## 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, or
- as first line treatment in the presence of 17p deletion or *TP53* mutation in patients unsuitable for chemo-immunotherapy.

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

### 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).

*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

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.

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.

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 $AUC_{inf}$. 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 $C_{max}$ and a 79% increase in $AUC_{inf}$ 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 $C_{max}$ and a ~440% increase in $AUC_{inf}$ 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** |
|---|---|---|
| **ALPHA-1 ADRENORECEPTOR ANTAGONISTS** | | |
| Alfuzosin | ↑ serum concentrations | Idelalisib should not be co-administered with alfuzosin. |
| **ANALGESICS** | | |
| 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 |
|---|---|---|
| **ANTIARRHYTHMICS** | | |
| Amiodarone, quinidine | ↑ serum concentrations | Idelalisib should not be co-administered with amiodarone or quinidine. |
| Bepridil, disopyramide, lidocaine | ↑ serum concentrations | Clinical monitoring is recommended. |
| **ANTI-CANCER AGENTS** | | |
| 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. |
| **ANTICOAGULANTS** | | |
| Dabigatran, rivaroxaban, warfarin | ↑ serum concentrations | It is recommended that the international normalised ratio (INR) be monitored upon co-administration and following ceasing treatment with idelalisib. |
| **ANTICONVULSANTS** | | |
| Carbamazepine | ↑ serum concentrations | Anticonvulsant drug levels should be monitored. |
| **ANTIDEPRESSANTS** | | |
| Trazodone | ↑ serum concentrations | Careful dose titration of the antidepressant and monitoring for antidepressant response is recommended. |
| **ANTI-GOUT** | | |
| 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. |
| **ANTI-HYPERTENSIVES** | | |
| Amlodipine, diltiazem, felodipine, nifedipine, nicardipine | ↑ serum concentrations | Clinical monitoring of therapeutic effect and adverse reactions is recommended. |
| **ANTI-INFECTIVES** | | |
| **Antifungals** | | |
| Ketoconazole, itraconazole, posaconazole, voriconazole | ↑ serum concentrations | Clinical monitoring is recommended. |
| **Antimycobacterials** | | |
| Rifabutin | ↑ serum concentrations | Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is recommended. |
| **HCV protease inhibitors** | | |
| Boceprevir, telaprevir | ↑ serum concentrations | Clinical monitoring is recommended. |

| Medicinal product | Expected effect of idelalisib on drug levels | Clinical recommendation upon co-administration with idelalisib |
|---|---|---|
| **Macrolide antibiotics** | | |
| 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.<br><br>Clinical monitoring is recommended for telithromycin. |
| **ANTI-PSYCHOTICS/NEUROLEPTICS** | | |
| Quetiapine, pimozide | ↑ serum concentrations | Idelalisib should not be co-administered with quetiapine or pimozide.<br><br>Alternative medicinal products, such as olanzapine, may be considered. |
| **ENDOTHELIN RECEPTOR ANTAGONISTS** | | |
| Bosentan | ↑ serum concentrations | Caution should be exercised and patients closely observed for bosentan-related toxicity. |
| **ERGOT ALKALOIDS** | | |
| Ergotamine, dihydroergotamine | ↑ serum concentrations | Idelalisib should not be co-administered with ergotamine or dihydroergotamine. |
| **GASTROINTESTINAL MOTILITY AGENTS** | | |
| Cisapride | ↑ serum concentrations | Idelalisib should not be co-administered with cisapride. |
| **GLUCOCORTICOIDS** | | |
| 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. |
| **HMG CO-A REDUCTASE INHIBITORS** | | |
| 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. |
| **IMMUNOSUPPRESSANTS** | | |
| 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 |
|---|---|---|
| **INHALED BETA AGONIST** | | |
| 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. |
| **PHOSPHODIESTERASE INHIBITORS** | | |
| | | For pulmonary arterial hypertension: |
| Sildenafil | ↑ serum concentrations | 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. |
| **SEDATIVES/HYPNOTICS** | | |
| 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 Zydelig, and for up to 1 month after ending treatment. Therefore, women of childbearing potential must use highly effective contraception while taking Zydelig 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 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 ≥ 3 |
|---|---|---|
| *Infections and infestations* | | |
| Infections | Very common | Very common |
| *Blood and lymphatic system disorders* | | |
| Neutropenia | Very common | Very common |
| *Respiratory, thoracic and mediastinal disorders* | | |
| Pneumonitis | Common | Common |
| *Gastrointestinal disorders* | | |
| Diarrhoea/colitis | Very common | Very common |
| *Hepatobiliary disorders* | | |
| Transaminase increased | Very common | Very common |
| *Skin and subcutaneous tissue disorders* | | |
| Rash* | Very common | Common |
| *General disorders and administration site conditions* | | |
| Pyrexia | Very common | Common |
| *Investigations* | | |
| Increased triglycerides | Very common | Common |

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

Description of selected adverse reactions

*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, rash, rash macular, rash maculo-papular, and rash pruritic) occurred in 13.6% of subjects who received idelalisib + rituximab and 5.6% who received placebo + rituximab. Of these, 2.7% who received idelalisib + rituximab and 0 subjects 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).

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.

### 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 p110δ (PI3Kδ), which is hyperactive in B-cell malignancies and is central to multiple signalling pathways that drive proliferation, survival, homing, and retention of malignant cells in lymphoid tissues and bone marrow. Idelalisib is a selective

inhibitor of adenosine-5'-triphosphate (ATP) binding to the catalytic domain of PI3Kδ, resulting in inhibition of the phosphorylation of the key lipid second messenger phosphatidylinositol 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$^2$ body surface area [BSA], subsequent cycles at 500 mg/m$^2$ 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; 64.5% 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.

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**

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

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 ≥ 50% decrease in the sum of products of the greatest perpendicular diameters of index lesions. Only subjects that had both baseline and ≥ 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**

| | | Idelalisib + R | Placebo + R |
|---|---|---|---|
| **17p deletion/*TP53* mutation** | | **N = 46** | **N = 49** |
| | PFS median (months) (95% CI) | NR (8.3, NR) | 4.0 (3.5, 5.7) |
| | Hazard ratio (95% CI) | 0.16 (0.07, 0.37) | |
| | ORR (95% CI) | 78.3% (63.6, 89.1) | 12.2% (4.6, 24.8) |
| **Unmutated *IGHV*** | | **N = 91** | **N = 93** |
| | PFS median (months) (95% CI) | NR (NR, NR) | 5.5 (3.8, 6.9) |
| | Hazard ratio (95% CI) | 0.14 (0.07, 0.27) | |
| | ORR (95% CI) | 73.6% (63.3, 82.3) | 15.1% (8.5, 24.0) |
| **Age ≥ 65 years** | | **N = 89** | **N = 83** |
| | PFS median (months) (95% CI) | NR (12.1, NR) | 5.5 (3.7, 7.1) |
| | Hazard ratio (95% CI) | 0.15 (0.07, 0.29) | |
| | ORR (95% CI) | 74.2% (63.8, 82.9) | 15.7% (8.6, 25.3) |

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

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$^2$ 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)* | 39 (54.2) |
| 95% CI | 42.0 – 66.0 |
| ORR (all subjects)* | 71 (56.8) |
| 95% CI | 47.6 – 65.6 |
| Response category (follicular lymphoma)* | |
| CR | 6 (8.3) |
| PR | 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 ≥ 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.

## 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 [$^{14}$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 5 and 7 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

2 years.

### 6.4 Special precautions for storage

Store below 30ºC.

### 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

EUSEP14LBJAN15