

**Changes to the Product information as approved by the CHMP on 21 July 2016, pending endorsement by the European Commission**

## **ANNEX I**

### **SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Zydelig 100 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of idelalisib.

Excipient(s) with known effect: Each tablet contains 0.1 mg sunset yellow FCF (E110) (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

Orange, oval-shaped, film-coated tablet of dimensions 9.7 mm by 6.0 mm, debossed on one side with “GSI” and “100” on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Zydelig is indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL):

- who have received at least one prior therapy (see section 4.4), or
- for continuing as first line treatment in patients with the presence of 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated Zydelig as first line treatment in patients who are not eligible for any other therapies (see section 4.4).

Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment (see section 4.4).

### 4.2 Posology and method of administration

Treatment with Zydelig should be conducted by a physician experienced in the use of anticancer therapies.

#### Posology

The recommended dose of Zydelig is 150 mg, taken orally, twice daily. Treatment should be continued until disease progression or unacceptable toxicity.

If the patient misses a dose of Zydelig within 6 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal dosing schedule. If a patient misses a dose by more than 6 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

### Dose modification

#### *Elevated liver transaminases*

Treatment with Zydelig must be withheld in the event of a Grade 3 or 4 aminotransferase elevation (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] > 5 x upper limit of normal [ULN]). Once values have returned to Grade 1 or below (ALT/AST ≤ 3 x ULN), treatment can be resumed at 100 mg twice daily.

If the event does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician.

If the event recurs, treatment with Zydelig must be withheld until the values return to Grade 1 or less, after which re-initiation at 100 mg twice daily may be considered at the discretion of the physician (see sections 4.4 and 4.8).

#### *Diarrhoea/colitis*

Treatment with Zydelig must be withheld in the event of Grade 3 or 4 diarrhoea/colitis. Once diarrhoea/colitis has returned to Grade 1 or below, treatment can be resumed at 100 mg twice daily. If diarrhoea/colitis does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician (see section 4.8).

#### *Pneumonitis*

Treatment with Zydelig must be withheld in the event of suspected pneumonitis. Once pneumonitis has resolved and if re-treatment is appropriate, resumption of treatment at 100 mg twice daily can be considered (see sections 4.4 and 4.8).

#### *Rash*

Treatment with Zydelig must be withheld in the event of Grade 3 or 4 rash. Once rash has returned to Grade 1 or below, treatment can be resumed at 100 mg twice daily. If rash does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician (see section 4.8).

#### *Neutropenia*

Treatment with Zydelig should be withheld in patients while absolute neutrophil count (ANC) is below 500 per mm<sup>3</sup>. ANC should be monitored at least weekly until ANC is ≥ 500 per mm<sup>3</sup> when treatment can be resumed at 100 mg twice daily (see section 4.4).

ANC 1,000 to < 1,500/mm <sup>3</sup>	ANC 500 to < 1,000/mm <sup>3</sup>	ANC < 500/mm <sup>3</sup>
Maintain Zydelig dosing.	Maintain Zydelig dosing.  Monitor ANC at least weekly.	Interrupt Zydelig dosing.  Monitor ANC at least weekly until ANC ≥ 500/mm <sup>3</sup> , then may resume Zydelig dosing at 100 mg twice daily.

### Special patient populations

#### *Elderly*

No specific dose adjustment is required for elderly patients (aged ≥ 65 years) (see section 5.2).

#### *Renal impairment*

No dose adjustment is required for patients with mild, moderate, or severe renal impairment (see section 5.2).

#### *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 adverse reactions is recommended (see sections 4.4 and 5.2).

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 an intensified monitoring of adverse reactions is recommended (see sections 4.4 and 5.2).

#### *Paediatric population*

The safety and efficacy of Zydelig in children under the age of 18 years have not been established. No data are available.

#### Method of administration

Zydelig is for oral use. Patients should be instructed to swallow the tablet whole. The film-coated tablet should not be chewed or crushed. The film-coated tablet can be taken with or without food (see section 5.2).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### 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 idelalisib, including opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP) and cytomegalovirus (CMV). Prophylaxis for PJP should therefore be administered to all patients throughout idelalisib 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 section 4.8).

Patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new respiratory symptoms promptly.

Regular clinical and laboratory screening/monitoring for CMV infection ~~should be conducted. Treatment with Zydelig should be discontinued if there is evidence of infection or viraemia is~~ recommended in patients with positive CMV serology at the start of treatment with idelalisib or with other evidence of a history of CMV infection. Patients with CMV viraemia without associated clinical signs of CMV infection should be carefully monitored. For patients with evidence of CMV viraemia and clinical signs of CMV infection, consideration should be given to interrupting idelalisib until the infection has resolved. If the benefits of resuming idelalisib are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy.

#### Neutropenia

Treatment-emergent Grade 3 or 4 neutropenia, including febrile neutropenia, have occurred in patients treated with idelalisib. Blood counts should be monitored in all patients at least every 2 weeks for the first 6 months of treatment with idelalisib, and at least weekly in patients while ANC is less than 1,000 per mm<sup>3</sup> (see section 4.2).

#### Transaminase elevations

Elevations in ALT and AST of Grade 3 and 4 (> 5 x ULN) have been observed in clinical studies of idelalisib. 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 section 4.2). ALT, AST, and total bilirubin must be monitored 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, patients must be monitored weekly until the values return to Grade 1 or below.

### Diarrhoea/colitis

Cases of severe drug-related colitis occurred relatively late (months) after the start of therapy, sometimes with rapid aggravation, but resolved within a few weeks with dose interruption and additional symptomatic treatment (e.g., anti-inflammatory agents such as enteric budesonide).

There is very limited experience from the treatment of patients with a history of inflammatory bowel disease.

### Pneumonitis

Cases of pneumonitis have been reported in clinical studies with idelalisib. Patients presenting with serious lung events that do not respond to conventional antimicrobial therapy should be assessed for drug-induced pneumonitis. If pneumonitis is suspected, idelalisib should be interrupted and the patient treated accordingly. Treatment must be discontinued for moderate or severe symptomatic pneumonitis.

### Stevens-Johnson syndrome and toxic epidermal necrolysis

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with fatal outcomes have been reported when idelalisib was administered concomitantly with other medicinal products associated with these syndromes. If SJS or TEN is suspected, idelalisib should be immediately interrupted and the patient treated accordingly.

### CYP3A inducers

Idelalisib exposure may be reduced when co-administered with CYP3A inducers such as rifampicin, phenytoin, St. John's wort (*Hypericum perforatum*), or carbamazepine. Since a reduction in idelalisib plasma concentrations may result in decreased efficacy, co-administration of Zydelig with moderate or strong CYP3A inducers should be avoided (see section 4.5).

### CYP3A substrates

The primary metabolite of idelalisib, GS-563117, is a strong CYP3A4 inhibitor. Thus, idelalisib has the potential to interact with medicinal products that are metabolised by CYP3A, which may lead to increased serum concentrations of the other product (see section 4.5). When idelalisib is co-administered with other medicinal products, the Summary of Product Characteristics (SmPC) for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors. Concomitant treatment of idelalisib with CYP3A substrates with serious and/or life-threatening adverse reactions (e.g., alfuzosin, amiodarone, cisapride, pimozone, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible.

### Hepatic impairment

Intensified monitoring of adverse reactions 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. No patients with severe hepatic impairment were included in clinical studies of idelalisib. Caution is recommended when administering Zydelig in this population.

### Chronic hepatitis

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.

### Women of childbearing potential

Women of childbearing potential must use highly effective contraception while taking idelalisib and for 1 month after stopping treatment (see section 4.6). Women using hormonal contraceptives should add a barrier method as a second form of contraception since it is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives.

### Excipients

Zydelig contains the azo colouring agent sunset yellow FCF (E110), which may cause allergic reactions.

## **4.5 Interaction with other medicinal products and other forms of interaction**

Idelalisib is metabolised primarily via aldehyde oxidase, and to a lesser extent via CYP3A and glucuronidation (UGT1A4). Its primary metabolite is GS-563117, which is not pharmacologically active. Idelalisib and GS-563117 are substrates of P-gp and BCRP.

### Effect of other medicinal products on idelalisib pharmacokinetics

#### *CYP3A inducers*

A clinical drug interaction study found that co-administration of a single dose of 150 mg idelalisib with rifampicin (a strong CYP3A inducer) resulted in a ~75% reduction in idelalisib AUC<sub>inf</sub>. Co-administration of Zydelig with moderate or strong CYP3A inducers such as rifampicin, phenytoin, St. John's wort, or carbamazepine should be avoided as this may result in decreased efficacy (see section 4.4).

#### *CYP3A/P-gp inhibitors*

A clinical drug interaction study found that co-administration of a single dose of 400 mg idelalisib with 400 mg once daily ketoconazole (a strong CYP3A, P-gp and BCRP inhibitor) resulted in a 26% increase in C<sub>max</sub> and a 79% increase in AUC<sub>inf</sub> of idelalisib. No initial dose adjustment of idelalisib is considered necessary when administered with CYP3A/P-gp inhibitors, but an intensified monitoring of adverse reactions is recommended.

### Effect of idelalisib on the pharmacokinetics of other medicinal products

#### *CYP3A substrates*

The primary metabolite of idelalisib, GS-563117, is a strong CYP3A inhibitor. A clinical drug interaction study found that co-administration of idelalisib with midazolam (a sensitive CYP3A substrate) resulted in a ~140% increase in C<sub>max</sub> and a ~440% increase in AUC<sub>inf</sub> of midazolam due to the CYP3A inhibition by GS-563117. Co-administration of idelalisib with CYP3A substrates may increase their systemic exposures and increase or prolong their therapeutic activity and adverse reactions. *In vitro*, the CYP3A4 inhibition was irreversible, and return to normal enzyme activity is therefore expected to take several days after stopping idelalisib administration.

Potential interactions between idelalisib and co-administered medicinal products that are CYP3A substrates are listed in Table 1 (increase is indicated as “↑”). This list is not exhaustive and is intended to serve as guidance only. In general, the SmPC for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors (see section 4.4).

**Table 1: Interactions between idelalisib and other medicinal products that are CYP3A substrates**

Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
<b>ALPHA-1 ADRENORECEPTOR ANTAGONISTS</b>		
Alfuzosin	↑ serum concentrations	Idelalisib should not be co-administered with alfuzosin.
<b>ANALGESICS</b>		
Fentanyl, alfentanil, methadone, buprenorphine/naloxone	↑ serum concentrations	Careful monitoring of adverse reactions (e.g., respiratory depression, sedation) is recommended.

Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
<b>ANTIARRHYTHMICS</b>		
Amiodarone, quinidine	↑ serum concentrations	Idelalisib should not be co-administered with amiodarone or quinidine.
Bepiridil, disopyramide, lidocaine	↑ serum concentrations	Clinical monitoring is recommended.
<b>ANTI-CANCER AGENTS</b>		
Tyrosine kinase inhibitors such as dasatinib and nilotinib, also vincristine and vinblastine	↑ serum concentrations	Careful monitoring of the tolerance to these anti-cancer agents is recommended.
<b>ANTICOAGULANTS</b>		
Warfarin	↑ serum concentrations	It is recommended that the international normalised ratio (INR) be monitored upon co-administration and following ceasing treatment with idelalisib.
<b>ANTICONVULSANTS</b>		
Carbamazepine	↑ serum concentrations	Anticonvulsant drug levels should be monitored.
<b>ANTIDEPRESSANTS</b>		
Trazodone	↑ serum concentrations	Careful dose titration of the antidepressant and monitoring for antidepressant response is recommended.
<b>ANTI-GOUT</b>		
Colchicine	↑ serum concentrations	Dose reductions of colchicine may be required. Idelalisib should not be co-administered with colchicine to patients with renal or hepatic impairment.
<b>ANTI-HYPERTENSIVES</b>		
Amlodipine, diltiazem, felodipine, nifedipine, nicardipine	↑ serum concentrations	Clinical monitoring of therapeutic effect and adverse reactions is recommended.
<b>ANTI-INFECTIVES</b>		
<b>Antifungals</b>		
Ketoconazole, itraconazole, posaconazole, voriconazole	↑ serum concentrations	Clinical monitoring is recommended.
<b>Antimycobacterials</b>		
Rifabutin	↑ serum concentrations	Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is recommended.
<b>HCV protease inhibitors</b>		
Boceprevir, telaprevir	↑ serum concentrations	Clinical monitoring is recommended.

Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
<b>Macrolide antibiotics</b>		
Clarithromycin, telithromycin	↑ serum concentrations	No dose adjustment of clarithromycin is required for patients with normal renal function or mild renal impairment (creatinine clearance [CrCl] 60-90 mL/min). Clinical monitoring is recommended for patients with CrCl < 90 mL/min. For patients with CrCl < 60 mL/min, alternative antibacterials should be considered.  Clinical monitoring is recommended for telithromycin.
<b>ANTI-PSYCHOTICS/NEUROLEPTICS</b>		
Quetiapine, pimozide	↑ serum concentrations	Idelalisib should not be co-administered with quetiapine or pimozide.  Alternative medicinal products, such as olanzapine, may be considered.
<b>ENDOTHELIN RECEPTOR ANTAGONISTS</b>		
Bosentan	↑ serum concentrations	Caution should be exercised and patients closely observed for bosentan-related toxicity.
<b>ERGOT ALKALOIDS</b>		
Ergotamine, dihydroergotamine	↑ serum concentrations	Idelalisib should not be co-administered with ergotamine or dihydroergotamine.
<b>GASTROINTESTINAL MOTILITY AGENTS</b>		
Cisapride	↑ serum concentrations	Idelalisib should not be co-administered with cisapride.
<b>GLUCOCORTICOIDS</b>		
Inhaled/nasal corticosteroids: Budesonide, fluticasone	↑ serum concentrations	Clinical monitoring is recommended.
Oral budesonide	↑ serum concentrations	Clinical monitoring is recommended for increased signs/symptoms of corticosteroid effects.
<b>HMG CO-A REDUCTASE INHIBITORS</b>		
Lovastatin, simvastatin	↑ serum concentrations	Idelalisib should not be co-administered with lovastatin or simvastatin.
Atorvastatin	↑ serum concentrations	Clinical monitoring is recommended and a lower starting dose of atorvastatin may be considered. Alternatively, switching to pravastatin, rosuvastatin, or pitavastatin may be considered.
<b>IMMUNOSUPPRESSANTS</b>		
Ciclosporin, sirolimus, tacrolimus	↑ serum concentrations	Therapeutic monitoring is recommended.



Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
<b>INHALED BETA AGONIST</b>		
Salmeterol	↑ serum concentrations	Concurrent administration of salmeterol and idelalisib is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
<b>PHOSPHODIESTERASE INHIBITORS</b>		
Sildenafil	↑ serum concentrations	For pulmonary arterial hypertension:  Idelalisib should not be co-administered with sildenafil.
Tadalafil	↑ serum concentrations	Caution should be exercised, including consideration of dose reduction, when co-administering tadalafil with idelalisib.
Sildenafil, tadalafil	↑ serum concentrations	For erectile dysfunction:  Particular caution must be used and dose reduction may be considered when prescribing sildenafil or tadalafil with idelalisib with increased monitoring for adverse events.
<b>SEDATIVES/HYPNOTICS</b>		
Midazolam (oral), triazolam	↑ serum concentrations	Idelalisib should not be co-administered with midazolam (oral) or triazolam.
Buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ serum concentrations	Concentration monitoring of sedatives/hypnotics is recommended and dose reduction may be considered.

#### *CYP2C8 substrates*

*In vitro*, idelalisib both inhibited and induced CYP2C8, but it is not known whether this translates to an *in vivo* effect on CYP2C8 substrates. Caution is advised if Zydelig is used together with narrow therapeutic index drugs that are substrates of CYP2C8 (paclitaxel).

#### *Substrates of inducible enzymes (e.g., CYP2C9, CYP2C19, CYP2B6 and UGT)*

*In vitro*, idelalisib was an inducer of several enzymes, and a risk for decreased exposure and thereby decreased efficacy of substrates of inducible enzymes such as CYP2C9, CYP2C19, CYP2B6 and UGT cannot be excluded. Caution is advised if Zydelig is used together with narrow therapeutic index drugs that are substrates of these enzymes (warfarin, phenytoin, S-mephenytoin).

#### *BCRP, OATP1B1, OATP1B3 and P-gp substrates*

Co-administration of multiple doses of idelalisib 150 mg twice daily to healthy subjects resulted in comparable exposures for rosuvastatin (AUC 90% CI: 87, 121) and digoxin (AUC 90% CI: 98, 111), suggesting no clinically relevant inhibition of BCRP, OATP1B1/1B3 or systemic P-gp by idelalisib. A risk for P-gp inhibition in the gastrointestinal tract, that could result in increased exposure of sensitive substrates for intestinal P-gp such as dabigatran etexilate, cannot be excluded.

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Women of childbearing potential

Based on findings in animals, idelalisib may cause foetal harm. Women should avoid becoming pregnant while taking Zydelyg, and for up to 1 month after ending treatment. Therefore, women of childbearing potential must use highly effective contraception while taking Zydelyg and for 1 month after stopping treatment. It is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method as a second form of contraception.

#### Pregnancy

There are no or limited amount of data from the use of idelalisib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Zydelyg is not recommended during pregnancy and in women of childbearing potential not using contraception.

#### Breast-feeding

It is not known whether idelalisib and its metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with Zydelyg.

#### Fertility

No human data on the effect of idelalisib on fertility are available. Animal studies indicate the potential for harmful effects of idelalisib on fertility and foetal development (see section 5.3).

### **4.7 Effects on ability to drive and use machines**

Zydelyg has no or negligible influence on the ability to drive and use machines.

### **4.8 Undesirable effects**

#### Summary of the safety profile

Assessment of adverse reactions is based on one Phase 3 study and seven Phase 1 and 2 studies. Phase 3 study 312-0116 was a randomised, double-blind, placebo-controlled study in which 220 patients with previously treated CLL were randomised 1:1 to receive idelalisib + rituximab or placebo + rituximab. The Phase 1 and 2 studies assessed the safety of idelalisib in 490 patients with haematologic malignancies, including 354 subjects who received idelalisib (any dose) as a single agent and 136 subjects who received idelalisib in combination with anti-CD20 monoclonal antibodies.

During treatment with idelalisib, the most frequently reported adverse drug reactions are reported in Table 2.

#### Tabulated list of adverse reactions

The adverse drug reactions reported with idelalisib alone or in combination with anti-CD20 monoclonal antibodies are provided in Table 2. Adverse reactions are listed by system organ class and frequency. Frequencies are defined as follows: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), and not known (cannot be estimated from available data).

**Table 2: Adverse drug reactions reported in clinical studies in patients with haematologic malignancies receiving idelalisib**

Reaction	Any grade	Grade $\geq$ 3
<i>Infections and infestations</i>		
Infections ( <u>including <i>Pneumocystis jirovecii</i> pneumonia and CMV</u> )*	Very common	Very common
<i>Blood and lymphatic system disorders</i>		
Neutropenia	Very common	Very common
<i>Respiratory, thoracic and mediastinal disorders</i>		
Pneumonitis	Common	Common
<i>Gastrointestinal disorders</i>		
Diarrhoea/colitis	Very common	Very common
<i>Hepatobiliary disorders</i>		
Transaminase increased	Very common	Very common
<i>Skin and subcutaneous tissue disorders</i>		
Rash**	Very common	Common
Stevens-Johnson syndrome/toxic epidermal necrolysis	Rare	Rare
<i>General disorders and administration site conditions</i>		
Pyrexia	Very common	Common
<i>Investigations</i>		
Increased triglycerides	Very common	Common

\* Comprised of opportunistic infections as well as bacterial and viral infections such as pneumonia, bronchitis, and sepsis.

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

#### Description of selected adverse reactions

##### Infections (see section 4.4)

Higher frequencies of infections overall, including Grade 3 and 4 infections, were observed in the idelalisib arms compared to the control arms of idelalisib 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 PJP and CMV, were among those identified. Nearly all PJP infections, including fatal cases, occurred in the absence of PJP prophylaxis. There have been cases of PJP after stopping idelalisib treatment.

##### Rash

Rash was generally mild to moderate and resulted in discontinuation of treatment in about 2% of patients. In study 312-0116, rash (reported as dermatitis exfoliative, drug eruption, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, and rash pruritic) occurred in 24.5% of subjects who received idelalisib + rituximab and 6.5% who received placebo + rituximab. Of these, 3.6% who received idelalisib + rituximab and 0.9% who received placebo + rituximab had rash of Grade 3, and no subjects had an adverse event of Grade 4. Rash typically resolved with treatment (e.g., topical and/or oral steroids, diphenhydramine) and dose interruption for severe cases (see section 5.3, phototoxicity).

##### Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4)

Rarely, cases of SJS and TEN have occurred when idelalisib was administered concomitantly with other medicinal products associated with these syndromes (bendamustine, rituximab, allopurinol, and amoxicillin). SJS or TEN occurred within one month of the medicinal combination and fatal outcomes have resulted.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### **4.9 Overdose**

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8). 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.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XX47

#### Mechanism of action

Idelalisib inhibits phosphatidylinositol 3-kinase p110 $\delta$  (PI3K $\delta$ ), 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 PI3K $\delta$ , resulting in inhibition of the phosphorylation of the key lipid second messenger phosphatidylinositol and prevention of Akt (protein kinase B) phosphorylation.

Idelalisib induces apoptosis and inhibits proliferation in cell lines derived from malignant B-cells and in primary tumour cells. Through inhibition of chemokine receptors CXCR4 and CXCR5 signalling induced by the chemokines CXCL12 and CXCL13, respectively, idelalisib inhibits homing and retention of malignant B-cells in the tumour microenvironment including lymphoid tissues and the bone marrow.

#### Pharmacodynamic effects

The effect of idelalisib (150 mg and 400 mg) on the QT/QTc interval was evaluated in a placebo- and positive-controlled (moxifloxacin 400 mg) crossover study in 40 healthy subjects. At a dose 2.7 times the maximum recommended dose, idelalisib did not prolong the QT/QTc interval (i.e., < 10 ms).

#### Clinical efficacy in chronic lymphocytic leukaemia

##### *Idelalisib in combination with immunotherapy*

Study 312-0116 was a Phase 3, randomised, double-blind, placebo-controlled study in 220 subjects with previously treated CLL who required treatment but were not considered suitable for cytotoxic chemotherapy. Subjects were randomised 1:1 to receive 8 cycles of rituximab (first cycle at 375 mg/m<sup>2</sup> body surface area [BSA], subsequent cycles at 500 mg/m<sup>2</sup> BSA) in combination with either an oral placebo twice daily or with idelalisib 150 mg taken twice daily until disease progression or unacceptable toxicity.

The median age was 71 years (range: 47 to 92) with 78.2% of patients over 65 years; 65.5% were male, and 90.0% were white; 64.1% had a Rai stage of III or IV, and 55.9% had Binet Stage C. Most subjects had adverse cytogenetic prognostic factors: 43.2% had a 17p chromosomal deletion and/or tumour protein 53 (TP53) mutation, and 83.6% had unmutated genes for the immunoglobulin heavy chain variable region (IGHV). The median time from diagnosis of CLL to randomisation was 8.5 years. Subjects had a median Cumulative Illness Rating Score (CIRS) of 8. The median number of prior therapies was 3.0. Nearly all (95.9%) subjects had received prior anti-CD20 monoclonal

antibodies. The primary endpoint was progression free survival (PFS). Efficacy results are summarised in Tables 3 and 4. The Kaplan-Meier curve for PFS is provided in Figure 1.

Compared with rituximab + placebo, treatment with idelalisib + rituximab resulted in statistically significant and clinically meaningful improvements in physical well-being, social well-being, functional well-being, as well as in the leukaemia-specific subscales of the Functional Assessment of Cancer Therapy: Leukaemia (FACT-LEU) instruments, and in statistically significant and clinically meaningful improvements in anxiety, depression and usual activities as measured by the EuroQoL Five-Dimensions (EQ-5D) instrument.

**Table 3: Efficacy results from study 312-0116**

	<b>Idelalisib + R</b> <b>N = 110</b>	<b>Placebo + R</b> <b>N = 110</b>
<b>PFS</b> Median (months) (95% CI)	19.4 (12.3, NR)	6.5 (4.0, 7.3)
Hazard ratio (95% CI)	0.15 (0.09, 0.25)	
P-value	< 0.0001	
<b>ORR*</b> n (%) (95% CI)	92 (83.6%) (75.4, 90.0)	17 (15.5%) (9.3, 23.6)
Odds ratio (95% CI)	27.76 (13.40, 57.49)	
P-value	< 0.0001	
<b>LNR**</b> n/N (%) (95% CI)	102/106 (96.2%) (90.6, 99.0)	7/104 (6.7%) (2.7, 13.4)
Odds ratio (95% CI)	225.83 (65.56, 777.94)	
P-value	< 0.0001	
<b>OS<sup>^</sup></b> Median (months) (95% CI)	NR (NR, NR)	20.8 (14.8, NR)
Hazard ratio (95% CI)	0.34 (0.19, 0.60)	
P-value	0.0001	

CI: confidence interval; R: rituximab; n: number of responding subjects; N: number of subjects per group; NR: not reached. The analyses of PFS, overall response rate (ORR) and lymph node response rate (LNR) were based on evaluation by an independent review committee (IRC).

\* ORR defined as the proportion of subjects who achieved a complete response (CR) or partial response (PR) based on the 2013 National Comprehensive Cancer Network (NCCN) response criteria and Cheson (2012).

\*\* LNR defined as the proportion of subjects who achieved a  $\geq 50\%$  decrease in the sum of products of the greatest perpendicular diameters of index lesions. Only subjects that had both baseline and  $\geq 1$  evaluable post-baseline assessments were included in this analysis.

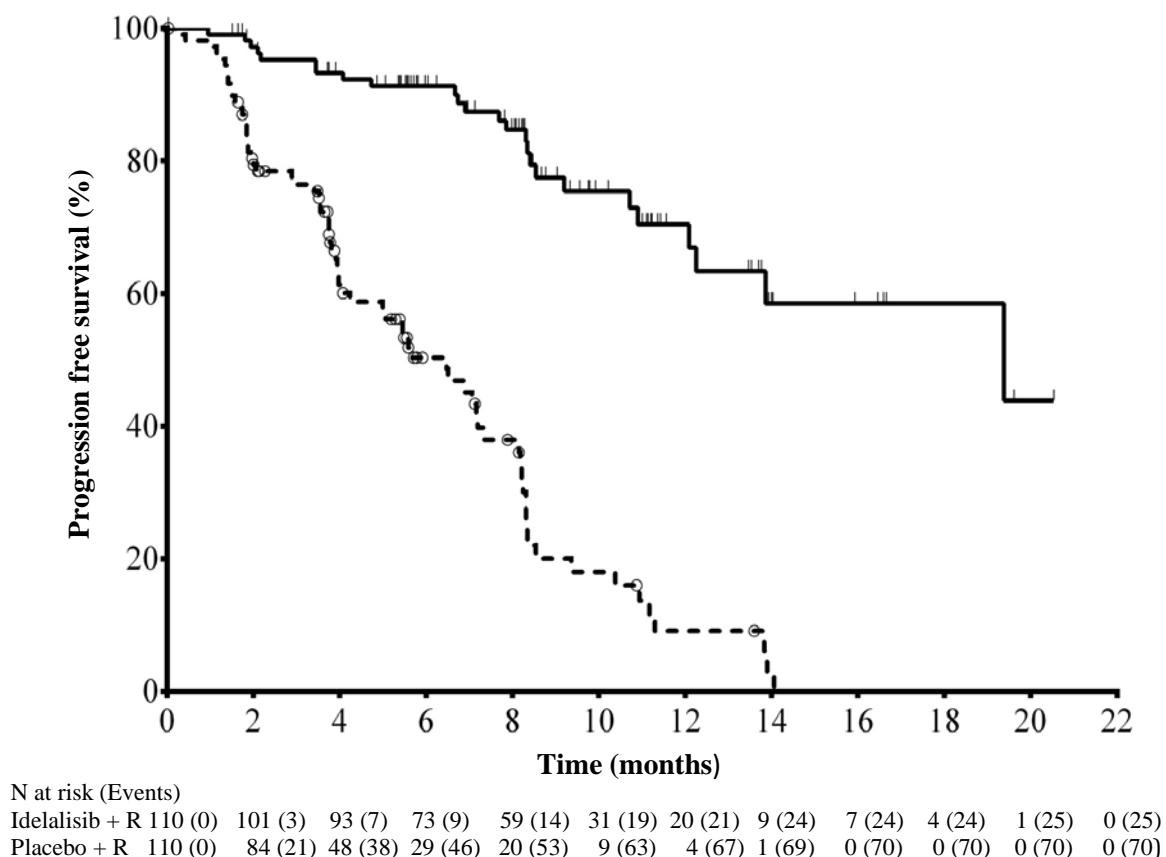
<sup>^</sup> Overall survival (OS) analysis includes data from subjects who received placebo + R on study 312-0116 and subsequently received idelalisib in an extension study, based on intent-to-treat analysis.

**Table 4: Summary of PFS and response rates in pre-specified subgroups from study 312-0116**

	<b>Idelalisib + R</b> <b>N = 46</b>	<b>Placebo + R</b> <b>N = 49</b>
<b>17p deletion/TP53 mutation</b>		
PFS median (months) (95% CI)	NR (12.3, NR)	4.0 (3.7, 5.7)
Hazard ratio (95% CI)	0.13 (0.07, 0.27)	
ORR (95% CI)	84.8% (71.1, 93.7)	12.2% (4.6, 24.8)
<b>Unmutated IGHV</b>	<b>N = 91</b>	<b>N = 93</b>
PFS median (months) (95% CI)	19.4 (13.9, NR)	5.6 (4.0, 7.2)
Hazard ratio (95% CI)	0.14 (0.08, 0.23)	
ORR (95% CI)	82.4% (73.0, 89.6)	15.1% (8.5, 24.0)
<b>Age <math>\geq 65</math> years</b>	<b>N = 89</b>	<b>N = 83</b>
PFS median (months) (95% CI)	19.4 (12.3, NR)	5.7 (4.0, 7.3)
Hazard ratio (95% CI)	0.14 (0.08, 0.25)	
ORR (95% CI)	84.3% (75.0, 91.1)	16.9% (9.5, 26.7)

CI: confidence interval; R: rituximab; N: number of subjects per group; NR: not reached

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



Solid line: idelalisib + R (N = 110), dashed line: placebo + R (N = 110)

R: rituximab; N: number of subjects per group

The analysis of PFS was based on evaluation by an IRC. For subjects in the placebo + R group, the summary includes data up to the first dosing of idelalisib in an extension study. Median PFS: idelalisib + R = 19.4 months, placebo + R = 6.5 months. Hazard ratio = 0.15, 95% CI (0.09, 0.24),  $p < 0.0001$ .

Study 101-08/99 enrolled 64 subjects with previously untreated CLL, including 5 subjects with small lymphocytic lymphoma (SLL). Subjects received idelalisib 150 mg twice daily and rituximab 375 mg/m<sup>2</sup> BSA weekly. The ORR was 96.9%, with 12 CRs (18.8%) and 50 PRs (78.1%), including 3 CRs and 6 PRs in subjects with a 17p deletion and/or *TP53* mutation and 2 CRs and 34 PRs in subjects with unmutated *IGHV*. The median duration of response (DOR) has not been reached.

#### Clinical efficacy in follicular lymphoma

The safety and efficacy of idelalisib were assessed in a single-arm, multicentre clinical study (study 101-09) conducted in 125 subjects with indolent B-cell non-Hodgkin lymphoma (iNHL), including: FL,  $n = 72$ ; SLL,  $n = 28$ ; lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia [LPL/WM],  $n = 10$ ; and marginal zone lymphoma [MZL],  $n = 15$ . All subjects were refractory to rituximab and 124 of 125 subjects were refractory to at least one alkylating agent. One hundred and twelve (89.6%) subjects were refractory to their last regimen prior to study entry.

Of the 125 subjects enrolled, 80 (64%) were male, the median age was 64 years (range: 33 to 87), and 110 (89%) were white. Subjects received 150 mg of idelalisib orally twice daily until evidence of disease progression or unacceptable toxicity.

The primary endpoint was the ORR defined as the proportion of subjects who achieved a CR or PR (based on the Revised Response Criteria for Malignant Lymphoma [Cheson]), and, for subjects with Waldenström macroglobulinaemia, a minor response (MR) (based on the Response Assessment for Waldenström macroglobulinaemia [Owen]). 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 are summarised in Table 5.

**Table 5: Summary of response in subjects with FL treated with idelalisib (IRC assessment)**

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

CI: confidence interval; n: number of responding subjects

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

The median DOR for all subjects was 12.5 months (12.5 months for SLL subjects, and not reached for FL, LPL/WM and MZL subjects). Among the 122 subjects with measurable lymph nodes at both baseline and post-baseline, 67 subjects (54.9%) achieved a  $\geq 50\%$  decrease from baseline in the sum of the products of the diameters (SPD) of index lesions. Of the subjects who did not respond, 10 (8.0%) had progressive disease as best response, and 2 (1.6%) were not evaluable. The median OS, including long-term follow-up for all 125 subjects, was 20.3 months.

#### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with idelalisib in one or more subsets of the paediatric population in the treatment of mature B-cell neoplasms (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

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

Following 150 mg twice daily administration of idelalisib, average (range)  $C_{max}$  and AUC at steady-state were 1,953 (272; 3,905) ng/mL and 10,439 (2,349; 29,315) ng•h/mL for idelalisib and 4,039 (669; 10,897) ng/mL and 39,744 (6,002; 119,770) ng•h/mL for GS-563117, respectively. The plasma exposures ( $C_{max}$  and AUC) of idelalisib are approximately dose proportional between 50 mg and 100 mg and less than dose proportional above 100 mg.

### Effects of food

Relative to fasting conditions, administration of an early capsule formulation of idelalisib 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.

### Distribution

Idelalisib is 93% to 94% bound to human plasma proteins at concentrations observed clinically. The mean blood-to-plasma concentration ratio was approximately 0.5. The apparent volume of distribution for idelalisib (mean) was approximately 96 L.

### Biotransformation

Idelalisib is metabolised primarily via aldehyde oxidase, and to a lesser extent via CYP3A and UGT1A4. The primary and only circulating metabolite, GS-563117, is inactive against PI3K $\delta$ .

### Elimination

The terminal elimination half-life of idelalisib was 8.2 (range: 1.9; 37.2) hours and the apparent clearance of idelalisib was 14.9 (range: 5.1; 63.8) L/h following idelalisib 150 mg twice daily oral administration. Following a single 150 mg oral dose of [<sup>14</sup>C]-labelled idelalisib, approximately 78% and 15% was excreted in faeces and urine, respectively. Unchanged idelalisib accounted for 23% of total radioactivity recovered in urine over 48 hours and 12% of total radioactivity recovered in faeces over 144 hours.

### In vitro interaction data

*In vitro* data indicated that idelalisib is not an inhibitor of the metabolising enzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A, or UGT1A1, or of the transporters OAT1, OAT3, or OCT2.

GS-563117 is not an inhibitor of the metabolising enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or UGT1A1, or of the transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

### Special populations

#### *Gender and race*

Population pharmacokinetic analyses indicated that gender and race had no clinically relevant effect on the exposures to idelalisib or GS-563117.

#### *Elderly*

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

#### *Renal impairment*

A study of pharmacokinetics and safety of idelalisib was performed in healthy subjects and subjects with severe renal impairment (estimated CrCl 15 to 29 mL/min). Following a single 150 mg dose, no clinically relevant changes in exposures to idelalisib or GS-563117 were observed in subjects with severe renal impairment compared to healthy subjects.

#### *Hepatic impairment*

A study of pharmacokinetics and safety of idelalisib was performed in healthy subjects and subjects with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. Following a single 150 mg dose, idelalisib AUC (total, i.e., bound plus unbound) was ~60% higher in moderate and severe impairment compared to matched controls. The idelalisib AUC (unbound), after accounting for differences in protein binding, was ~80% (1.8-fold) higher in moderate and ~152% (2.5-fold) higher in severe impairment compared to matched controls.

#### *Paediatric population*

The pharmacokinetics of idelalisib in paediatric subjects have not been established (see section 4.2).

## **5.3 Preclinical safety data**

### Repeated dose toxicity

Idelalisib induced lymphoid depletion in spleen, thymus, lymph nodes and gut-associated lymphoid tissue. In general, B-lymphocyte dependent areas were more affected than T-lymphocyte dependent areas. In rats, idelalisib has the potential to inhibit T-dependent antibody responses. However, idelalisib did not inhibit the normal host response to *Staphylococcus aureus* and did not exacerbate the myelosuppressive effect of cyclophosphamide. Idelalisib is not considered to have broad immunosuppressive activity.

Idelalisib induced inflammatory changes in both rats and dogs. In studies up to 4 weeks in rats and dogs, hepatic necrosis was observed at 7 and 5 times the human exposure based on AUC, respectively. Serum transaminase elevations correlated with hepatic necrosis in dogs, but were not observed in rats.



No hepatic impairment or chronic transaminase elevations were observed in rats or dogs in studies of 13 weeks and longer duration.

#### Genotoxicity

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, and was not genotoxic in the *in vivo* rat micronucleus study.

#### Carcinogenicity

Carcinogenicity studies with idelalisib have not been conducted.

#### Reproductive and developmental toxicity

In an embryo-foetal development study in rats, increased post-implantation loss, malformations (absence of caudal vertebrae and in some cases also of sacral vertebrae), skeletal variations and lower foetal body weights were observed. Malformations were observed at exposures from 12 times the human exposure based on AUC. Effects on embryo-foetal development were not investigated in a second species.

Degeneration of the seminiferous tubules in the testes was observed in 2- to 13-week repeated dose studies in dogs and rats, but not in studies of 26 weeks and longer duration. In a rat male fertility study, decreases in epididymides and testes weight were observed but no adverse effects on mating or fertility parameters, and no degeneration or loss in spermatogenesis were observed. Female fertility was not affected in rats.

#### Phototoxicity

Evaluation of the potential for phototoxicity in the embryonic murine fibroblast cell line BALB/c 3T3 was inconclusive for idelalisib due to cytotoxicity in the *in vitro* assay. The major metabolite, GS-563117, may enhance phototoxicity when cells are simultaneously exposed to UVA light. There is a potential risk that idelalisib, via its major metabolite, GS-563117, may cause photosensitivity in treated patients.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Microcrystalline cellulose  
Hydroxypropyl cellulose (E463)  
Croscarmellose sodium  
Sodium starch glycolate  
Magnesium stearate

#### Film-coating

Polyvinyl alcohol (E1203)  
Macrogol 3350 (E1521)  
Titanium dioxide (E171)  
Talc (E553B)  
Sunset yellow FCF (E110)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

#### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

#### **6.5 Nature and contents of container**

High density polyethylene (HDPE) bottle, capped with a polypropylene child-resistant closure, containing 60 film-coated tablets and a polyester coil.

Each carton contains 1 bottle.

#### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### **7. MARKETING AUTHORISATION HOLDER**

Gilead Sciences International Ltd  
Cambridge  
CB21 6GT  
United Kingdom

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/938/001

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 18 September 2014

### **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Zydelig 150 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of idelalisib.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, oval-shaped, film-coated tablet of dimensions 10.0 mm by 6.8 mm, debossed on one side with “GSI” and “150” on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Zydelig is indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL):

- who have received at least one prior therapy (see section 4.4), or
- ~~for continuing as first line treatment in patients with the presence of~~ 17p deletion or TP53 mutation ~~who were unsuitable for chemo-immunotherapy and who had already initiated Zydelig as first line treatment in patients who are not eligible for any other therapies~~ (see section 4.4).

Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment (see section 4.4).

### 4.2 Posology and method of administration

Treatment with Zydelig should be conducted by a physician experienced in the use of anticancer therapies.

#### Posology

The recommended dose of Zydelig is 150 mg, taken orally, twice daily. Treatment should be continued until disease progression or unacceptable toxicity.

If the patient misses a dose of Zydelig within 6 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal dosing schedule. If a patient misses a dose by more than 6 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

#### Dose modification

##### *Elevated liver transaminases*

Treatment with Zydelig must be withheld in the event of a Grade 3 or 4 aminotransferase elevation (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] > 5 x upper limit of normal

[ULN]). Once values have returned to Grade 1 or below ( $\text{ALT/AST} \leq 3 \times \text{ULN}$ ), treatment can be resumed at 100 mg twice daily.

If the event does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician.

If the event recurs, treatment with Zydlig must be withheld until the values return to Grade 1 or less, after which re-initiation at 100 mg twice daily may be considered at the discretion of the physician (see sections 4.4 and 4.8).

#### *Diarrhoea/colitis*

Treatment with Zydlig must be withheld in the event of Grade 3 or 4 diarrhoea/colitis. Once diarrhoea/colitis has returned to Grade 1 or below, treatment can be resumed at 100 mg twice daily. If diarrhoea/colitis does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician (see section 4.8).

#### *Pneumonitis*

Treatment with Zydlig must be withheld in the event of suspected pneumonitis. Once pneumonitis has resolved and if re-treatment is appropriate, resumption of treatment at 100 mg twice daily can be considered (see sections 4.4 and 4.8).

#### *Rash*

Treatment with Zydlig must be withheld in the event of Grade 3 or 4 rash. Once rash has returned to Grade 1 or below, treatment can be resumed at 100 mg twice daily. If rash does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician (see section 4.8).

#### *Neutropenia*

Treatment with Zydlig should be withheld in patients while absolute neutrophil count (ANC) is below 500 per  $\text{mm}^3$ . ANC should be monitored at least weekly until ANC is  $\geq 500$  per  $\text{mm}^3$  when treatment can be resumed at 100 mg twice daily (see section 4.4).

ANC 1,000 to < 1,500/ $\text{mm}^3$	ANC 500 to < 1,000/ $\text{mm}^3$	ANC < 500/ $\text{mm}^3$
Maintain Zydlig dosing.	Maintain Zydlig dosing.  Monitor ANC at least weekly.	Interrupt Zydlig dosing.  Monitor ANC at least weekly until $\text{ANC} \geq 500/\text{mm}^3$ , then may resume Zydlig dosing at 100 mg twice daily.

#### *Special patient populations*

##### *Elderly*

No specific dose adjustment is required for elderly patients (aged  $\geq 65$  years) (see section 5.2).

##### *Renal impairment*

No dose adjustment is required for patients with mild, moderate, or severe renal impairment (see section 5.2).

##### *Hepatic impairment*

No dose adjustment is required when initiating treatment with Zydlig in patients with mild or moderate hepatic impairment, but an intensified monitoring of adverse reactions is recommended (see sections 4.4 and 5.2).

There is insufficient data to make dose recommendations for patients with severe hepatic impairment. Therefore, caution is recommended when administering Zydlig in this population and an intensified monitoring of adverse reactions is recommended (see sections 4.4 and 5.2).

### *Paediatric population*

The safety and efficacy of Zydelig in children under the age of 18 years have not been established. No data are available.

### Method of administration

Zydelig is for oral use. Patients should be instructed to swallow the tablet whole. The film-coated tablet should not be chewed or crushed. The film-coated tablet can be taken with or without food (see section 5.2).

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## **4.4 Special warnings and precautions for use**

### 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 idelalisib, including opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP) and cytomegalovirus (CMV). Prophylaxis for PJP should therefore be administered to all patients throughout idelalisib 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 section 4.8).

Patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new respiratory symptoms promptly.

Regular clinical and laboratory screening-monitoring for CMV infection ~~should be conducted. Treatment with Zydelig should be discontinued if there is evidence of infection or viraemia is recommended in patients with positive CMV serology at the start of treatment with idelalisib or with other evidence of a history of CMV infection. Patients with CMV viraemia without associated clinical signs of CMV infection should be carefully monitored. For patients with evidence of CMV viraemia and clinical signs of CMV infection, consideration should be given to interrupting idelalisib until the infection has resolved. If the benefits of resuming idelalisib are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy.~~

### Neutropenia

Treatment-emergent Grade 3 or 4 neutropenia, including febrile neutropenia, have occurred in patients treated with idelalisib. Blood counts should be monitored in all patients at least every 2 weeks for the first 6 months of treatment with idelalisib, and at least weekly in patients while ANC is less than 1,000 per mm<sup>3</sup> (see section 4.2).

### Transaminase elevations

Elevations in ALT and AST of Grade 3 and 4 (> 5 x ULN) have been observed in clinical studies of idelalisib. 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 section 4.2). ALT, AST, and total bilirubin must be monitored 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, patients must be monitored weekly until the values return to Grade 1 or below.

### Diarrhoea/colitis

Cases of severe drug-related colitis occurred relatively late (months) after the start of therapy, sometimes with rapid aggravation, but resolved within a few weeks with dose interruption and additional symptomatic treatment (e.g., anti-inflammatory agents such as enteric budesonide).

There is very limited experience from the treatment of patients with a history of inflammatory bowel disease.

#### Pneumonitis

Cases of pneumonitis have been reported in clinical studies with idelalisib. Patients presenting with serious lung events that do not respond to conventional antimicrobial therapy should be assessed for drug-induced pneumonitis. If pneumonitis is suspected, idelalisib should be interrupted and the patient treated accordingly. Treatment must be discontinued for moderate or severe symptomatic pneumonitis.

#### Stevens-Johnson syndrome and toxic epidermal necrolysis

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with fatal outcomes have been reported when idelalisib was administered concomitantly with other medicinal products associated with these syndromes. If SJS or TEN is suspected, idelalisib should be immediately interrupted and the patient treated accordingly.

#### CYP3A inducers

Idelalisib exposure may be reduced when co-administered with CYP3A inducers such as rifampicin, phenytoin, St. John's wort (*Hypericum perforatum*), or carbamazepine. Since a reduction in idelalisib plasma concentrations may result in decreased efficacy, co-administration of Zydelig with moderate or strong CYP3A inducers should be avoided (see section 4.5).

#### CYP3A substrates

The primary metabolite of idelalisib, GS-563117, is a strong CYP3A4 inhibitor. Thus, idelalisib has the potential to interact with medicinal products that are metabolised by CYP3A, which may lead to increased serum concentrations of the other product (see section 4.5). When idelalisib is co-administered with other medicinal products, the Summary of Product Characteristics (SmPC) for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors. Concomitant treatment of idelalisib with CYP3A substrates with serious and/or life-threatening adverse reactions (e.g., alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible.

#### Hepatic impairment

Intensified monitoring of adverse reactions 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. No patients with severe hepatic impairment were included in clinical studies of idelalisib. Caution is recommended when administering Zydelig in this population.

#### Chronic hepatitis

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.

#### Women of childbearing potential

Women of childbearing potential must use highly effective contraception while taking idelalisib and for 1 month after stopping treatment (see section 4.6). Women using hormonal contraceptives should add a barrier method as a second form of contraception since it is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Idelalisib is metabolised primarily via aldehyde oxidase, and to a lesser extent via CYP3A and glucuronidation (UGT1A4). Its primary metabolite is GS-563117, which is not pharmacologically active. Idelalisib and GS-563117 are substrates of P-gp and BCRP.

## Effect of other medicinal products on idelalisib pharmacokinetics

### *CYP3A inducers*

A clinical drug interaction study found that co-administration of a single dose of 150 mg idelalisib with rifampicin (a strong CYP3A inducer) resulted in a ~75% reduction in idelalisib AUC<sub>inf</sub>. Co-administration of Zydelyg with moderate or strong CYP3A inducers such as rifampicin, phenytoin, St. John's wort, or carbamazepine should be avoided as this may result in decreased efficacy (see section 4.4).

### *CYP3A/P-gp inhibitors*

A clinical drug interaction study found that co-administration of a single dose of 400 mg idelalisib with 400 mg once daily ketoconazole (a strong CYP3A, P-gp and BCRP inhibitor) resulted in a 26% increase in C<sub>max</sub> and a 79% increase in AUC<sub>inf</sub> of idelalisib. No initial dose adjustment of idelalisib is considered necessary when administered with CYP3A/P-gp inhibitors, but an intensified monitoring of adverse reactions is recommended.

## Effect of idelalisib on the pharmacokinetics of other medicinal products

### *CYP3A substrates*

The primary metabolite of idelalisib, GS-563117, is a strong CYP3A inhibitor. A clinical drug interaction study found that co-administration of idelalisib with midazolam (a sensitive CYP3A substrate) resulted in a ~140% increase in C<sub>max</sub> and a ~440% increase in AUC<sub>inf</sub> of midazolam due to the CYP3A inhibition by GS-563117. Co-administration of idelalisib with CYP3A substrates may increase their systemic exposures and increase or prolong their therapeutic activity and adverse reactions. *In vitro*, the CYP3A4 inhibition was irreversible, and return to normal enzyme activity is therefore expected to take several days after stopping idelalisib administration.

Potential interactions between idelalisib and co-administered medicinal products that are CYP3A substrates are listed in Table 1 (increase is indicated as “↑”). This list is not exhaustive and is intended to serve as guidance only. In general, the SmPC for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors (see section 4.4).

**Table 1: Interactions between idelalisib and other medicinal products that are CYP3A substrates**

Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
<b>ALPHA-1 ADRENORECEPTOR ANTAGONISTS</b>		
Alfuzosin	↑ serum concentrations	Idelalisib should not be co-administered with alfuzosin.
<b>ANALGESICS</b>		
Fentanyl, alfentanil, methadone, buprenorphine/naloxone	↑ serum concentrations	Careful monitoring of adverse reactions (e.g., respiratory depression, sedation) is recommended.
<b>ANTIARRHYTHMICS</b>		
Amiodarone, quinidine	↑ serum concentrations	Idelalisib should not be co-administered with amiodarone or quinidine.
Bepiridil, disopyramide, lidocaine	↑ serum concentrations	Clinical monitoring is recommended.
<b>ANTI-CANCER AGENTS</b>		
Tyrosine kinase inhibitors such as dasatinib and nilotinib, also vincristine and vinblastine	↑ serum concentrations	Careful monitoring of the tolerance to these anti-cancer agents is recommended.

Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
<b>ANTICOAGULANTS</b>		
Warfarin	↑ serum concentrations	It is recommended that the international normalised ratio (INR) be monitored upon co-administration and following ceasing treatment with idelalisib.
<b>ANTICONVULSANTS</b>		
Carbamazepine	↑ serum concentrations	Anticonvulsant drug levels should be monitored.
<b>ANTIDEPRESSANTS</b>		
Trazodone	↑ serum concentrations	Careful dose titration of the antidepressant and monitoring for antidepressant response is recommended.
<b>ANTI-GOUT</b>		
Colchicine	↑ serum concentrations	Dose reductions of colchicine may be required. Idelalisib should not be co-administered with colchicine to patients with renal or hepatic impairment.
<b>ANTI-HYPERTENSIVES</b>		
Amlodipine, diltiazem, felodipine, nifedipine, nicardipine	↑ serum concentrations	Clinical monitoring of therapeutic effect and adverse reactions is recommended.
<b>ANTI-INFECTIVES</b>		
<b>Antifungals</b>		
Ketoconazole, itraconazole, posaconazole, voriconazole	↑ serum concentrations	Clinical monitoring is recommended.
<b>Antimycobacterials</b>		
Rifabutin	↑ serum concentrations	Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is recommended.
<b>HCV protease inhibitors</b>		
Boceprevir, telaprevir	↑ serum concentrations	Clinical monitoring is recommended.
<b>Macrolide antibiotics</b>		
Clarithromycin, telithromycin	↑ serum concentrations	<p>No dose adjustment of clarithromycin is required for patients with normal renal function or mild renal impairment (creatinine clearance [CrCl] 60-90 mL/min). Clinical monitoring is recommended for patients with CrCl &lt; 90 mL/min. For patients with CrCl &lt; 60 mL/min, alternative antibacterials should be considered.</p> <p>Clinical monitoring is recommended for telithromycin.</p>



Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
<b>ANTI-PSYCHOTICS/NEUROLEPTICS</b>		
Quetiapine, pimozide	↑ serum concentrations	Idelalisib should not be co-administered with quetiapine or pimozide.  Alternative medicinal products, such as olanzapine, may be considered.
<b>ENDOTHELIN RECEPTOR ANTAGONISTS</b>		
Bosentan	↑ serum concentrations	Caution should be exercised and patients closely observed for bosentan-related toxicity.
<b>ERGOT ALKALOIDS</b>		
Ergotamine, dihydroergotamine	↑ serum concentrations	Idelalisib should not be co-administered with ergotamine or dihydroergotamine.
<b>GASTROINTESTINAL MOTILITY AGENTS</b>		
Cisapride	↑ serum concentrations	Idelalisib should not be co-administered with cisapride.
<b>GLUCOCORTICOIDS</b>		
Inhaled/nasal corticosteroids: Budesonide, fluticasone	↑ serum concentrations	Clinical monitoring is recommended.
Oral budesonide	↑ serum concentrations	Clinical monitoring is recommended for increased signs/symptoms of corticosteroid effects.
<b>HMG CO-A REDUCTASE INHIBITORS</b>		
Lovastatin, simvastatin	↑ serum concentrations	Idelalisib should not be co-administered with lovastatin or simvastatin.
Atorvastatin	↑ serum concentrations	Clinical monitoring is recommended and a lower starting dose of atorvastatin may be considered. Alternatively, switching to pravastatin, rosuvastatin, or pitavastatin may be considered.
<b>IMMUNOSUPPRESSANTS</b>		
Ciclosporin, sirolimus, tacrolimus	↑ serum concentrations	Therapeutic monitoring is recommended.
<b>INHALED BETA AGONIST</b>		
Salmeterol	↑ serum concentrations	Concurrent administration of salmeterol and idelalisib is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.

Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
<b>PHOSPHODIESTERASE INHIBITORS</b>		
Sildenafil	↑ serum concentrations	For pulmonary arterial hypertension:  Idelalisib should not be co-administered with sildenafil.
Tadalafil	↑ serum concentrations	Caution should be exercised, including consideration of dose reduction, when co-administering tadalafil with idelalisib.  For erectile dysfunction:
Sildenafil, tadalafil	↑ serum concentrations	Particular caution must be used and dose reduction may be considered when prescribing sildenafil or tadalafil with idelalisib with increased monitoring for adverse events.
<b>SEDATIVES/HYPNOTICS</b>		
Midazolam (oral), triazolam	↑ serum concentrations	Idelalisib should not be co-administered with midazolam (oral) or triazolam.
Buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ serum concentrations	Concentration monitoring of sedatives/hypnotics is recommended and dose reduction may be considered.

#### *CYP2C8 substrates*

*In vitro*, idelalisib both inhibited and induced CYP2C8, but it is not known whether this translates to an *in vivo* effect on CYP2C8 substrates. Caution is advised if Zydelyg is used together with narrow therapeutic index drugs that are substrates of CYP2C8 (paclitaxel).

#### *Substrates of inducible enzymes (e.g., CYP2C9, CYP2C19, CYP2B6 and UGT)*

*In vitro*, idelalisib was an inducer of several enzymes, and a risk for decreased exposure and thereby decreased efficacy of substrates of inducible enzymes such as CYP2C9, CYP2C19, CYP2B6 and UGT cannot be excluded. Caution is advised if Zydelyg is used together with narrow therapeutic index drugs that are substrates of these enzymes (warfarin, phenytoin, S-mephenytoin).

#### *BCRP, OATP1B1, OATP1B3 and P-gp substrates*

Co-administration of multiple doses of idelalisib 150 mg twice daily to healthy subjects resulted in comparable exposures for rosuvastatin (AUC 90% CI: 87, 121) and digoxin (AUC 90% CI: 98, 111), suggesting no clinically relevant inhibition of BCRP, OATP1B1/1B3 or systemic P-gp by idelalisib. A risk for P-gp inhibition in the gastrointestinal tract, that could result in increased exposure of sensitive substrates for intestinal P-gp such as dabigatran etexilate, cannot be excluded.

#### Paediatric population

Interaction studies have only been performed in adults.

## **4.6 Fertility, pregnancy and lactation**

#### Women of childbearing potential

Based on findings in animals, idelalisib may cause foetal harm. Women should avoid becoming pregnant while taking Zydelyg, and for up to 1 month after ending treatment. Therefore, women of childbearing potential must use highly effective contraception while taking Zydelyg and for 1 month after stopping treatment. It is currently unknown whether idelalisib may reduce the effectiveness of

hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method as a second form of contraception.

#### Pregnancy

There are no or limited amount of data from the use of idelalisib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Zydelig is not recommended during pregnancy and in women of childbearing potential not using contraception.

#### Breast-feeding

It is not known whether idelalisib and its metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with Zydelig.

#### Fertility

No human data on the effect of idelalisib on fertility are available. Animal studies indicate the potential for harmful effects of idelalisib on fertility and foetal development (see section 5.3).

### **4.7 Effects on ability to drive and use machines**

Zydelig has no or negligible influence on the ability to drive and use machines.

### **4.8 Undesirable effects**

#### Summary of the safety profile

Assessment of adverse reactions is based on one Phase 3 study and seven Phase 1 and 2 studies. Phase 3 study 312-0116 was a randomised, double-blind, placebo-controlled study in which 220 patients with previously treated CLL were randomised 1:1 to receive idelalisib + rituximab or placebo + rituximab. The Phase 1 and 2 studies assessed the safety of idelalisib in 490 patients with haematologic malignancies, including 354 subjects who received idelalisib (any dose) as a single agent and 136 subjects who received idelalisib in combination with anti-CD20 monoclonal antibodies.

During treatment with idelalisib, the most frequently reported adverse drug reactions are reported in Table 2.

#### Tabulated list of adverse reactions

The adverse drug reactions reported with idelalisib alone or in combination with anti-CD20 monoclonal antibodies are provided in Table 2. Adverse reactions are listed by system organ class and frequency. Frequencies are defined as follows: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), and not known (cannot be estimated from available data).

**Table 2: Adverse drug reactions reported in clinical studies in patients with haematologic malignancies receiving idelalisib**

Reaction	Any grade	Grade $\geq 3$
<i>Infections and infestations</i>		
Infections <u>(including <i>Pneumocystis jirovecii</i> pneumonia and CMV)*</u>	Very common	Very common

Reaction	Any grade	Grade $\geq 3$
<i>Blood and lymphatic system disorders</i>		
Neutropenia	Very common	Very common
<i>Respiratory, thoracic and mediastinal disorders</i>		
Pneumonitis	Common	Common
<i>Gastrointestinal disorders</i>		
Diarrhoea/colitis	Very common	Very common
<i>Hepatobiliary disorders</i>		
Transaminase increased	Very common	Very common
<i>Skin and subcutaneous tissue disorders</i>		
Rash**	Very common	Common
Stevens-Johnson syndrome/ toxic epidermal necrolysis	Rare	Rare
<i>General disorders and administration site conditions</i>		
Pyrexia	Very common	Common
<i>Investigations</i>		
Increased triglycerides	Very common	Common

\* Comprised of opportunistic infections as well as bacterial and viral infections such as pneumonia, bronchitis, and sepsis.

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

#### Description of selected adverse reactions

##### Infections (see section 4.4)

Higher frequencies of infections overall, including Grade 3 and 4 infections, were observed in the idelalisib arms compared to the control arms of idelalisib 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 PJP and CMV, were among those identified. Nearly all PJP infections, including fatal cases, occurred in the absence of PJP prophylaxis. There have been cases of PJP after stopping idelalisib treatment.

##### Rash

Rash was generally mild to moderate and resulted in discontinuation of treatment in about 2% of patients. In study 312-0116, rash (reported as dermatitis exfoliative, drug eruption, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, and rash pruritic) occurred in 24.5% of subjects who received idelalisib + rituximab and 6.5% who received placebo + rituximab. Of these, 3.6% who received idelalisib + rituximab and 0.9% who received placebo + rituximab had rash of Grade 3, and no subjects had an adverse event of Grade 4. Rash typically resolved with treatment (e.g., topical and/or oral steroids, diphenhydramine) and dose interruption for severe cases (see section 5.3, phototoxicity).

##### Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4)

Rarely, cases of SJS and TEN have occurred when idelalisib was administered concomitantly with other medicinal products associated with these syndromes (bendamustine, rituximab, allopurinol, and amoxicillin). SJS or TEN occurred within one month of the medicinal combination and fatal outcomes have resulted.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8). 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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: **L01XX47**

#### Mechanism of action

Idelalisib inhibits phosphatidylinositol 3-kinase p110 $\delta$  (PI3K $\delta$ ), 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 PI3K $\delta$ , resulting in inhibition of the phosphorylation of the key lipid second messenger phosphatidylinositol and prevention of Akt (protein kinase B) phosphorylation.

Idelalisib induces apoptosis and inhibits proliferation in cell lines derived from malignant B-cells and in primary tumour cells. Through inhibition of chemokine receptors CXCR4 and CXCR5 signalling induced by the chemokines CXCL12 and CXCL13, respectively, idelalisib inhibits homing and retention of malignant B-cells in the tumour microenvironment including lymphoid tissues and the bone marrow.

#### Pharmacodynamic effects

The effect of idelalisib (150 mg and 400 mg) on the QT/QTc interval was evaluated in a placebo- and positive-controlled (moxifloxacin 400 mg) crossover study in 40 healthy subjects. At a dose 2.7 times the maximum recommended dose, idelalisib did not prolong the QT/QTc interval (i.e., < 10 ms).

#### Clinical efficacy in chronic lymphocytic leukaemia

##### *Idelalisib in combination with immunotherapy*

Study 312-0116 was a Phase 3, randomised, double-blind, placebo-controlled study in 220 subjects with previously treated CLL who required treatment but were not considered suitable for cytotoxic chemotherapy. Subjects were randomised 1:1 to receive 8 cycles of rituximab (first cycle at 375 mg/m<sup>2</sup> body surface area [BSA], subsequent cycles at 500 mg/m<sup>2</sup> BSA) in combination with either an oral placebo twice daily or with idelalisib 150 mg taken twice daily until disease progression or unacceptable toxicity.

The median age was 71 years (range: 47 to 92) with 78.2% of patients over 65 years; 65.5% were male, and 90.0% were white; 64.1% had a Rai stage of III or IV, and 55.9% had Binet Stage C. Most subjects had adverse cytogenetic prognostic factors: 43.2% had a 17p chromosomal deletion and/or tumour protein 53 (*TP53*) mutation, and 83.6% had unmutated genes for the immunoglobulin heavy chain variable region (*IGHV*). The median time from diagnosis of CLL to randomisation was 8.5 years. Subjects had a median Cumulative Illness Rating Score (CIRS) of 8. The median number of prior therapies was 3.0. Nearly all (95.9%) subjects had received prior anti-CD20 monoclonal antibodies. The primary endpoint was progression free survival (PFS). Efficacy results are summarised in Tables 3 and 4. The Kaplan-Meier curve for PFS is provided in Figure 1.

Compared with rituximab + placebo, treatment with idelalisib + rituximab resulted in statistically significant and clinically meaningful improvements in physical well-being, social well-being, functional well-being, as well as in the leukaemia-specific subscales of the Functional Assessment of Cancer Therapy: Leukaemia (FACT-LEU) instruments, and in statistically significant and clinically

meaningful improvements in anxiety, depression and usual activities as measured by the EuroQoL Five-Dimensions (EQ-5D) instrument.

**Table 3: Efficacy results from study 312-0116**

	<b>Idelalisib + R</b> <b>N = 110</b>	<b>Placebo + R</b> <b>N = 110</b>
<b>PFS</b> Median (months) (95% CI)	19.4 (12.3, NR)	6.5 (4.0, 7.3)
Hazard ratio (95% CI)	0.15 (0.09, 0.25)	
P-value	< 0.0001	
<b>ORR*</b> n (%) (95% CI)	92 (83.6%) (75.4, 90.0)	17 (15.5%) (9.3, 23.6)
Odds ratio (95% CI)	27.76 (13.40, 57.49)	
P-value	< 0.0001	
<b>LNR**</b> n/N (%) (95% CI)	102/106 (96.2%) (90.6, 99.0)	7/104 (6.7%) (2.7, 13.4)
Odds ratio (95% CI)	225.83 (65.56, 777.94)	
P-value	< 0.0001	
<b>OS^</b> Median (months) (95% CI)	NR (NR, NR)	20.8 (14.8, NR)
Hazard ratio (95% CI)	0.34 (0.19, 0.60)	
P-value	0.0001	

CI: confidence interval; R: rituximab; n: number of responding subjects; N: number of subjects per group; NR: not reached. The analyses of PFS, overall response rate (ORR) and lymph node response rate (LNR) were based on evaluation by an independent review committee (IRC).

\* ORR defined as the proportion of subjects who achieved a complete response (CR) or partial response (PR) based on the 2013 National Comprehensive Cancer Network (NCCN) response criteria and Cheson (2012).

\*\* LNR defined as the proportion of subjects who achieved a  $\geq 50\%$  decrease in the sum of products of the greatest perpendicular diameters of index lesions. Only subjects that had both baseline and  $\geq 1$  evaluable post-baseline assessments were included in this analysis.

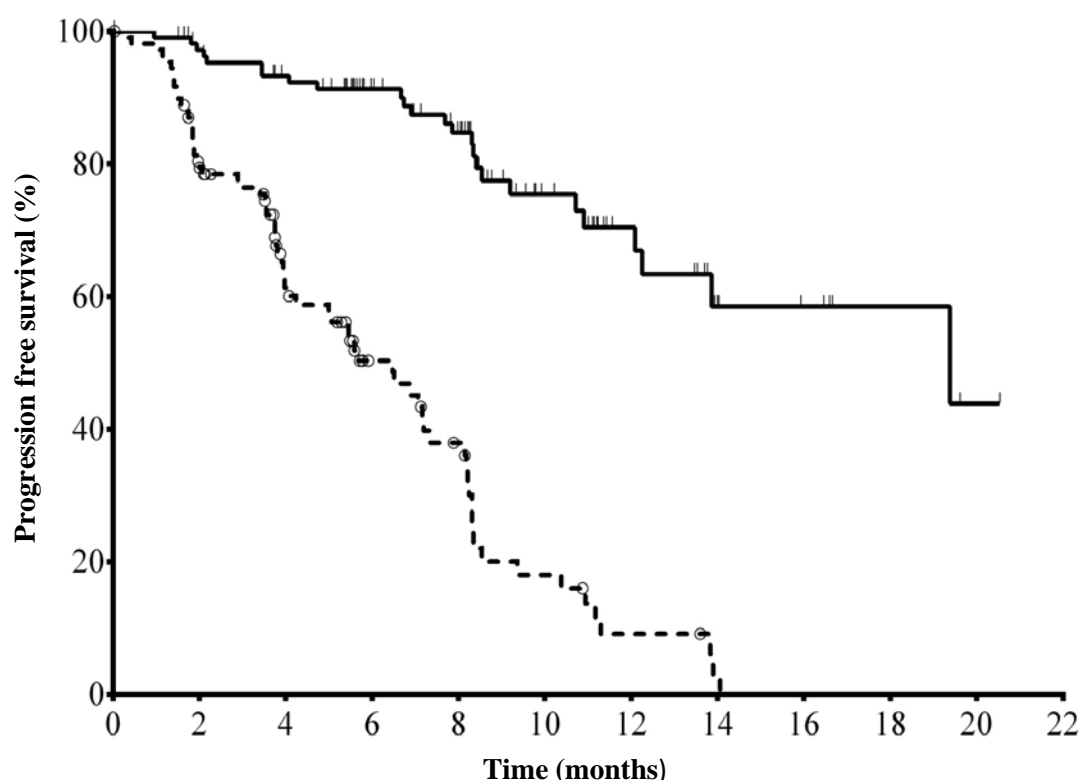
^ Overall survival (OS) analysis includes data from subjects who received placebo + R on study 312-0116 and subsequently received idelalisib in an extension study, based on intent-to-treat analysis.

**Table 4: Summary of PFS and response rates in pre-specified subgroups from study 312-0116**

	<b>Idelalisib + R</b> <b>N = 46</b>	<b>Placebo + R</b> <b>N = 49</b>
<b>17p deletion/TP53 mutation</b>		
PFS median (months) (95% CI)	NR (12.3, NR)	4.0 (3.7, 5.7)
Hazard ratio (95% CI)	0.13 (0.07, 0.27)	
ORR (95% CI)	84.8% (71.1, 93.7)	12.2% (4.6, 24.8)
<b>Unmutated IGHV</b>	<b>N = 91</b>	<b>N = 93</b>
PFS median (months) (95% CI)	19.4 (13.9, NR)	5.6 (4.0, 7.2)
Hazard ratio (95% CI)	0.14 (0.08, 0.23)	
ORR (95% CI)	82.4% (73.0, 89.6)	15.1% (8.5, 24.0)
<b>Age <math>\geq 65</math> years</b>	<b>N = 89</b>	<b>N = 83</b>
PFS median (months) (95% CI)	19.4 (12.3, NR)	5.7 (4.0, 7.3)
Hazard ratio (95% CI)	0.14 (0.08, 0.25)	
ORR (95% CI)	84.3% (75.0, 91.1)	16.9% (9.5, 26.7)

CI: confidence interval; R: rituximab; N: number of subjects per group; NR: not reached

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



N at risk (Events)

Idelalisib + R	110 (0)	101 (3)	93 (7)	73 (9)	59 (14)	31 (19)	20 (21)	9 (24)	7 (24)	4 (24)	1 (25)	0 (25)
Placebo + R	110 (0)	84 (21)	48 (38)	29 (46)	20 (53)	9 (63)	4 (67)	1 (69)	0 (70)	0 (70)	0 (70)	0 (70)

Solid line: idelalisib + R (N = 110), dashed line: placebo + R (N = 110)

R: rituximab; N: number of subjects per group

The analysis of PFS was based on evaluation by an IRC. For subjects in the placebo + R group, the summary includes data up to the first dosing of idelalisib in an extension study. Median PFS: idelalisib + R = 19.4 months, placebo + R = 6.5 months. Hazard ratio = 0.15, 95% CI (0.09, 0.24), p < 0.0001.

Study 101-08/99 enrolled 64 subjects with previously untreated CLL, including 5 subjects with small lymphocytic lymphoma (SLL). Subjects received idelalisib 150 mg twice daily and rituximab 375 mg/m<sup>2</sup> BSA weekly. The ORR was 96.9%, with 12 CRs (18.8%) and 50 PRs (78.1%), including 3 CRs and 6 PRs in subjects with a 17p deletion and/or *TP53* mutation and 2 CRs and 34 PRs in subjects with unmutated *IGHV*. The median duration of response (DOR) has not been reached.

#### Clinical efficacy in follicular lymphoma

The safety and efficacy of idelalisib were assessed in a single-arm, multicentre clinical study (study 101-09) conducted in 125 subjects with indolent B-cell non-Hodgkin lymphoma (iNHL, including: FL, n = 72; SLL, n = 28; lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia [LPL/WM], n = 10; and marginal zone lymphoma [MZL], n = 15). All subjects were refractory to rituximab and 124 of 125 subjects were refractory to at least one alkylating agent. One hundred and twelve (89.6%) subjects were refractory to their last regimen prior to study entry.

Of the 125 subjects enrolled, 80 (64%) were male, the median age was 64 years (range: 33 to 87), and 110 (89%) were white. Subjects received 150 mg of idelalisib orally twice daily until evidence of disease progression or unacceptable toxicity.

The primary endpoint was the ORR defined as the proportion of subjects who achieved a CR or PR (based on the Revised Response Criteria for Malignant Lymphoma [Cheson]), and, for subjects with Waldenström macroglobulinaemia, a minor response (MR) (based on the Response Assessment for

Waldenström macroglobulinaemia [Owen]). 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 are summarised in Table 5.

**Table 5: Summary of response in subjects with FL treated with idelalisib (IRC assessment)**

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

CI: confidence interval; n: number of responding subjects

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

The median DOR for all subjects was 12.5 months (12.5 months for SLL subjects, and not reached for FL, LPL/WM and MZL subjects). Among the 122 subjects with measurable lymph nodes at both baseline and post-baseline, 67 subjects (54.9%) achieved a  $\geq 50\%$  decrease from baseline in the sum of the products of the diameters (SPD) of index lesions. Of the subjects who did not respond, 10 (8.0%) had progressive disease as best response, and 2 (1.6%) were not evaluable. The median OS, including long-term follow-up for all 125 subjects, was 20.3 months.

#### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with idelalisib in one or more subsets of the paediatric population in the treatment of mature B-cell neoplasms (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

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

Following 150 mg twice daily administration of idelalisib, average (range)  $C_{max}$  and AUC at steady-state were 1,953 (272; 3,905) ng/mL and 10,439 (2,349; 29,315) ng•h/mL for idelalisib and 4,039 (669; 10,897) ng/mL and 39,744 (6,002; 119,770) ng•h/mL for GS-563117, respectively. The plasma exposures ( $C_{max}$  and AUC) of idelalisib are approximately dose proportional between 50 mg and 100 mg and less than dose proportional above 100 mg.

### *Effects of food*

Relative to fasting conditions, administration of an early capsule formulation of idelalisib 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.

### Distribution

Idelalisib is 93% to 94% bound to human plasma proteins at concentrations observed clinically. The mean blood-to-plasma concentration ratio was approximately 0.5. The apparent volume of distribution for idelalisib (mean) was approximately 96 L.

### Biotransformation

Idelalisib is metabolised 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.



### Elimination

The terminal elimination half-life of idelalisib was 8.2 (range: 1.9; 37.2) hours and the apparent clearance of idelalisib was 14.9 (range: 5.1; 63.8) L/h following idelalisib 150 mg twice daily oral administration. Following a single 150 mg oral dose of [<sup>14</sup>C]-labelled idelalisib, approximately 78% and 15% was excreted in faeces and urine, respectively. Unchanged idelalisib accounted for 23% of total radioactivity recovered in urine over 48 hours and 12% of total radioactivity recovered in faeces over 144 hours.

### In vitro interaction data

*In vitro* data indicated that idelalisib is not an inhibitor of the metabolising enzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A, or UGT1A1, or of the transporters OAT1, OAT3, or OCT2.

GS-563117 is not an inhibitor of the metabolising enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or UGT1A1, or of the transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

### Special populations

#### *Gender and race*

Population pharmacokinetic analyses indicated that gender and race had no clinically relevant effect on the exposures to idelalisib or GS-563117.

#### *Elderly*

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

#### *Renal impairment*

A study of pharmacokinetics and safety of idelalisib was performed in healthy subjects and subjects with severe renal impairment (estimated CrCl 15 to 29 mL/min). Following a single 150 mg dose, no clinically relevant changes in exposures to idelalisib or GS-563117 were observed in subjects with severe renal impairment compared to healthy subjects.

#### *Hepatic impairment*

A study of pharmacokinetics and safety of idelalisib was performed in healthy subjects and subjects with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. Following a single 150 mg dose, idelalisib AUC (total, i.e., bound plus unbound) was ~60% higher in moderate and severe impairment compared to matched controls. The idelalisib AUC (unbound), after accounting for differences in protein binding, was ~80% (1.8-fold) higher in moderate and ~152% (2.5-fold) higher in severe impairment compared to matched controls.

#### *Paediatric population*

The pharmacokinetics of idelalisib in paediatric subjects have not been established (see section 4.2).

## **5.3 Preclinical safety data**

### Repeated dose toxicity

Idelalisib induced lymphoid depletion in spleen, thymus, lymph nodes and gut-associated lymphoid tissue. In general, B-lymphocyte dependent areas were more affected than T-lymphocyte dependent areas. In rats, idelalisib has the potential to inhibit T-dependent antibody responses. However, idelalisib did not inhibit the normal host response to *Staphylococcus aureus* and did not exacerbate the myelosuppressive effect of cyclophosphamide. Idelalisib is not considered to have broad immunosuppressive activity.

Idelalisib induced inflammatory changes in both rats and dogs. In studies up to 4 weeks in rats and dogs, hepatic necrosis was observed at 7 and 5 times the human exposure based on AUC, respectively.

Serum transaminase elevations correlated with hepatic necrosis in dogs, but were not observed in rats. No hepatic impairment or chronic transaminase elevations were observed in rats or dogs in studies of 13 weeks and longer duration.

#### Genotoxicity

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, and was not genotoxic in the *in vivo* rat micronucleus study.

#### Carcinogenicity

Carcinogenicity studies with idelalisib have not been conducted.

#### Reproductive and developmental toxicity

In an embryo-foetal development study in rats, increased post-implantation loss, malformations (absence of caudal vertebrae and in some cases also of sacral vertebrae), skeletal variations and lower foetal body weights were observed. Malformations were observed at exposures from 12 times the human exposure based on AUC. Effects on embryo-foetal development were not investigated in a second species.

Degeneration of the seminiferous tubules in the testes was observed in 2- to 13-week repeated dose studies in dogs and rats, but not in studies of 26 weeks and longer duration. In a rat male fertility study, decreases in epididymides and testes weight were observed but no adverse effects on mating or fertility parameters, and no degeneration or loss in spermatogenesis were observed. Female fertility was not affected in rats.

#### Phototoxicity

Evaluation of the potential for phototoxicity in the embryonic murine fibroblast cell line BALB/c 3T3 was inconclusive for idelalisib due to cytotoxicity in the *in vitro* assay. The major metabolite, GS-563117, may enhance phototoxicity when cells are simultaneously exposed to UVA light. There is a potential risk that idelalisib, via its major metabolite, GS-563117, may cause photosensitivity in treated patients.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Microcrystalline cellulose  
Hydroxypropyl cellulose (E463)  
Croscarmellose sodium  
Sodium starch glycolate  
Magnesium stearate

#### Film-coating

Polyvinyl alcohol (E1203)  
Macrogol 3350 (E1521)  
Titanium dioxide (E171)  
Talc (E553B)  
Iron oxide red (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

High density polyethylene (HDPE) bottle, capped with a polypropylene child-resistant closure, containing 60 film-coated tablets and a polyester coil.

Each carton contains 1 bottle.

### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Gilead Sciences International Ltd  
Cambridge  
CB21 6GT  
United Kingdom

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/938/002

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 18 September 2014

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

Gilead Sciences Ireland UC  
IDA Business & Technology Park  
Carrigtohill  
County Cork  
Ireland

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

### **• Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

### **• Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

<b>Description</b>	<b>Due date</b>
The applicant should submit the final study report for Phase 3 extension study GS-US-312-0117, to evaluate the efficacy and safety of idelalisib (GS-1101) in combination with rituximab for previously treated CLL. Updates on PFS, OS and duration of response for patients with or without 17p deletion/ <i>TP53</i> mutation and the whole population should be submitted.	31 December 2017
The applicant should submit the final study report for Phase 2 study 101-09 to evaluate the efficacy and safety of idelalisib in subjects with indolent B-cell NHL refractory to rituximab and alkylating agents. Updates on safety and efficacy results including overall survival and updates of the analyses of subjects with baseline lymphopenia, should be submitted.	31 December 2016
The applicant should submit the final study report for the extension study 101-99.	30 September 2017

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON LABEL****1. NAME OF THE MEDICINAL PRODUCT**

Zydelig 100 mg film-coated tablets  
Idelalisib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 100 mg of idelalisib.

**3. LIST OF EXCIPIENTS**

Contains sunset yellow FCF (E110), see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets  
60 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

<b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b>
--

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
---

Gilead Sciences International Ltd  
Cambridge  
CB21 6GT  
United Kingdom

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
--

EU/1/14/938/001

<b>13. BATCH NUMBER</b>
-------------------------

Lot

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
--

Medicinal product subject to medical prescription.

<b>15. INSTRUCTIONS ON USE</b>
--------------------------------

<b>16. INFORMATION IN BRAILLE</b>
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Zydelig 100 mg

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING****BOTTLE LABEL****1. NAME OF THE MEDICINAL PRODUCT**

Zydelig 100 mg film-coated tablets  
Idelalisib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 100 mg of idelalisib.

**3. LIST OF EXCIPIENTS**

Contains sunset yellow FCF (E110), see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets  
60 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Gilead Sciences International Ltd  
Cambridge  
CB21 6GT  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/938/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON LABEL****1. NAME OF THE MEDICINAL PRODUCT**

Zydelig 150 mg film-coated tablets  
Idelalisib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 150 mg of idelalisib.

**3. LIST OF EXCIPIENTS****4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets  
60 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS****10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
---

Gilead Sciences International Ltd  
Cambridge  
CB21 6GT  
United Kingdom

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
--

EU/1/14/938/002

<b>13. BATCH NUMBER</b>
-------------------------

Lot

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
--

Medicinal product subject to medical prescription.

<b>15. INSTRUCTIONS ON USE</b>
--------------------------------

<b>16. INFORMATION IN BRAILLE</b>
-----------------------------------

Zydelig 150 mg

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING****BOTTLE LABEL****1. NAME OF THE MEDICINAL PRODUCT**

Zydelig 150 mg film-coated tablets  
Idelalisib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 150 mg of idelalisib.

**3. LIST OF EXCIPIENTS****4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets  
60 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS****10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
---

Gilead Sciences International Ltd  
Cambridge  
CB21 6GT  
United Kingdom

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
--

EU/1/14/938/002

<b>13. BATCH NUMBER</b>
-------------------------

Lot

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
--

Medicinal product subject to medical prescription.

<b>15. INSTRUCTIONS ON USE</b>
--------------------------------

<b>16. INFORMATION IN BRAILLE</b>
-----------------------------------



## **B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### Zydelig 100 mg film-coated tablets

Idelalisib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

#### **Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Zydelig is and what it is used for
2. What you need to know before you take Zydelig
3. How to take Zydelig
4. Possible side effects
5. How to store Zydelig
6. Contents of the pack and other information

#### **1. What Zydelig is and what it is used for**

Zydelig is a cancer medicine that contains the active substance idelalisib. It works by blocking the effects of an enzyme involved in multiplication and survival of certain white blood cells called lymphocytes. Because this enzyme is overactivated in certain cancerous white blood cells, by blocking it, Zydelig will kill and reduce the number of cancer cells.

Zydelig may be used for the treatment of two different cancers:

##### **Chronic lymphocytic leukaemia**

*Chronic lymphocytic leukaemia* (CLL) is a cancer of a type of white blood cell called B-lymphocytes. In this disease, the lymphocytes multiply too quickly and live for too long, so that there are too many of them circulating in the blood.

In CLL Zydelig treatment ~~can be continued~~ is used in combination with another medicine called rituximab in patients who have certain high-risk factors ~~and who are already taking Zydelig. In CLL it can also be used in combination with rituximab~~ or in patients whose cancer has come back after at least one previous treatment.

##### **Follicular lymphoma**

*Follicular lymphoma* (FL) is a cancer of a type of white blood cell called B-lymphocytes. In follicular lymphoma, the B-lymphocytes multiply too quickly and live for too long, so there are too many of them in the lymph nodes. In FL Zydelig is used on its own in patients whose cancer has not responded to treatment with two previous cancer treatments.

## 2. What you need to know before you take Zydelig

### Do not take Zydelig

- if you are **allergic** to idelalisib or any of the other ingredients of this medicine (listed in section 6).  
→ **Talk to your doctor** if this applies to you.

### Warnings and precautions

Talk to your doctor before taking Zydelig. Tell your doctor:

- if you have liver problems
- if you have any other medical conditions or illness (especially an infection or fever)

Serious and fatal infections have occurred in patients taking Zydelig. You should take additional medicine provided by your doctor while you are taking Zydelig to prevent one type of infection. Your doctor will monitor you for evidence of infection. Tell your doctor right away if you become ill (especially with a fever, cough or breathing difficulties) while you are taking Zydelig.

**You will need regular blood tests** before and during treatment with Zydelig. This is to check that you do not have an infection, that your liver is working properly, and that your blood counts are normal. If necessary, your doctor may decide to stop treatment for a while, before starting treatment again at the same or a lower dose. Your doctor may also decide to permanently stop treatment with Zydelig.

Zydelig can cause severe diarrhoea. Tell your doctor right away at the first sign of diarrhoea.

Zydelig can cause lung inflammation. Tell your doctor right away:

- if you have a new or worsening cough
- if you have shortness of breath or difficulty breathing

Severe skin blistering conditions have been reported in some people who have received Zydelig while also receiving other medicines known to cause these potentially life-threatening conditions. Blistering can also involve the lining of the mouth, genitals, and/or eyes. Peeling away of the skin may lead to serious infection. Tell your doctor right away:

- if you have redness and blistering of the skin
- if you have swelling and blistering of the lining of the mouth, genitals, and/or eyes

### Children and adolescents

Do not give this medicine to children and adolescents under 18 years of age because it has not been studied in this age group.

### Other medicines and Zydelig

**Zydelig should not be used with any other medicines unless your doctor has told you it is safe to do so.**

**Tell your doctor if you are taking, have recently taken or might take any other medicines.** This is extremely important, as using more than one medicine at the same time can strengthen or weaken their effect.

Taking Zydelig with certain medicines may stop them working properly, or may make side effects worse. In particular, tell your doctor if you are taking any of the following:

- **alfuzosin**, a medicine used to treat an enlarged prostate
- **dabigatran, warfarin**, medicines used to thin the blood
- **amiodarone, bepridil, disopyramide, lidocaine, quinidine**, medicines used to treat heart problems
- **dihydroergotamine, ergotamine**, medicines used to treat migraine headache

- **cisapride**, a medicine used to relieve certain stomach problems
- **pimozide**, a medicine used to treat abnormal thoughts or feelings
- **midazolam, triazolam**, when taken by mouth to help you sleep and/or relieve anxiety
- **quetiapine**, a medicine used to treat schizophrenia, bipolar disorder and major depressive disorder
- **amlodipine, diltiazem, felodipine, nicardipine, nifedipine**, medicines used to treat high blood pressure and heart problems
- **bosentan**, a medicine used to treat pulmonary arterial hypertension
- **sildenafil, tadalafil**, medicines used to treat impotence and pulmonary hypertension, a lung disease that makes breathing difficult
- **budesonide, fluticasone**, medicines used to treat hayfever and asthma, and **salmeterol**, used to treat asthma
- **rifabutin**, a medicine used to treat bacterial infections including tuberculosis
- **itraconazole, ketoconazole, posaconazole, voriconazole**, medicines used to treat fungal infections
- **boceprevir, telaprevir**, medicines used to treat hepatitis C
- **carbamazepine, S-mephenytoin, phenytoin**, medicines used to prevent seizures
- **rifampicin**, a medicine 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, methadone, buprenorphine/naloxone**, medicines used for pain relief
- **ciclosporin, sirolimus, tacrolimus**, medicines used to control your body's immune response after a transplant
- **colchicine**, a medicine used to treat gout
- **trazodone**, a medicine used to treat depression
- **buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem**, medicines used to treat nervous system disorders
- **dasatinib, nilotinib, paclitaxel, vinblastine, vincristine**, medicines used to treat cancer
- **oral or implanted hormonal contraceptives**, used to prevent pregnancy
- **clarithromycin, telithromycin**, medicines used to treat bacterial infections
- **atorvastatin, lovastatin, simvastatin**, medicines used to lower cholesterol

Zydelig may be prescribed in combination with other medicines for the treatment of CLL. It is very important that you read the package leaflets that are provided with these medicines too.

Ask your doctor if you have any questions about any of your medicines.

### **Pregnancy and breastfeeding**

- **Zydelig should not be used during pregnancy.** There is no information about the safety of this medicine in pregnant women.
- **Use a reliable method of contraception** to avoid becoming pregnant while you are being treated with Zydelig, and for 1 month after your last treatment.
- **Zydelig may make the contraceptive “pill” and implanted hormonal contraceptives work less well.** You must also use a barrier method of contraception such as condoms or the “coil” while taking Zydelig and for 1 month after your last treatment.
- **Tell your doctor immediately if you become pregnant.**

**You should not breastfeed while taking Zydelig.** If you are currently breastfeeding, talk to your doctor before starting treatment. It is not known whether the active substance in Zydelig passes into human milk.

### **Driving and using machines**

Zydelig is unlikely to affect your ability to drive or use machines.

**Zydelig contains sunset yellow FCF (E110)**

Tell your doctor if you have an allergy to sunset yellow FCF (E110). Zydelig contains sunset yellow FCF which may cause allergic reactions.

**3. How to take Zydelig**

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

**The recommended dose** is 150 mg by mouth twice a day. However, your doctor may reduce this dose to 100 mg twice a day if you experience particular side effects.

Zydelig can be taken with or without food.

**Swallow the tablet whole.** Do not chew or crush the tablet. Tell your doctor if you have problems swallowing tablets.

**If you take more Zydelig than you should**

If you accidentally take more than the recommended dose of Zydelig, you may be at increased risk of side effects with this medicine (see section 4, *Possible side effects*).

Contact your doctor or nearest emergency department immediately for advice. Keep the bottle and this leaflet with you so that you can easily describe what you have taken.

**If you forget to take Zydelig**

Take care to not miss a dose of Zydelig. If you miss a dose by less than 6 hours, take the missed dose right away. Then take your next dose as usual. If you miss a dose by more than 6 hours, wait and take the next dose at your usual time.

**Do not stop taking Zydelig**

Do not stop taking this medicine unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Some side effects could be serious.**

**STOP taking Zydelig and seek medical help immediately if you experience any of the following:**

- redness and blistering of the skin
- swelling and blistering of the lining of the mouth, genitals, and/or eyes

**Other side effects****Very common side effects**

*(may affect more than 1 in 10 people)*

- diarrhoea/inflammation of the large intestine
- rash
- decreased number of white blood cells
- infections
- fever

### **Common side effects**

*(may affect up to 1 in 10 people)*

- inflammation of the lungs

*Blood tests may also show:*

- increased blood levels of liver enzymes or fats

### **Reporting of side effects**

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Zydelig**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Zydelig contains**

- **The active substance is** idelalisib. Each film-coated tablet contains 100 mg of idelalisib.
- **The other ingredients are:**  
*Tablet core:*  
Microcrystalline cellulose, hydroxypropyl cellulose (E463), croscarmellose sodium, sodium starch glycolate, magnesium stearate.  
  
*Film-coating:*  
Polyvinyl alcohol (E1203), macrogol 3350 (E1521), titanium dioxide (E171), talc (E553B), sunset yellow FCF (E110).

### **What Zydelig looks like and contents of the pack**

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

The following pack size is available: outer carton containing 1 plastic bottle of 60 film-coated tablets.

### **Marketing Authorisation Holder**

Gilead Sciences International Ltd  
Cambridge  
CB21 6GT  
United Kingdom

**Manufacturer**

Gilead Sciences Ireland UC  
IDA Business & Technology Park  
Carrigtohill  
County Cork  
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**

Gilead Sciences Belgium SPRL-BVBA  
Tél/Tel: + 32 (0) 24 01 35 50

**Lietuva**

Gilead Sciences Sweden AB  
Tel: + 46 (0) 8 5057 1849

**България**

Gilead Sciences International Ltd  
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**Luxembourg/Luxemburg**

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**Malta**

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**Nederland**

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Gilead Sciences Ελλάς Μ.ΕΠΕ.  
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Gilead Sciences, S.L.  
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**Polska**

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**Portugal**

Gilead Sciences, Lda.  
Tel: + 351 21 7928790

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**Slovenija**

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~~International Ltd~~  
~~Tel: + 44 (0) 20 7136 8820~~

**Italia**

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**Suomi/Finland**

Gilead Sciences Sweden AB  
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**Κύπρος**

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Τηλ: + 30 210 8930 100

**Sverige**

Gilead Sciences Sweden AB  
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**Latvija**

Gilead Sciences Sweden AB  
Tel: + 46 (0) 8 5057 1849

**United Kingdom**

Gilead Sciences Ltd  
Tel: + 44 (0) 1223 897555

**This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>



## Package leaflet: Information for the patient

### Zydelig 150 mg film-coated tablets

Idelalisib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

#### **Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Zydelig is and what it is used for
2. What you need to know before you take Zydelig
3. How to take Zydelig
4. Possible side effects
5. How to store Zydelig
6. Contents of the pack and other information

#### **1. What Zydelig is and what it is used for**

Zydelig is a cancer medicine that contains the active substance idelalisib. It works by blocking the effects of an enzyme involved in multiplication and survival of certain white blood cells called lymphocytes. Because this enzyme is overactivated in certain cancerous white blood cells, by blocking it, Zydelig will kill and reduce the number of cancer cells.

Zydelig may be used for the treatment of two different cancers:

##### **Chronic lymphocytic leukaemia**

*Chronic lymphocytic leukaemia* (CLL) is a cancer of a type of white blood cell called B-lymphocytes. In this disease, the lymphocytes multiply too quickly and live for too long, so that there are too many of them circulating in the blood.

In CLL Zydelig treatment ~~can be continued~~ is used in combination with another medicine called rituximab in patients who have certain high-risk factors ~~and who are already taking Zydelig. In CLL it can also be used in combination with rituximab~~ or in patients whose cancer has come back after at least one previous treatment.

##### **Follicular lymphoma**

*Follicular lymphoma* (FL) is a cancer of a type of white blood cell called B-lymphocytes. In follicular lymphoma, the B-lymphocytes multiply too quickly and live for too long, so there are too many of them in the lymph nodes. In FL Zydelig is used on its own in patients whose cancer has not responded to treatment with two previous cancer treatments.

## 2. What you need to know before you take Zydelig

### Do not take Zydelig

- if you are **allergic** to idelalisib or any of the other ingredients of this medicine (listed in section 6).  
→ **Talk to your doctor** if this applies to you.

### Warnings and precautions

Talk to your doctor before taking Zydelig. Tell your doctor:

- if you have liver problems
- if you have any other medical conditions or illness (especially an infection or fever)

Serious and fatal infections have occurred in patients taking Zydelig. You should take additional medicine provided by your doctor while you are taking Zydelig to prevent one type of infection. Your doctor will monitor you for evidence of infection. Tell your doctor right away if you become ill (especially with a fever, cough or breathing difficulties) while you are taking Zydelig.

**You will need regular blood tests** before and during treatment with Zydelig. This is to check that you do not have an infection, that your liver is working properly, and that your blood counts are normal. If necessary, your doctor may decide to stop treatment for a while, before starting treatment again at the same or a lower dose. Your doctor may also decide to permanently stop treatment with Zydelig.

Zydelig can cause severe diarrhoea. Tell your doctor right away at the first sign of diarrhoea.

Zydelig can cause lung inflammation. Tell your doctor right away:

- if you have a new or worsening cough
- if you have shortness of breath or difficulty breathing

Severe skin blistering conditions have been reported in some people who have received Zydelig while also receiving other medicines known to cause these potentially life-threatening conditions. Blistering can also involve the lining of the mouth, genitals, and/or eyes. Peeling away of the skin may lead to serious infection. Tell your doctor right away:

- if you have redness and blistering of the skin
- if you have swelling and blistering of the lining of the mouth, genitals, and/or eyes

### Children and adolescents

Do not give this medicine to children and adolescents under 18 years of age because it has not been studied in this age group.

### Other medicines and Zydelig

**Zydelig should not be used with any other medicines unless your doctor has told you it is safe to do so.**

**Tell your doctor if you are taking, have recently taken or might take any other medicines.** This is extremely important, as using more than one medicine at the same time can strengthen or weaken their effect.

Taking Zydelig with certain medicines may stop them working properly, or may make side effects worse. In particular, tell your doctor if you are taking any of the following:

- **alfuzosin**, a medicine used to treat an enlarged prostate
- **dabigatran, warfarin**, medicines used to thin the blood
- **amiodarone, bepridil, disopyramide, lidocaine, quinidine**, medicines used to treat heart problems
- **dihydroergotamine, ergotamine**, medicines used to treat migraine headache

- **cisapride**, a medicine used to relieve certain stomach problems
- **pimozide**, a medicine used to treat abnormal thoughts or feelings
- **midazolam, triazolam**, when taken by mouth to help you sleep and/or relieve anxiety
- **quetiapine**, a medicine used to treat schizophrenia, bipolar disorder and major depressive disorder
- **amlodipine, diltiazem, felodipine, nicardipine, nifedipine**, medicines used to treat high blood pressure and heart problems
- **bosentan**, a medicine used to treat pulmonary arterial hypertension
- **sildenafil, tadalafil**, medicines used to treat impotence and pulmonary hypertension, a lung disease that makes breathing difficult
- **budesonide, fluticasone**, medicines used to treat hayfever and asthma, and **salmeterol**, used to treat asthma
- **rifabutin**, a medicine used to treat bacterial infections including tuberculosis
- **itraconazole, ketoconazole, posaconazole, voriconazole**, medicines used to treat fungal infections
- **boceprevir, telaprevir**, medicines used to treat hepatitis C
- **carbamazepine, S-mephenytoin, phenytoin**, medicines used to prevent seizures
- **rifampicin**, a medicine 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, methadone, buprenorphine/naloxone**, medicines used for pain relief
- **ciclosporin, sirolimus, tacrolimus**, medicines used to control your body's immune response after a transplant
- **colchicine**, a medicine used to treat gout
- **trazodone**, a medicine used to treat depression
- **buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem**, medicines used to treat nervous system disorders
- **dasatinib, nilotinib, paclitaxel, vinblastine, vincristine**, medicines used to treat cancer
- **oral or implanted hormonal contraceptives**, used to prevent pregnancy
- **clarithromycin, telithromycin**, medicines used to treat bacterial infections
- **atorvastatin, lovastatin, simvastatin**, medicines used to lower cholesterol

Zydelig may be prescribed in combination with other medicines for the treatment of CLL. It is very important that you read the package leaflets that are provided with these medicines too.

Ask your doctor if you have any questions about any of your medicines.

### **Pregnancy and breastfeeding**

- **Zydelig should not be used during pregnancy.** There is no information about the safety of this medicine in pregnant women.
- **Use a reliable method of contraception** to avoid becoming pregnant while you are being treated with Zydelig, and for 1 month after your last treatment.
- **Zydelig may make the contraceptive “pill” and implanted hormonal contraceptives work less well.** You must also use a barrier method of contraception such as condoms or the “coil” while taking Zydelig and for 1 month after your last treatment.
- **Tell your doctor immediately if you become pregnant.**

**You should not breastfeed while taking Zydelig.** If you are currently breastfeeding, talk to your doctor before starting treatment. It is not known whether the active substance in Zydelig passes into human milk.

### **Driving and using machines**

Zydelig is unlikely to affect your ability to drive or use machines.

### 3. How to take Zydelig

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

**The recommended dose** is 150 mg by mouth twice a day. However, your doctor may reduce this dose to 100 mg twice a day if you experience particular side effects.

Zydelig can be taken with or without food.

**Swallow the tablet whole.** Do not chew or crush the tablet. Tell your doctor if you have problems swallowing tablets.

#### **If you take more Zydelig than you should**

If you accidentally take more than the recommended dose of Zydelig, you may be at increased risk of side effects with this medicine (see section 4, *Possible side effects*).

Contact your doctor or nearest emergency department immediately for advice. Keep the bottle and this leaflet with you so that you can easily describe what you have taken.

#### **If you forget to take Zydelig**

Take care to not miss a dose of Zydelig. If you miss a dose by less than 6 hours, take the missed dose right away. Then take your next dose as usual. If you miss a dose by more than 6 hours, wait and take the next dose at your usual time.

#### **Do not stop taking Zydelig**

Do not stop taking this medicine unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor.

### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Some side effects could be serious.**

**STOP taking Zydelig and seek medical help immediately if you experience any of the following:**

- redness and blistering of the skin
- swelling and blistering of the lining of the mouth, genitals, and/or eyes

#### **Other side effects**

##### **Very common side effects**

*(may affect more than 1 in 10 people)*

- diarrhoea/inflammation of the large intestine
- rash
- decreased number of white blood cells
- infections
- fever

##### **Common side effects**

*(may affect up to 1 in 10 people)*

- inflammation of the lungs

*Blood tests may also show:*

- increased blood levels of liver enzymes or fats

### **Reporting of side effects**

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Zydelig**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Zydelig contains**

- **The active substance is** idelalisib. Each film-coated tablet contains 150 mg of idelalisib.
- **The other ingredients are:**  
*Tablet core:*  
Microcrystalline cellulose, hydroxypropyl cellulose (E463), croscarmellose sodium, sodium starch glycolate, magnesium stearate.  
  
*Film-coating:*  
Polyvinyl alcohol (E1203), macrogol 3350 (E1521), titanium dioxide (E171), talc (E553B), iron oxide red (E172).

### **What Zydelig looks like and contents of the pack**

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

The following pack size is available: outer carton containing 1 plastic bottle of 60 film-coated tablets.

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United Kingdom

### **Manufacturer**

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IDA Business & Technology Park  
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>