (see ADVERSE EVENTS). Most cases resolved within a few weeks with drug interruption and additional treatment (e.g., antidiarrhoeal and anti-inflammatory agents such as enteric budesonide) but some had a fatal outcome (see DOSAGE AND ADMINISTRATION). Of these patients, 32% resumed treatment without any recurrence of diarrhoea. In the pivotal study of patients with CLL, in the ZYDELIG + rituximab group both the incidence and prevalence of all Grade and Grade ≥ 3 diarrhoea/colitis increased with time (after 24 weeks compared to the incidence and prevalence in the 12 - 24 week period). Infectious causes (e.g., *Clostridum difficile,* CMV) should be excluded when assessing patients with colitis (see PRECAUTIONS Serious Infections). 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.

Intestinal Perforation

Fatal and serious intestinal perforation has 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.

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. Infectious causes (e.g., CMV) should be considered when assessing patients with pneumonitis (see PRECAUTIONS Serious Infections). Where moderate-severe symptomatic pneumonitis occurs, ZYDELIG should not be reinstituted (see DOSAGE and ADMINISTRATION).

Immunisation

Due to an increased risk of infections during ZYDELIG treatment, pneumococcal and influenza vaccines are recommended. For patients who are at substantial risk of an infection (e.g., influenza or pneumococcal sepsis), the vaccine should be provided prior to ZYDELIG treatment.

The safety of immunisation with live or inactivated live vaccines in association with ZYDELIG therapy has not been studied, and therefore vaccination with live vaccines is not recommended.

Neutropenia, Anaemia, Lymphopenia and Thrombocytopenia

Treatment-emergent Grade 3 or 4 neutropenia, including febrile neutropenia, have occurred in patients treated with ZYDELIG. Monitor blood counts in all patients at least every 2 weeks for the first 6 months of treatment with ZYDELIG, and at least weekly in patients while absolute neutrophil count is less than 1.0×10^9/L (see DOSAGE AND ADMINISTRATION, Table 13: Dose Modifications for Toxicities Due to ZYDELIG). Management of neutropenia, including administration of G-CSF should be per established clinical guidelines and institutional standard of care. The absence of neutropenia does not exclude idelalisib-mediated immunosuppression and risk of serious infection.

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 or life-threatening (Grade ≥ 3) cutaneous reactions have been reported in ZYDELIG-treated patients. In the pivotal study of patients with CLL, in the ZYDELIG + rituximab group both the incidence and prevalence of rash (any Grade) increased with time (after 24 weeks compared to the incidence and prevalence in the 12 - 24 week period).

Fatal cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have occurred when patients were treated with ZYDELIG administered concomitantly with other medications associated with SJS-TEN. If SJS or TEN is suspected, treatment with ZYDELIG should be interrupted immediately, and where there is a severe cutaneous reaction, ZYDELIG should be permanently discontinued.

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.

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.

Use in the Elderly

In clinical trials of ZYDELIG in patients with FL, SLL, and CLL, 62% were 65 years of age and older, while 22% were 75 years of age and older. No overall differences in effectiveness were observed between older and younger patients.

In patients 65 years of age or older with CLL in comparison to younger patients, older patients had a higher incidence of discontinuation due to an adverse reaction (28% vs 21%), higher incidence of serious adverse reactions (68% vs 60%), and similar incidence of death (8% vs 7%).

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

Summary of Clinical Trials in Chronic Lymphocytic Leukemia

Assessment of adverse reactions is based on 2 Phase 3 studies (312-0116 and 312-0119). Study 312-0116 was a randomized, double-blind, placebo-controlled study in which 110 patients with relapsed CLL received ZYDELIG + rituximab. In addition, 86 patients from this study who were randomised to receive placebo + rituximab went on to receive ZYDELIG as a single agent in an extension study. Study 312-0119 was an open label study in which 173 patients with relapsed CLL received ZYDELIG + ofatumumab. Table 7 and Table 8 summarise common adverse reactions and laboratory abnormalities reported for Zydelig + rituximab and placebo + rituximab arms in Study 312-0116.

Table 7 Adverse Events Reported in ≥5% of Patients with CLL and which Occurred at ≥2% Higher Incidence in Patients Receiving ZYDELIG in Study 312-0116

	ZYD + R N=110 (%)		R + Placebo N=108 (%)	
Adverse Events	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Gastrointestinal disorders				
diarrhea *	35 (32)	12 (11)	20 (19)	0
nausea	30 (27)	1 (1)	25 (23)	0
abdominal pain *	20 (18)	1 (1)	17 (16)	2 (2)
vomiting	17 (15)	0	9 (8)	0
gastroesophageal reflux disease	11 (10)	1 (1)	0	0
stomatitis	7 (6)	2 (2)	1 (1)	0
Nervous system disorders				
lethargy	6 (5)	0	2 (2)	0
General disorders and administration site conditions				
pyrexia	44 (40)	3 (3)	20 (19)	1 (1)
chills	27 (25)	2 (2)	17 (16)	0
pain	8 (7)	0	1 (1)	0
Skin and subcutaneous tissue disorders				

	ZYD + R N=110 (%)		R + Placebo N=108 (%)	
rash *	27 (25)	4 (4)	7 (6)	1 (1)
Respiratory, thoracic, and mediastinal disorders				
pneumonia *	33 (30)	23 (21)	20 (19)	14 (13)
Infections and infestations				
sepsis *	10 (9)	10 (9)	4 (4)	4 (4)
sinusitis	9 (8)	0	6 (6)	0
urinary tract infection	9 (8)	1 (1)	4 (4)	2 (2)
bronchitis	8 (7)	1 (1)	5 (5)	1 (1)
oral herpes	6 (5)	1 (1)	3 (3)	0
Musculoskeletal and connective tissue disorders				
arthralgia	9 (8)	1 (1)	4 (4)	0
Metabolism and Nutrition Disorders				
decreased appetite	18 (16)	2 (2)	12 (11)	2 (2)
dehydration	7 (6)	3 (3)	0	0
Psychiatric disorders				
insomnia	10 (9)	0	7 (6)	0

ZYD: ZYDELIG; R: rituximab
* Includes multiple ADR terms

Table 8 Treatment-emergent Laboratory Abnormalities Reported in ≥10% of CLL Patients Occurring at a ≥5% Higher Incidence in Patients Receiving ZYDELIG in Study 312-0116

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

ZYD: ZYDELIG; R: rituximab

Table 9 and Table 10 summarise common adverse reactions and laboratory abnormalities reported for ZYDELIG + ofatumumab and ofatumumab alone arms in Study 312-0119.

Table 9 Adverse Events Reported in ≥10% of Patients with CLL and which Occurred at ≥2% Higher Incidence in Patients Receiving ZYDELIG in Study 312-0119

	ZYD + O N = 173 (%)		O N = 86 (%)	
Adverse Events	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Gastrointestinal Disorders				
diarrhea *	86 (50)	36 (21)	20 (23)	1 (1)
nausea	52 (30)	1 (1)	23 (27)	1 (1)
constipation	36 (21)	0	13 (15)	1 (1)
abdominal pain *	40 (23)	5 (3)	11 (13)	0
Nervous System Disorders				
headache	33 (19)	0	9 (10)	0
General Disorders and Administration Site Conditions				
fatigue	55 (32)	6 (3)	24 (28)	4 (5)
pyrexia	56 (32)	12 (7)	20 (23)	2 (2)
oedema peripheral	29 (17)	0	9 (10)	0
Skin and Subcutaneous Tissue Disorders				
rash *	49 (28)	7 (4)	8 (9)	1 (1)

	ZYD + O N = 173 (%)		O N = 86 (%)	
Adverse Events	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
pruritus	19 (11)	0	6 (7)	0
Respiratory, Thoracic and Mediastinal Disorders				
Pneumonia*	58 (34)	42 (24)	18 (21)	11 (13)
cough	52 (30)	1 (1)	18 (21)	0
dyspnoea	29 (17)	7 (4)	10 (11)	1 (1)
Infections and Infestations				
upper respiratory tract infection	31 (18)	0	9 (10)	0
urinary tract infection	23 (13)	6 (3)	6 (7)	0
sinusitis	19 (11)	1 (1)	2 (2)	0
bronchitis	19 (11)	5 (3)	0	0
sepsis *	22 (13)	22 (13)	5 (6)	5 (6)
Muscoskeletal and Connection Tissue Disorders				
muscle spasms	17 (10)	0	2 (2)	0
Investigations				
weight decreased	18 (10)	1 (1)	5 (6)	1 (10)
Metabolism and Nutrition Disorders				
decreased appetite	30 (17)	1 (1)	7 (8)	1 (1)

ZYD: ZYDELIG; O: ofatumumab
* Includes multiple ADR terms

Table 10 Treatment-emergent Laboratory Abnormalities Reported in ≥10% of CLL Patients Occurring at a ≥5% Higher Incidence in Patients Receiving ZYDELIG in Study 312-0119

	ZYD + O N=173 (%)		O N=86 (%)	
Laboratory Parameter	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Hematology abnormalities				
neutrophil count decreased	122 (71)	82 (47)	50 (58)	28 (33)
lymphocyte count increased	31 (18)	18 (10)	5 (6)	3 (3)
platelet count decreased	58 (34)	23 (13)	21 (24)	10 (12)
Serum chemistry abnormalities				

	ZYD + O N=173 (%)		O N=86 (%)	
albumin decreased	52 (30)	3 (2)	17 (20)	1 (1)
alkaline phosphatase increased	43 (25)	3 (2)	13 (15)	1 (1)
ALT increased	90 (52)	20 (12)	18 (21)	1 (1)
AST increased	61 (35)	14 (8)	17 (20)	1 (1)
bilirubin increased	26 (15)	2 (1)	7 (8)	0
cholesterol high	18 (10)	0	2 (2)	0
creatinine clearance decreased	33 (19)	5 (3)	12 (14)	3 (3)
GGT increased	69 (40)	7 (4)	17 (20)	0
hypoglycemia	26 (15)	21 (12)	7 (8)	4 (5)
potassium decreased	36 (21)	10 (6)	8 (9)	2 (2)
phosphate decreased	29 (17)	14 (8)	3 (3)	1 (1)
triglycerides (hypertriglyceridemia)	102 (59)	12 (7)	45 (52)	2(2)

Grades were obtained per CTCAE version 4.03.
ZYD: ZYDELIG; O: ofatumumab

Summary of Clinical Trials in Follicular Lymphoma

Assessment of adverse reactions is based a single-arm, multicentre clinical trial (Study 101-09) conducted in 125 patients with indolent B-cell non-Hodgkin lymphoma, of which 72 patients were diagnosed with FL.

Table 11 and Table 12 summarise common adverse reactions and laboratory abnormalities reported for ZYDELIG monotherapy in Study 101-09.

Table 11 Adverse Events Reported in ≥ 10% of Patients with FL Receiving ZYDELIG in Study 101-09

	ZYD N = 72 (%)	
Adverse Events by System Organ Class	**Any Grade**	**Grade 3–4**
Infections and Infestations		
Pneumonia	8 (11.1)	5 (6.9)
Upper respiratory tract infection	12 (16.7)	0
Gastrointestinal Disorders		
Diarrhoea	37 (51.4)	10 (13.9)
Nausea	20 (27.8)	2 (2.8)
Constipation	8 (11.1)	0
Vomiting	12 (16.7)	2 (2.8)
Abdominal pain	10 (13.9)	2 (2.8)
General Disorders and Administration Site Conditions		
Fatigue	20 (27.8)	0
Pyrexia	22 (30.6)	3 (4.2)
Chills	8 (11.1)	0
Asthenia	8 (11.1)	0
Blood and Lymphatic System Disorders		
Neutropenia	17 (23.6)	14 (19.4)
Anaemia	9 (12.5)	4 (5.6)
Thrombocytopenia	9 (12.5)	3 (4.2)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	23 (31.9)	0
Dyspnoea	14 (19.4)	2 (2.8)
Skin and Subcutaneous Tissue Disorders		
Rash	14 (19.4)	2 (2.8)
Night sweats	11 (15.3)	0
Metabolism and Nutrition Disorders		
Decreased appetite	13 (18.1)	0
Hypokalaemia	8 (11.1)	7 (9.7)
Nervous System Disorders		
Headache	11 (15.3)	1 (1.4)
Musculoskeletal and Connective Tissue Disorders		
Back pain	9 (12.5)	1 (1.4)
Investigations		

	ZYD N = 72 (%)	
Adverse Events by System Organ Class	**Any Grade**	**Grade 3–4**
Weight decreased	11 (15.3)	0
Alanine aminotransferase increased	11 (15.3)	5 (6.9)
Aspartate aminotransferase increased	9 (12.5)	5 (6.9)

ZYD: ZYDELIG

Table 12 Treatment-emergent Laboratory Abnormalities Reported in ≥ 10% of Patients with FL Receiving ZYDELIG in Study 101-09

	ZYD N = 72 (%)	
Laboratory Parameter	**Any Grade**	**Grade ≥3**
Hematology abnormalities		
Anemia	22 (30.6)	1 (1.4)
Lymphocyte count decreased	29 (40.3)	15 (20.8)
Neutrophil count decreased	37 (51.4)	16 (22.2)
Platelet count decreased	15 (20.8)	3 (4.2)
White blood cell decreased	35 (40.6)	11 (15.3)
Serum chemistry abnormalities		
Hypoalbuminemia	21 (29.2)	1 (1.4)
Alkaline phosphatase increased	18 (25)	0
Alanine aminotransferase increased	36 (50.0)	8 (11.1)
Aspartate aminotransferase increased	27 (37.5)	8 (11.1)
Blood bilirubin increased	9 (12.5)	0
Hypercalcemia	8 (11.1)	1 (1.4)
Cholesterol high	9 (12.5)	0
Creatinine increased	33 (45.8)	0
GTT increased	25 (34.7)	4 (5.6)
Hypokalemia	13 (18.1)	4 (5.6)
Hyponatremia	9 (12.5)	0
Hypertriglyceridemia	35 (48.6)	2 (2.8)
Hyperuricemia	10 (13.9)	1 (1.4)

Postmarketing Experience

In addition to adverse reactions from clinical studies, the following adverse reactions were identified during postapproval 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 PRECAUTIONS).

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.

Refer to the CLINICAL TRIALS section, ZYDELIG in combination with chemotherapy and immunotherapy, Study 312-0119, for details of the recommended ofatumumab dosing regimen used in combination with ZYDELIG in the clinical study. The dose of ofatumumab was lower when used in combination with ZYDELIG than when used alone in Study 312-0119. For patients in the ZYDELIG + ofatumumab group, the first dose of ofatumumab was administered at 300 mg, followed by 1000 mg weekly for 7 doses.

Dose Modification

See Table 13 for dose modification instructions for specific toxicities related to ZYDELIG.

Table 13 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 diarrhoea 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 dose.	Maintain ZYDELIG dose. Monitor ANC at least weekly. Consider G-CSF support according to established clinical guidelines.	Interrupt ZYDELIG. Monitor ANC at least weekly until ANC ≥0.5 x10^9/L, then may resume ZYDELIG at 100 mg BID. Consider G-CSF support according to established clinical guidelines.
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 (Grade 1 or 2)**	**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, after considering the benefits and risks of further treatment, ZYDELIG may be resumed 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.
CMV	**Patients with positive baseline CMV serology**		**Comment**
	Monitor patients with CMV viraemia (positive PCR or antigen test). Consider interrupting ZYDELIG until the infection has resolved. Provide treatment according to established clinical guidelines. Patients with CMV viraemia without associated clinical signs of CMV infections should be carefully monitored.		If the benefits of resuming ZYDELIG are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy.
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; CMV, cytomegalovirus; PCR, polymerase chain reaction; G-CSF, granulocyte colony-stimulating factor * Monitor blood counts in all patients at least every 2 weeks for the first 6 months of treatment with ZYDELIG. ** ZYDELIG should be interrupted immediately where SJS or TEN is suspected and permanently discontinued where there is a severe cutaneous reaction.			

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

Date of most recent amendment: 1 February 2017