07 July 2016
EMA/586939/2016
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Invented name: Zydelig

INN: idelalisib

Procedure number: EMEA/H/A-20/1439/C/003843/0023

Note

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted

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1. Information on the procedure

On 10 March 2016, the European Commission was informed that an increased risk of death and higher incidence of serious adverse events (SAE) among subjects receiving idelalisib compared to the control groups had been observed in three clinical trials by the independent safety data monitoring group. The trials evaluated treatment combinations with chemotherapy and immunotherapy which are currently not authorised for Zydelig (idelalisib) in populations with earlier disease characteristics than the currently approved indication. However, in light of the emerging safety data, the European Commission (EC) considered that the findings from the clinical trials and all available safety data related to idelalisib should be reviewed in order to assess their potential impact on the benefit-risk balance of Zydelig in the approved indications and relevant ongoing variations.

On 11 March 2016 the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of Zydelig (idelalisib) and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Idelalisib is a targeted, selective competitive inhibitor of adenosine-5'-triphosphate binding to the catalytic subunit of phosphatidylinositol 3-kinase (PI3K) p110δ (PI3Kδ), which has been shown to be prominently expressed in cells of hematopoietic origin (Leverrier, 2003 [1]). PI3Kδ is critical for multiple signalling pathways that are hyperactive in B-cell malignancies. Inhibition of PI3Kδ modulates B-cell receptor (BCR) signalling as well as signalling through cytokine, chemokine and integrin receptors. These signalling pathways act via downstream enzymes (most importantly the serine/threonine protein kinase [Akt]) to regulate proliferation, apoptosis, motility, homing, and retention of malignant B-cells in lymphoid tissues and bone marrow compartments. By inhibiting PI3Kδ-dependent signalling, idelalisib inhibits proliferation, survival, homing, motility, and retention in the tumour microenvironment in many B-cell malignancies. PI3Kδ also mediates signalling though T-cell receptors, receptor tyrosine kinases, and high-affinity IgE receptor (FcεR1). It has roles in immune signalling in T lymphocytes, natural killer (NK) cells, T regulatory cells (Tregs), and dendritic cells (DC).

Zydelig (idelalisib) is authorised in the European Union (EU) since 18 September 2014. As of 22 January 2016, 2,458 patients had been exposed in clinical trials and cumulative post-marketing use is estimated to 2,835 patient-years. At time of referral of the matter to the PRAC, it was 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.

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

[1] Leverrier Y, Okkenhaug K et al. Class I phosphoinositide 3-kinase p110beta is required for apoptotic cell and Fcgamma receptor-mediated phagocytosis by macrophages. J Biol Chem 2003;278 (40):38437-42

In addition an extension of indication to authorise the use of idelalisib in combination with ofatumumab in CLL received a positive CHMP opinion in February 2016. The PRAC was requested assess the impact of the emerging new safety information on this extension of indication before the final decision of the European Commission (EC) is adopted.

This review was triggered on the basis of emergent safety information from the interim results of studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125[2] evaluating the addition of idelalisib to standard therapy in first line CLL and indolent non-Hodgkin lymphoma/small lymphocytic lymphoma (iNHL/SLL). These results suggested an increased risk of death and serious infection with idelalisib compared to the control group, which was not seen in other trials. The clinical trials, which have been stopped, evaluated idelalisib in different treatment combination and/or in patients at earlier stages of the diseases than currently authorised. Although the potential impact of these new safety findings in the authorised indications was unknown, based on the very limited and preliminary information available at the start of the procedure, the PRAC considered that provisional measures were needed while the issue was being further reviewed[3]. The PRAC considered that as a precautionary measure, idelalisib should not be initiated as a first line treatment in CLL patients with 17p deletion or *TP53* mutation and recommended provisional amendments of the indication of idelalisib. The committee considered that idelalisib could be used for continuing treatment in those patients who had already initiated the medicine as first line treatment based on individual benefit-risk balance assessment. The committee also recommended provisional risk minimisation measures including the update of the posology and warnings to take due account that treatment should not be initiated in patients with systemic infections, patients should be monitored for respiratory symptoms and be administered *Pneumocystis jirovecii* pneumonia prophylaxis. Regular clinical and laboratory screening for cytomegalovirus should also be performed. In addition, given the higher risk for infection, advice on dose reduction or treatment interruption in the event of severe neutropenia was also introduced in the product information. The European Commission issued a decision on the provisional measures on 23 March 2016.

Of note, four other studies in first line settings in CLL and iNHL and one in early line in pancreatic adenocarcinoma were also terminated further to the emergence of this safety signal (101-08, GS-US-312-0118, GS-US-312-0133, GS-US-313-1414 and GS-US-385-1577)[4].

Chronic lymphocytic leukaemia (CLL) is a progressive hematologic disease characterised by an accumulation of monoclonal mature B cells in the blood, bone marrow, and secondary lymph organs. Altered p53 function resulting from 17p deletion and/or *TP53* gene mutation is associated with poor prognosis in CLL patients. While under 10% of CLL patients have detectable 17p deletion or *TP53* mutation at the time of diagnosis, the proportion increases up one-third in relapsed patients (Rossi,

[2] GS-US-312-0123 a phase 3, randomised, double blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously untreated CLL
GS-US-313-0124 a phase 3, randomised, double blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with rituximab for previously treated iNHL
GS-US-313-0125 a phase 3, randomised, double blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously treated iNHL
[3] More information is available in the published assessment report on provisional measures
[4] 101-08 a phase 2 single arm study to investigate the safety and clinical activity of idelalisib in combination with rituximab in elderly patients with previously untreated CLL or SLL
GS-US-312-0118 a phase 3, randomised, open-label study evaluating the efficacy and safety of idelalisib in combination with obinutuzumab compared to chlorambucil in combination with obinutuzumab for previously untreated CLL
GS-US-312-0133 a phase 2, single arm study evaluating the efficacy and safety of idelalisib in combination with rituximab in subjects with previously untreated CLL with del(17p) or *TP53* Mutation
GS-US-313-1414 a phase 2, single arm study evaluating the safety and efficacy of idelalisib in combination with rituximab for previously untreated iNHL
GS-US-385-1577 a phase 1b study of single agent idelalisib followed by idelalisib in combination with chemotherapy in subjects with metastatic pancreatic ductal adenocarcinoma

2014 [5] and Schnaiter, 2013 [6]). Indolent non-Hodgkin lymphoma (iNHL) comprises 4 clinical entities of which the most common is follicular lymphoma (FL).

2.2. Data on safety

2.2.1. Safety signal identified in studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125

Interim results of studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125 showed decreased overall survivals in the idelalisib arms of those studies, predominantly attributable to deaths from adverse events, as shown in table 1. The fatal adverse events observed were mostly of infectious and respiratory origin, as detailed in table 2.

Table 1. Incidence of deaths, fatal AEs and SAEs in studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125

	GS-US-312-0123 (1st line CLL)		GS-US-313-0125 (iNHL with median of 2 prior therapies)		GS-US-313-0124 (iNHL with median of 1 prior therapy)	
	Idelalisib + BR (n = 156)	Placebo + BR (n = 154)	Idelalisib + BR (n = 318)	Placebo + BR (n = 155)	Idelalisib + R (n = 190)	Placebo + R (n = 93)
All Deaths	8%	3%	8%	6%	5%	1%
AE leading to death	8%	2%	6%	3%	4%	0%
SAEs	71%	42%	72%	35%	48%	10%

BR = bendamustine plus rituximab, R = rituximab

Table 2. Treatment-emergent adverse events (TEAE) leading to death in combined idelalisib arms of studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125

System Organ Class / Preferred Term	Idelalisib n = 664	Placebo n = 402
Total TEAE Leading to Death	**33 (5%)**	**7 (1.7%)**
Infections and Infestations	13 (2.0%)	3(0.7%)
Sepsis	4 (0.6%)	0
Cytomegalovirus Infection	1 (0.2%)	0
Neutropenic Sepsis	1 (0.2%)	0
Pneumonia (3) and bronchopneumonia (1)	4 (0.6%)	0
Atypical Pneumonia	1 (0.2%)	0
Septic Shock	2 (0.3%)	1 (0.2%)
Strongyloidiasis	0	1 (0.2%)
Encephalitis	0	1 (0.2%)
Cardiac Disorders	5 (0.8%)	2 (0.5%)

[5] Rossi D, Khiabanian H, et al. Clinical impact of small TP53 mutated subclones in chronic lymphocytic leukaemia Blood. 2014 Apr 3;123(14):2139-47.
[6] Schnaiter A, Stilgenbauer S. 17p deletion in chronic lymphocytic leukaemias: risk stratification and therapeutic approach. Hematol Oncol Clin North Am. 2013 Apr;27(2):289-301. Review.

System Organ Class / Preferred Term	Idelalisib n = 664	Placebo n = 402
Gastrointestinal disorders: Enterocolitis	1 (0.2%)	0
Metabolism and nutrition disorders: malnutrition (1) cachexia (1)	2 (0.3%)	0
Neoplasms benign, malignant and unspecified: CLL (1) MDS (1)	2 (0.3%)	0
Not Coded	0	1 (0.2%)
General Disorders: Death (1), Pyrexia (1)	2 (0.3%)	0
Investigations: Hepatic Enzyme Increased	1 (0.2%)	0
Respiratory Disorders	8 (1.2%)	0
Respiratory Failure (5) and acute respiratory failure (1)	6 (0.9%)	0
Pneumonitis	1 (0.2%)	0
Pulmonary Embolism	1 (0.2%)	0
Blood and Lymphatic System Disorders: Febrile Neutropenia	1 (0.2%)	0
Vascular Disorders: Internal Haemorrhage	0	1 (0.2%)

2.2.2. Key safety data from all relevant studies

The MAH submitted data from all relevant clinical studies, including the pivotal studies supporting the initial marketing authorisation and extension of indication in combination with ofatumumab as well as studies that evaluated the safety and efficacy of idelalisib in new treatment combinations and/or study populations (including studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125). Some of these studies were completed and a final or interim (including completed primary analysis) clinical study report (CSR) was available while for the three most recent the data was interim and therefore limited analyses were available. An overview of the most relevant studies is presented in the table below.

Table 3. Overview of key studies submitted

Study ID and design	Population	Treatment
Previously treated CLL		
GS-US-312-0116 (RCT)	CLL*. Relapsed/refractory within at least 24 months of at least one prior treatment (median 3 prior lines of therapy), mean 9 years since diagnosis. Advanced poor prognosis. 95 (43%) patients with 17p deletion/*TP53* mutation.	Idelalisib + rituximab (n=110) / placebo + rituximab (n=110)
GS-US-312-0119 (RCT)	CLL*. Previously treated refractory or relapsed CLL (median 3 prior lines of therapy), mean 8 years since diagnosis. 103 (39%) patients with 17p deletion/*TP53* mutation	Idelalisib + ofatumumab (n=173) / ofatumumab (n=86)
GS-US-312-0115 (RCT)	CLL†. Previously treated relapsed CLL (median 2 prior lines of therapy), mean 7 years since diagnosis.137 (33%) patients with 17p deletion/*TP53* mutation.	Idelalisib + rituximab + bendamustine (n=207) / placebo + rituximab + bendamustine (n=209)
Previously untreated CLL		
GS-US-312-123	CLL. First line, mean 3.5 years since diagnosis. 38	Idelalisib + rituximab +

Study ID and design	Population	Treatment
(RCT)	(12%) patients with 17p deletion/*TP53* mutation.	bendamustine (n=156) / placebo + rituximab + bendamustine (n=154)
101-08 (single arm)	Elderly patients (>65 y) with CLL (n= 59; 5 patients with SLL). First line, mean 4 years since diagnosis. 15 (14%) patients with 17p deletion/*TP53* mutation)	Cohort 1: n=64 idelalisib + rituximab, cohort 2: n=41 idelalisib
Previously treated iNHL		
101-09 (single arm)	Refractory iNHL. Mean 6 years since diagnosis. Median 4 prior lines of therapy	Idelalisib (n=125)
GS-US-313-0124 (RCT)	Previously treated iNHL. Mean 7 years since diagnosis. Median 1 prior lines of therapy	Idelalisib + rituximab (n=198) / placebo + rituximab (n=95)
GS-US-313-0125 (RCT)	Previously treated iNHL. Mean 6.5 years since diagnosis. Median 2 prior lines of therapy	Idelalisib + rituximab + bendamustine (n=317) / placebo + rituximab + bendamustine (n=155)

Serious infections

The MAH presented the key safety data in CLL and iNHL patients in all relevant clinical trials and compared the results of the different trials with the aim to identify the different factors that may have led to the increased risk observed in studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125, while acknowledging the limitations attached to direct comparison of study results.

The baseline demographics and disease characteristics were balanced within studies and mostly comparable across studies.

Due to the first line setting of CLL studies GS-US-312-0123 and 101-08, time since diagnosis was shorter in these patients (see table 3). The median time since completion of last regimen before treatment initiation was comparable between studies GS-US-312-0116 (9.2 months) and GS-US-312-0119 (9.0 months) and higher in study GS-US-312-0115 (18.2 months). The median number of prior regimens was slightly higher for GS-US-312-0116 and GS-US-312-0119 (3 prior regimens) compared to study GS-US-312-0115 (2 prior regimens).

Within all iNHL studies the FL subpopulation were equally distributed at approximately 60%. Time since initial diagnosis was comparable between treatment and control arms within studies and also across studies. The median number of prior regimens was similar in studies GS-US-313-0124 and GS-US-313-0125 and higher in study 101-09 (see table 3). The median time since completion of the last regimen before treatment initiation was also equally distributed between treatment and control arms and comparable between studies: GS-US-313-0124 (25.3) and GS-US-313-0125 (20.3 months); time since completion of last regimen was shorter in study 101-09 (3.9 months).

An abstract of the key safety data from those studies is presented in the below tables. Of note, however, when comparing the event rates, it should be kept in mind that time at risk was 2 to 4 times longer for patients in the idelalisib arms of the completed studies.

Table 4. Overview of key safety data for subjects with CLL (Safety Analysis Set)

	GS-US-312-0116		GS-US-312-0119		GS-US-312-0115		GS-US-312-0123		101-08	
	Relapsed/Refractory CLL		Relapsed CLL		Relapsed CLL		Front-Line CLL		Front-Line CLL or SLL	
	IDL + R (N = 110) n (%)	PL + R (N = 108) n (%)	IDL + O (N = 173) n (%)	O (N = 86) n (%)	IDL + BR (N = 207) n (%)	PL + BR (N = 209) n (%)	IDL + BR (N = 156) n (%)	PL + BR (N = 154) n (%)	Cohort 1 IDL + R (N = 64) n (%)	Cohort 2 IDL (N = 41) n (%)
Any SAE	65 (59.1)	43 (39.8)	132 (76.3)	36 (41.9)	145 (70.0)	94 (45.0)	113 (72.4)	66 (42.9)	31 (48.4)	28 (68.3)
infections and infestations SAE	34 (30.9)	26 (24.1)	65 (37.6)	25 (29.1)	83 (40.1)	49 (23.4)	48 (30.8)	14 (9.1)	13 (20.3)	9 (22.0)
≤ 1 month on treatment	8 (7.3)	9 (8.3)	12 (6.9)	8 (9.3)	10 (4.8)	12 (5.7)	15 (9.6)	3 (1.9)	0	0
1 prior regimen	4 (3.6)	3 (2.8)	10 (5.8)	3 (3.5)	22 (10.6)	9 (4.3)	NA	NA	NA	NA
2 prior regimen	9 (8.2)	5 (4.6)	17 (9.8)	4 (4.7)	24 (11.6)	12 (5.7)	NA	NA	NA	NA
3 prior regimen	5 (4.5)	8 (7.4)	15 (8.7)	0	13 (6.3)	10 (4.8)	NA	NA	NA	NA
4 prior regimen	16 (14.5)	10 (9.3)	23 (13.3)	18 (20.9)	24 (11.6)	18 (8.6)	NA	NA	NA	NA
Deaths	10 (9.1)	15 (13.9)	58 (33.5)	30 (34.9)	52 (25.1)	67 (32.1)	12 (7.7)	5 (3.2)	4 (6.3)	2 (4.9)
Deaths during the study	10 (9.1)	15 (13.9)	37 (21.4)	8 (9.3)	33 (15.9)	32 (15.3)	11 (7.1)	3 (1.9)	3 (4.7)	1 (2.4)
1 prior regimen	1 (0.9)	2 (1.9)	5 (2.9)	0	7 (3.4)	1 (0.5)	NA	NA	NA	NA
2 prior regimen	1 (0.9)	1 (0.9)	8 (4.6)	1 (1.2)	7 (3.4)	10 (4.8)	NA	NA	NA	NA
3 prior regimen	2 (1.8)	4 (3.7)	12 (6.9)	1 (1.2)	7 (3.4)	7 (3.3)	NA	NA	NA	NA
4 prior regimen	6 (5.5)	8 (7.4)	12 (6.9)	6 (7.0)	12 (5.8)	14 (6.7)	NA	NA	NA	NA
Deaths during long-term follow-up	0	0	21 (12.1)	22 (25.6)	19 (9.2)	35 (16.7)	1 (0.6)	2 (1.3)	1 (1.6)	1 (2.4)
Study treatment discontinuation	110 (100)	108 (100)	137 (79.2)	86 (100)	128 (61.8)	207 (99.0)	76 (48.7)	30 (19.5)	64 (100)	28 (68.3)
Discontinuation due to AE	19 (17.3)	14 (13.0)	64 (37.0)	ND	59 (28.5)	29 (13.9)	43 (27.6)	6 (3.9)	17 (26.6)	20 (48.8)
Discontinuation due to disease Progression	7 (6.4)	48 (44.4)	37 (21.4)	ND	38 (18.4)	112 (53.6)	0	12 (7.8)	0	1 (2.4)
Any grade *Pneumocystis* infections (HLT) AEs	4 (3.6)	1 (0.9)	11 (6.4)	1 (1.2)	4 (1.9)	0	1 (0.6)	0	1 (1.6)	1 (2.4)
Any grade Cytomegaloviral infections (HLT) AEs	1 (0.9)	0	2 (1.2)	0	12 (5.8)	3 (1.4)	8 (5.1)	2 (1.3)	1 (1.6)	2 (4.9)

AE = adverse event, BR = bendamustine plus rituximab, CLL = chronic lymphocytic leukaemia, HLT = High Level Term, IDL = idelalisib, NA = not applicable, ND = no data, O = ofatumumab, PL = placebo, R = rituximab, SAE = serious adverse event, SLL = small lymphocytic lymphoma.

Table 5. Overview of key safety data for subjects with iNHL (Safety Analysis Set)

	101-09	GS-US-313-0124		GS-US-313-0125	
	Refractory iNHL	Relapsed iNHL		Relapsed iNHL	
	IDL (N = 125) n (%)	IDL + R (N = 198) n (%)	PL + R (N = 95) n (%)	IDL + BR (N = 317) n (%)	PL + BR (N = 155) n (%)
Any SAE	72 (57.6)	100 (50.5)	9 (9.5)	230 (72.6)	54 (34.8)
Infections and Infestations SAE	28 (22.4)	36 (18.2)	1 (1.1)	99 (31.2)	24 (15.5)
≤ 1 Month	1 (0.8)	5 (2.5)	0	24 (7.6)	4 (2.6)
Deaths	51 (40.8)	11 (5.6)	2 (2.1)	29 (9.1)	10 (6.5)
Deaths ≤ 30 Days Following Study Drug Discontinuation	13 (10.4)	8 (4.0)	0	24 (7.6)	4 (2.6)
Deaths > 30 Days Following Study Drug Discontinuation	38 (30.4)	3 (1.5)	1 (1.1)	5 (1.6)	6 (3.9)
Study treatment discontinuation	118 (94.4)	118 (59.6)	39 (41.1)	214 (67.5)	79 (51.0)
Discontinuation due to AE	30 (24.0)	77 (38.9)	6 (6.3)	117 (36.9)	16 (10.3)
Discontinuation due to disease Progression	67 (53.6)	18 (9.1)	23 (24.2)	14 (4.4)	37 (23.9)
Any grade *Pneumocystis* infections (HLT) AEs	2 (1.6)	1 (0.5)	0	10 (3.2)	0
Any grade Cytomegaloviral infections (HLT) AEs	2 (1.6)	2 (1.0)	0	15 (4.7)	0

AE = adverse event, BR = bendamustine plus rituximab, HLT = High Level Term, IDL = idelalisib, iNHL = indolent non-Hodgkin Lymphoma, PL = placebo, R = rituximab, SAE = serious adverse event.

In CLL studies -0116, -0119 and -0115 PJP accounted respectively for 5-12 % and 0-4% of serious infection cases in the idelalisib and control arms respectively and cytomegalovirus (CMV) accounted for 0% of the serious infection cases in studies -0116 and -0119 and 7.2% and 6.1% in the idelalisib and control arms of study -0115, respectively. In iNHL studies, PJP cases accounted for 3-10% and CMV for 6-8% of the serious infection cases in the idelalisib arms and both accounted for 0% of serious infection case in the control arms.

Of all grade ≥3 infection and infestation AE, the MAH provided the proportion of those that occurred concomitantly with grade ≥ 3 diarrhoea/colitis and pneumonitis which might indicate an autoimmune reaction. Among subjects with CLL in studies -0116, -0119, -0115, and -0123, of the subjects treated with idelalisib who had a ≥ grade 3 infection (291 of 646 subjects, 45.0%), 24 subjects (8.2%) had concomitant ≥ grade 3 diarrhoea and/or colitis, and 9 subjects (3.1%) had concomitant ≥ grade 3 pneumonitis. Among subjects in the control group who had a ≥ grade 3 infection (141 of 557 subjects, 25.3%), 1 subject (0.7%) had concomitant ≥ grade 3 diarrhoea and/or colitis, and 2 subjects (1.4%) had concomitant ≥ grade 3 pneumonitis. While among subjects with iNHL who received combination therapy in studies -0124, -0125, of the subjects treated with idelalisib who had a ≥ grade 3 infection (166 of 515 subjects, 32.0%), 12 subjects (7.2%) had concomitant ≥ grade 3 diarrhoea and/or colitis, and 3 subjects (1.8%) had concomitant ≥ grade 3 pneumonitis. Among subjects in the control group who had a ≥ grade 3 infection (33 of 250 subjects, 13.2%), none had a concomitant ≥ grade 3 diarrhoea and/or colitis, or pneumonitis.

In study -0123 the causes of death for 9 of the 12 subjects (75%) on the idelalisib plus bendamustine and rituximab arm were events either directly reported as infectious events (including one case of CMV sepsis and one PJP associated with cardiopulmonary failure) or associated with infection, compared with 2 of 11 subjects (18.2%) on the idelalisib plus rituximab arm in study -0124 and 15 of 28 subjects (53.6%) on the idelalisib plus bendamustine and rituximab arm in study -0125 (including two cases of

PJP). In the cases where the cause of death was not associated with infectious aetiologies, it mainly consisted of progressive disease. Death rates in the single arm study 101-08 were comparable to those observed in the front line setting treatment arm (6.3% and 4.9% in cohort 1 and 2, respectively). Whilst all deaths in study GS-US-312-0116 occurred during treatment, a very large proportion of deaths in study GS-US-312-0119 and GS-US-312-0115 occurred during long term follow-up (12.1% and 9.2% respectively). Broken down by time periods ≤1, >1-≤2, >2-≤3, >3-≤6 and >6 months and adjusted for the number of patients at risk, the death rates for each periods in first line CLL were 1.9%, 0.7%, 1.4%, 2.1% and 1.5% respectively compared to 1.9%, 1.0%, 1.0%, 3.0% and 19.7%, respectively in relapsed/refractory patients.

Of note, in the two other studies in front line CLL that were terminated, as of 14 March 2016, no subjects had died in study GS-US-312-0118, while seven subjects had died in study GS-US-312-0133 including one during the long term follow up (102 days after end of treatment).

Discussion

The PRAC reviewed the safety data from all the studies submitted by the MAH, including the interim results of studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125 in the context of the results from other studies. The PRAC noted the limitations associated with comparison of results across studies and the premature nature of the data extracted from studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125. Comparison of the events occurring in the first month of treatment was considered of more relevance in view of the longer time-at-risk for patients in the treatment arms of the completed studies.

The rate of SAEs in CLL patients was broadly consistent in all control arms despite varying treatment combinations and different patient populations in the different trials. SAE rates were consistently higher in the treatment arms compared to control arms. The infectious SAE rate in the idelalisib + rituximab + bendamustine arm in treatment naïve patients was comparable or slightly lower than rates in the relapsed/refractory CLL studies were idelalisib was administered in combination with rituximab, ofatumumab or rituximab and bendamustine. However, in the control arms the rate of infectious SAEs in treatment naïve patients was markedly lower compared to that in the other CLL studies.

In the iNHL studies the overall rates of any SAEs and that of infectious SAE were similar in patients given idelalisib alone or in combination with rituximab but higher in patients administered bendamustine in addition to idelalisib and rituximab. A similar difference was observed in the control arms with and without bendamustine. There was a notable difference in the rates of infection between treatment arm and control arm in study GS-US-313-0124, which was also seen, albeit to a lesser extent, in study GS-US-313-0125. There was no apparent relationship between treatment duration and risk of infectious SAE. In the two placebo-controlled trials in relapsed iNHL patients, the risk of infectious SAE attributable to idelalisib was comparable. In the iNHL placebo controlled studies, deaths rates were lower than in the single arm study. The incidence of deaths that occurred on study treatment appeared to decrease with increasing number of prior regimens in studies GS-US-313-0124, GS-US-313-0125, and 101-09, however, the numbers in each group are too small to allow any firm conclusion.

Analyses suggest that treatment with idelalisib in CLL versus placebo in combination with rituximab, ofatumumab or bendamustine and rituximab, results in a higher incidence of early infections across all quartiles of treatment-free intervals. There was no increased incidence of infection in patients with treatment-free intervals compared to shorter ones for the idelalisib-treated population. Hence, in relapsing CLL a long treatment-free interval before starting idelalisib does not appear to be associated with an increased risk for early infectious events. The death event rate was numerically higher in the

idelalisib + rituximab + bendamustine of study -0123 compared to the control irrespective of time interval while in study -0115 this was only the case in the first month of the study. However, broken down by time periods, the rates were similar in treatment arms of both studies. Similarly, in studies -0124 and -0125 there is overall no relationship between time off therapy and infectious events. No clear relationship could be determined between risk of infection and deaths and number of prior therapies or time off treatment prior to idelalisib initiation either. It appeared that the different disease pathophysiology of CLL compared to iNHL contributed to an overall lower rate of infectious diseases and deaths in iNHL patients.

When looking at immune related adverse events overall, numbers were small and there was no apparent association between the occurrence of infections and other adverse events in idelalisib treated patients based on the data presented. There was no obvious difference between first line and relapsed/refractory patients.

The characteristics of patients in studies -0123, -0124 and -0125 are compatible with a better prognosis than the patients populations defined in the authorised indications. Patients with 17p deletion and/or *TP53* mutation represented a small proportion of the population in study -0123 and studies -0124 and -0125 included patients who had experienced few relapses and had a longer time since completion of the last regimen before treatment initiation, indicative of a slowly progressing disease. As suggested by the relatively low rates of serious infections in the control arms these patients were also less immunocompromised than those in later line trials.

The SAG considered that the new evidence from study -0123 did not add evidence as to a possible benefit or detriment of idelalisib in first line treatment of CLL patients with 17p deletion or *TP53* mutation, nor in relapse/refractory patients, to which the PRAC agreed. While there were some concerns at the SAG that the toxicity might be higher in first-line treatment, further analysis showed that the risk was similar across treatment lines. The PRAC concluded that based on the review of all the relevant safety data, the evidence was not supportive of an increased risk in treatment naïve CLL patients. The results of study -0123 are explained by the good prognosis and therefore low disease-related mortality of the patients leading to the impossibility to observe the benefits from the idelalisib treatment early in the study while its known toxicity is observed as in the other trials. In addition, in this study bendamustine was added to the authorised combination of idelalisib and rituximab, which led to an increased toxicity. Considering that Zydelig is authorised in patients with a worse prognosis, due to either the p17 deletion or *TP53* mutation or relapsed/refractory disease, these results are therefore considered of limited relevance, even more so as they were seen with a triple treatment combination. Following the same reasoning, the results appear to be of limited relevance for the use of idelalisib in combination with ofatumumab in the CLL indications. However it is acknowledged that safety and efficacy data are limited in treatment naïve patients with the p17 deletion or *TP53* mutation as was reflected in the wording of the indication, initially restricted to patients unsuitable for chemoimmunotherapy. Based on the very limited data available at the start of the procedure, the PRAC recommended as a precaution that idelalisib should not be initiated as a first line treatment in CLL patients with 17p deletion or *TP53* mutation while the review is ongoing. However based on the in-depth review of the data, the PRAC considered that idelalisib could now be initiated again in these CLL patients and taking into account the initial restriction of the indication as well as the recent availability of another treatment option for treatment-naïve CLL patients, recommended as a precaution that only patients with these genetic mutations who are not eligible for other therapies are administered idelalisib. It should be further explained in section 4.4 of the SmPC that idelalisib is only to be used as a first line treatment in patients with the p17 deletion or TP53 mutation that are not eligible for any other therapies due to the limited efficacy and safety data available in this indication.

The PRAC considered that this would also be relevant for idelalisib when used in combination with ofatumumab in the same indications.

Similarly in the iNHL studies -0124 and -0125 the imbalance in the rate of deaths observed is thought to be due to the relatively good prognosis and low rate of disease related infectious SAEs of the patients enrolled, leading to an increased relative risk of idelalisib-related infectious SAEs early in the studies as the benefits are not yet observed. The results also reflect the additional toxicity of rituximab or rituximab + bendamustine, in contrast to the authorised use which is as monotherapy. It was discussed at the SAG, that the study that supported the initial granting of the indication in refractory follicular lymphoma did not include a comparator arm and that a confirmatory trial in this indication would add valuable information to the available evidence, which is acknowledged. However the SAG noted that the feasibility of a comparative trial appears to be limited, and considered that it would be of interest in view of the results of studies -0124 and -0125 to obtain observational safety data from clinical practice in a representative sample of institutions, to which the PRAC concurred. The MAH has agreed to conduct a category 3 post-authorisation safety study and is requested to submit the protocol of this study for assessment by EMA within 3 months of the European Commission decision on this article 20 procedure.

While PRAC considered that the results of studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125 were not directly relevant to the authorised use of Zydelig, they highlighted the risks linked to off-label use in first line CLL and early line iNHL and the importance of the risk of infection, including PJP and CMV (please see below) associated with idelalisib. However, while the PJP and CMV risks are important, these infections represented a relatively small proportion of the serious infections cases observed in the studies reviewed. Therefore, more general risk minimisation measures for serious infection are warranted. The risks of infections and neutropenia related to idelalisib treatment are known and are listed as very common adverse events in the product information. In study -0116, there was a modest increase in the risk of infections overall and in the risk of serious infections in the treatment arm compared to the control arm. However, in this study, measures were in place to mitigate the risk of infection with idelalisib: PJP prophylaxis was recommended, idelalisib treatment was to be avoided in patients with active infection, patients were to be monitored for neutrophil count every two weeks for the first 6 months (with dose modification guidance) and for respiratory infections. The PRAC considered that risk minimisation measures were warranted in order to bring the use in clinical practice closer to that in the clinical trials where a positive benefit-risk was observed. In this regard, the provisional measures which specified that patients should not start taking idelalisib in case of systemic bacterial, fungal or viral infection and that patients should be monitored for respiratory signs and symptoms throughout treatment and advised to report promptly any new respiratory symptoms were considered justified and should be maintained. Further, as neutropenia leads to a higher risk of infection and infections were reported from the first month in the study, in line with measures applied in clinical trials and as implemented in the provisional measures, blood counts should be monitored every two weeks during the first six months of treatment. Blood counts monitoring should be intensified to weekly in patients with absolute neutrophil counts (ANC) below 1,000 per mm^3 and treatment withheld while ANC is below 500 per mm^3. Treatment may then be restarted at a reduced dose of 100 mg twice daily. In addition, it should be further specified in a footnote to the tabulated list of adverse reactions that the serious infections reported included opportunistic infections as well as bacterial and viral infections such as pneumonia, bronchitis, and sepsis. These measures and those related to PJP and CMV infections are expected to improve the benefit-risk balance in the authorised indications and ongoing extension of indication. The PRAC further requested that “serious infections including opportunistic infections such as PJP and CMV” and “off label use” in first line CLL therapy in patients without p17 deletion or *TP53* mutation should be added to the

risk management plan (RMP) as important identified risks. Neutropenia was already included in the RMP as an important identified risk.

The MAH was also proposed to implement a targeted follow questionnaire for cases of serious infections, which is endorsed. This questionnaire has been included in a revised RMP and will collect information on concomitant medication in cases of serious infection, compliance with monitoring requirements and prophylactic treatment. Results will be discussed in future PSURs.

The MAH also proposed to measure the effectiveness of the risk minimisation measures through a European healthcare professional (HCP) Survey, which will evaluate awareness and self-reported changes in clinical practice in response to the implemented risk minimisation measures, which is also endorsed. The MAH is required to submit the protocol of this category 3 study to EMA for evaluation within 3 months of European Commission decision.

***Pneumocystis jirovecii* pneumonia**

An increased incidence of PJP cases was observed in the treatment arms compared to the controls in the CLL and iNHL studies. While a few patients in the control arms of CLL studies experienced PJP infections, this was not the case in the iNHL studies. The majority of cases (66% [23/35]) occurred within the first 6 months of treatment. Overall, there was no clear relationship to treatment duration or number of prior regimen.

Depending on trials, between 20 and 70% patients were administered PJP prophylaxis defined as ≥ 4 weeks of at least one antibiotic, as detailed in tables 7 and 8.

Table 6. PJP cases in subjects with or without PJP prophylaxis in CLL studies GS-US-312-0116, GS-US-312-0119, GS-US-312-0115 and GS-US-312-0123

	GS-US-312-0116		GS-US-312-0119		GS-US-312-0115		GS-US-312-0123	
	Relapsed/Refractory CLL		Relapsed CLL		Relapsed CLL		Front-Line CLL	
	IDL + R (N = 110) n (%)	PL + R (N = 108) n (%)	IDL + O (N = 173) n (%)	O (N = 86) n (%)	IDL + BR (N = 207) n (%)	PL + BR (N = 209) n (%)	IDL + BR (N = 156) n (%)	PL + BR (N = 154) n (%)
Number of Subjects who Received Prophylaxis	51 (46.4)	54 (50.0)	114 (65.9)	61 (70.9)	123 (59.4)	141 (67.5)	68 (43.6)	71 (46.1)
PJP cases in patients not given prophylaxis	4 (3.6)	1 (0.9)	10 (5.8)	1(1.2)	3 (1.4)	0 (0)	1(0.6)	0 (0)
PJP cases within 4 weeks of prophylaxis	0 (0)	0 (0)	1 (0.6)	0 (0)	1 (0.5)	0 (0)	0 (0)	0 (0)
PJP cases 4 weeks after prophylaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

IDL = idelalisib, BR = bendamustine plus rituximab, O = ofatumumab, R = rituximab

In study 101-08, 26.6% and 34.1% of subjects in the idelalisib + rituximab and the idelalisib alone groups, respectively, received prophylaxis at some point during the study. One subject (1.6%) treated with idelalisib + rituximab and 1 subject (2.4%) treated with idelalisib alone experienced PJP, of which neither subject received prophylaxis.

Table 7. PJP cases in subjects with or without PJP prophylaxis in iNHL studies 101-09, GS-US-313-0124, and GS-US-313-0125

	101-09	GS-US-313-0124		GS-US-313-0125	
	Refractory iNHL	Relapsed iNHL		Relapsed iNHL	
	IDL (N = 125) n (%)	IDL + R (N = 198) n (%)	PL + R (N = 95) n (%)	IDL + BR (N = 317) n (%)	PL + BR (N = 155) n (%)
Number of Subjects who received Prophylaxis	32 (25.6%)	48 (24.2%)	22 (23.2%)	125 (39.4%)	64 (41.3%)
PJP cases in patients not given prophylaxis	1 (0.8)	1 (0.5)	0 (0)	8 (2.5)	0 (0)
PJP cases within 4 weeks of prophylaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PJP cases 4 weeks after prophylaxis	1 (0.8)	0 (0)	0 (0)	2 (0.6)	0 (0)

IDL = idelalisib, BR = bendamustine plus rituximab, R = rituximab

A pooling of the CLL studies -0116, 0119, -0115, -0123, and 101-08 show that two (0.5%) of the 387 idelalisib-treated patients who received prophylaxis developed PJP infection compared to 20 (5%) of the 364 idelalisib-treated patients who did not receive prophylaxis. In these five studies, there were two deaths due to PJP infection in idelalisib-treated patients; both occurred in patients who had not received prophylaxis (one in study -0116 and one in study -0123).

In the iNHL studies 101-09, -0124 and -0125, three (1.5%) of the 205 idelalisib-treated patients who received PJP prophylaxis developed PJP infection compared to 10 (2.3%) of the 435 idelalisib-treated patients who did not receive prophylaxis. In these studies, there were three deaths in idelalisib-treated patients (one in study -101-09 and two in study -0125), of which two occurred in patients who had not received prophylaxis.

Pooled subjects treated with idelalisib with and without bendamustine and with best overall response in the following categories: complete response, complete response with incomplete marrow recovery, minor response, partial response, stable disease, or very good partial response without ≥ grade 2 neutropenia, were examined for the effect of PJP prophylaxis. In subjects treated with idelalisib plus bendamustine and rituximab who received PJP prophylaxis, 1 subject (0.3%) experienced a PJP event, compared to 3 subjects (0.9%) in the group without PJP prophylaxis. In subjects treated with other idelalisib combinations (excluding bendamustine plus rituximab) who received PJP prophylaxis, 1 subject (0.5%) experienced a PJP event, compared to 6 subjects (2.3%) without PJP prophylaxis.

Of note, three PJP events occurred after the end of treatment. One PJP event occurred 22 days after end of treatment in Study GS-US-312-0116, and 2 PJP events occurred in Study GS-US-313-0125 respectively 5 and 56 days after end of treatment. Overall 5 (14%) out of the 35 cases of PJP in idelalisib-treated patients in CLL and iNHL studies resulted in death with 4 of the 5 deaths occurring in patients who had not received PJP prophylaxis.

Discussion

Globally prophylaxis was administered proportionally across the different arms of the studies, therefore the higher incidence of *Pneumocystis* observed in the idelalisib groups in CLL was most likely due to idelalisib and not the small differences in PJP prophylaxis. Although this retrospective analysis of prospectively collected data has important limitations (e.g. the decision to administer PJP prophylaxis was at the discretion of the investigator, which may have resulted in selection bias), the data show that PJP prophylaxis was associated with a reduced risk of PJP infection in patients receiving idelalisib. This was especially the case in CLL where the relative risk reduction was 90%, which is comparable with published data for the efficacy of PJP prophylaxis in non-human immunodeficiency virus (HIV) immunocompromised patients (Stern, 2014). The use of PJP prophylaxis in idelalisib-treated subjects

was notably lower in the iNHL studies than in the CLL studies; however, this was not associated with a higher incidence of PJP. The risk of PJP in patients who did not receive prophylaxis appears to be lower in the iNHL group than the CLL group (2.3% vs 5%). This may reflect a lower susceptibility to PJP infection in the iNHL group of patients, although this should be interpreted with caution because of the limitations of comparing safety outcomes across studies. In addition, patients with adequate neutrophil counts and stable disease seem to benefit less from prophylaxis; however, the small numbers make interpretation difficult.

Considering the significant morbidity and mortality associated with PJP infection, and the absence of a clearly identified low-risk group, PJP prophylaxis throughout treatment as recommended in the provisional measures is considered justified. While more cases occurred during the first 6 months on treatment, considering the proportion of cases occurring later it was not considered appropriate to limit the administration of PJP prophylaxis to this fixed time window. Further, the risk of PJP infection may persist when idelalisib treatment is stopped as a few cases where reported until 2 months after end of treatment. The SAG was of the view that the PJP prophylaxis should be prolonged after the end of treatment with idelalisib. Recent European conference on infections in leukaemia (ECIL) guidelines for preventing PJP in patients with haematological malignancies and stem cell transplant recipients recommend prophylaxis for ≥ 6 months after completion of other CLL treatments carrying a risk of PJP; for patients with acute lymphoblastic leukaemia, however, prophylaxis is recommended only from end of induction until end of maintenance (Maertens, 2016 [7]). In the idelalisib studies, the occurrence of clinical PJP was not associated with low (<140 cells/µL) CD4 counts, as is seen in fludarabine treatment or in patients with HIV. The MAH has indicated that the mechanism of idelalisib-associated PJP is most likely that of a functional impairment of T cells. Therefore monitoring of CD4 counts is unlikely to be of help in determining the duration of prophylaxis after idelalisib treatment is stopped. The duration of PJP prophylaxis after stopping idelalisib cannot be precisely defined based on the limited available data. However, in line with the SAG advice and in light of the occurrence of cases of PJP after stopping idelalisib as well as published guidelines (albeit in different patient populations), the MAH proposed that PJP prophylaxis should continue for 2-6 months after stopping idelalisib in a case by case basis. Section 4.4 of the SmPC should be further substantiated to advise physicians that factors to consider for adapting the duration of prophylaxis after the end of idelalisib treatment include concomitant corticosteroid treatment and prolonged neutropenia. In addition a cross reference to section 4.8 should be included, where the already listed adverse reaction “infection” with the frequency “very common” should be further qualified to mention that these included PJP. It should be further described that PJP was amongst the opportunistic infections observed in clinical studies, including after stopping idelalisib treatment and that most PJP cases, including fatal cases, occurred in patients that did not receive prophylaxis. The PRAC was also of the view that cases of PJP should be closely monitored; to this effect a targeted follow up questionnaire has been included in a revised RMP. The MAH should implement these questionnaires and their results should be discussed in future PSURs.

Cytomegaloviral infection

In relapsed/refractory CLL patients serious CMV infections occurred only in association with bendamustine, whilst small numbers of non-serious CMV cases were observed in all studies; in relapsed and refractory iNHL patients serious CMV infections were observed in the treatment arms of all studies including idelalisib monotherapy, idelalisib + rituximab, and idelalisib + rituximab + bendamustine regimens, whilst no cases of serious CMV infections were seen in the respective control arms. CMV infections occurred predominantly in the treatment arms of studies evaluating idelalisib in

[7] Maertens J, Cesaro S, et al. ECIL guidelines for preventing Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother 2016.

combination with both rituximab and bendamustine. The majority of CMV cases (75% [39/52]) occurred within the first 6 month of treatment. Overall, there was no clear relationship to treatment duration or number of prior regimen.

Of the 52 (2.4%) cases of treatment-emergent CMV across the 8 CLL and iNHL studies (n = 2,204), the location for the CMV infection was reported for 10 subjects in the gastrointestinal tract, 7 subjects in peripheral blood, 5 subjects in the lung, 4 subjects in multi-organ locations and 3 subjects in the eye. For the remaining 23 subjects, the location of infection was unspecified and therefore interpreted as peripheral blood.

Of the 481 patients treated with idelalisib in studies -0116, -0119, -0124 (without bendamustine) 5 subjects (1.0%) experienced a CMV AE with a median time to onset of 2.6 months.

Discussion

Consistently more CMV cases occurred in the treatment arms of the controlled studies. In the control arms of the studies in CLL that include bendamustine treatment a few patients experienced CMV, while in the control arm of the other CLL studies no patient experienced CMV events. No patients experienced CMV in the control arm of the studies in iNHL. Considering the CMV events reported, based on the limited data available at the start of the procedure the PRAC recommended as a precaution that clinical and laboratory screening for CMV infection should be conducted and that Zydelig should be discontinued if there is evidence of infection or viraemia. There does not appear to be a clear difference in the risk CMV in CLL and iNHL populations, but as already noted, this should be interpreted with caution given the significant limitations of comparing outcomes across different studies. Similarly as for PJP infection, while more cases occurred during the first 6 months of treatment considering the proportion of cases also occurring later, it was not considered appropriate to limit the CMV monitoring to this fixed period of time. However, overall in the clinical studies, the risk of CMV appears particularly evident in patients administered idelalisib and rituximab in combination with bendamustine. While it is acknowledged that the frequency of CMV might have been underestimated as symptoms of CMV infection are relatively unspecific and no regular screening for CMV (e.g. polymerase chain reaction [PCR]) was performed in the studies, in patients treated with idelalisib in combination with rituximab or ofatumumab in controlled studies (-0116, -0119 and -0124), the event rate of CMV was low (1%). The SAG advised that monitoring was only needed in patients with positive serology at start of treatment with idelalisib. This was agreed by the PRAC, which added that patients with other evidence of a history of CMV infection should also be monitored. In addition, the SAG considered that patients with increased viraemia compared to baseline should be carefully monitored but that idelalisib treatment should be continued. If clinical signs of CMV infection occur in these patients, then consideration should be given to interrupting idelalisib until the infection has resolved, weighting the need for idelalisib treatment against the severity of the CMV symptoms. The PRAC considered these recommendations appropriate. The SAG further advised that if the benefits of resuming idelalisib are judged to outweigh the risk, consideration should be given to administering pre-emptive CMV therapy. The PRAC considered that the precautionary warning included in the product information should be refined in line with these recommendations for healthcare professionals. Further, as for PJP, CMV should be added to further qualify the nature of the serious infections listed as adverse reactions in section 4.8 of the SmPC and that it should be further described that these were amongst the opportunistic infections reported in the idelalisib arms of clinical studies. The MAH should closely monitor cases of CMV and discuss these in detail in future PSURs.

2.3. Data on efficacy

The MAH provided relevant efficacy data including that previously submitted for the initial marketing authorisation on in CLL and FL, ongoing extension of indication with ofatumumab and limited interim data available from the three studies in which the safety signal was observed.

2.3.1. Data that supported the CLL indications

Idelalisib in combination with rituximab

Efficacy in CLL was mainly based upon the interim report from the pivotal phase 3 study GS-US-312-0116 in combination therapy and is further supported by reports of three additional studies, including study 101-08.

Table 8. Efficacy results from study GS-US-312-0116

		Idelalisib + R N = 110	Placebo + R N = 110
PFS	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	
ORR*	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	
LNR**	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	
OS^	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 ≥ 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.

In this study 43% of patients carried a 17p deletion and/or *TP53* mutation. Subgroup analysis showed a clinically relevant improvement in progression free survival (PFS) in these patients and overall response rate (ORR) results were consistent with the overall population (see table 9).

Table 9. Summary of PFS and response rates in 17p deletion and/or TP53 mutation pre-specified subgroup from study GS-US-312-0116

	Idelalisib + R N = 46	Placebo + R N = 49
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)

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

In study 101-08, a phase 2 single-arm study evaluating the safety and efficacy of continuous idelalisib + rituximab (cohort 1) or idelalisib monotherapy (cohort 2) in subjects with previously untreated CLL or SLL, 9 subjects (14.1%) in cohort 1 and 6 subjects (14.6%) in cohort 2 had documented 17p deletion or *TP53* mutation status. The ORR based on investigator assessment was 97% in cohort 1 and 85% in cohort 2. In cohort 1, all 9 subjects with either 17p deletion or *TP53* mutation responded. Three of these subjects had a complete response. In cohort 2, 4 subjects with either 17p deletion or *TP53* mutation had a partial response and 1 subject with 17p deletion or *TP53* mutation had a partial response with lymphocytosis for an ORR of 83%.

Idelalisib in combination with ofatumumab

The efficacy of idelalisib in combination with ofatumumab in patients with CLL has been confirmed in study GS-US-312-0119 which supported the extension of indication application for which the CHMP issued a positive opinion in February 2016. Study -0119 demonstrated an improved PFS in relapsed patients treated with idelalisib + ofatumumab compared to ofatumumab alone (idelalisib + ofatumumab median PFS=16.3 months; ofatumumab alone median PFS=8.0 months; HR+0.27, 95%CI (0.19, 0.39), p<0.0001). The overall survival was not significantly different between the two treatment groups (adjusted HR [95% CI] of 0.74 [0.44, 1.24]; p = 0.27), however, methodological factors including differences in drop-outs, duration of treatment exposure and follow-up time between the treatment arms might be responsible for these results, as already discussed and accepted by CHMP in February 2016 (EMA/H/C/3843/II/0011). The efficacy of idelalisib + ofatumumab was consistent in the subgroups, including patients with high-risk prognostic features such as 17p deletion or *TP53* mutations.

2.3.2. Data that supported the indication in refractory FL

Efficacy in FL was based upon the interim report from the pivotal single arm study 101-09 in idelalisib monotherapy, further supported by data in the reports of two phase 1/2 or 1 studies. Study 101-09 was a phase 2, open label, single-arm, multicentre study conducted in 125 subjects with previously treated iNHL (including 72 patients with FL) that was refractory both to rituximab and to alkylating-agent-containing chemotherapy. A summary of the results is presented in the below table.

Table 10. Summary of response in patients with FL treated with idelalisib in study 101-09

Characteristic	Study subjects n (%)
Overall response rate (follicular lymphoma) 95%CI	39(54.2) 42.0 - 66.0
Overall response rate (all subjects) 95%CI	71 (56.8) 47.6 – 65.6

Characteristic	Study subjects n (%)
Response category (follicular lymphoma)	
Complete response	6 (8.3)
Partial response	33(45.8)

The median duration of response (DOR) was 12.5 months. Due to the lack of a comparator for these patients, the ORR and DOR for idelalisib were compared with that of the last therapy prior to idelalisib treatment. The efficacy data of the subjects' previous therapy was inferior with an ORR of 23.2% and median DOR of 5.9 months.

2.3.3. Interim results of studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125

In the interim results of studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125 overall survival was numerically lower in the idelalisib arms.

Table 11. Kaplan Meier of overall survival at 3 months in studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125

Study 123 (previously untreated CLL)	**Idelalisib + BR**	**Placebo + BR**
KM of OS at 3 months (95% CI)	96.1 (91.6, 98.2)	100 (NR, NR)
Study 124 (previously treated iNHL)	**Idelalisib + R**	**Placebo + R**
KM of OS at 3 months (95% CI)	97.7 (94, 99.1)	100 (NR, NR)
Study 125 (previously treated iNHL)	**Idelalisib + BR**	**Placebo + BR**
KM of OS at 3 months (95% CI)	97.7 (95.2, 98.9)	99.3 (95.5, 99.9)

BR = bendamustine plus rituximab, R = rituximab, NR: not reached

The MAH presented the preliminary PFS, OS and best overall response data of a sub-analysis of the 38 first line patients with 17p deletion and/or *TP53* mutation that were included in study -0123.

Table 12. Progression-Free survival and overall survival in subjects with 17p deletion/*TP53* mutation by treatment arm, investigator assessment (Intent to Treat Analysis Set)

	IDL + BR (N = 18)	**Placebo + BR (N = 20)**
Number (%) of Subjects with Events	2 (11.1%)	8 (40.0%)
Disease Progression	0	7 (35.0%)
Death	2 (11.1%)	1 (5.0%)
Number (%) of Subjects Censored	16 (88.9%)	12 (60.0%)
Ongoing	16 (88.9%)	12 (60.0%)
Discontinued study	0	0
KM of PFS (Months)		
Q1 (95% CI)	NR (0.8, NR)	6.8 (2.3, 10)
Median (95% CI)	NR (NR, NR)	9.5 (6.8, NR)
Q3 (95% CI)	NR (NR, NR)	10 (9.5, NR)
KM of PFS Rate [95% CI]		
At 24 weeks	93.8 (63.2, 99.1)	85 (60.4, 94.9)
At 48 weeks	86.5 (55.8, 96.5)	22.7 (1.2, 61)
Hazard Ratio [95% CI]	0.25 (0.05, 1.20)	

	IDL + BR (N = 18)	Placebo + BR (N = 20)
KM of OS (Months)		
Q1 (95% CI)	NR (0.8, NR)	NR (6.6, NR)
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
Q3 (95% CI)	NR (NR, NR)	NR (NR, NR)
KM of OS Rate (95% CI)		
At 3 months	94.4 (66.6, 99.2)	100 (NR, NR)
Hazard Ratio (95% CI)	0.79 (0.13, 4.73)	

BR = bendamustine plus rituximab

Table 13. Best overall response in subjects with 17p deletion/TP53 mutation by treatment arm, investigator assessment (ITT Analysis Set)

	IDL + BR (N = 18)	Placebo + BR (N = 20)
Not evaluable	4 (22.2%)	0
Progressive disease	0	3 (15.0%)
Stable disease	0	5 (25.0%)
Partial response	9 (50.0%)	10 (50.0%)
Complete response	5 (27.8%)	2 (10.0%)

Discussion

The efficacy of idelalisib in combination with rituximab in patients with relapsed/remitting CLL has been confirmed in study GS-US-312-0116 which supported the authorisation of this indication. A significant benefit was seen for PFS, ORR and OS.

The demonstrated benefits of idelalisib + rituximab treatment seen in relapsed CLL patients who carried the 17p deletion or *TP53* mutation were extrapolated to first line CLL patients who carry either of these mutations. This was further supported by results of study 101-08 in which a response to first line idelalisib + rituximab treatment was seen in all 17p deletion and/or *TP53* mutation patients despite their poor prognosis. In study -0123 there were no statistically significant differences between the treatment groups for PFS, best overall response or OS in previously untreated CLL subjects with 17p deletion and/or *TP53* mutation. However, the immaturity of the data and small number of patients are noted as a plausible reason for the lack of observed benefit. Although the dataset for first line patients with 17p deletion and/or *TP53* mutation is too limited to draw direct conclusions, the overall assessment does not challenge the extrapolation of the benefits observed in relapsed/refractory CLL patients with 17p deletion or *TP53* mutation to treatment naïve patients, for idelalisib in combination with rituximab or ofatumumab. However, the limited availability of the data should be reflected in the product information and, in view of availability of an additional treatment option for these patients the indication should, as a precaution, be reworded to include only patient that are not eligible for any other therapies.

It was discussed at the SAG that conclusive evidence on the benefits and risks of idelalisib in this subset and line of treatment would require a randomised study in this setting but that due to the small number of patients and the availability of suitable alternative treatment such trial would likely not be feasible nor appropriate. This was agreed by the PRAC.

In follicular lymphoma, idelalisib showed consistent activity based on previous treatment responses in FL patients refractory to two prior lines of treatment.

3. Expert consultation

The PRAC consulted the oncology scientific advisory group (SAG) which provided advice on a number of issues as summarised below.

The SAG experts considered that the unexpected safety findings from studies -0123, -0124, -0125, did not add conclusive evidence as to a possible benefit or detriment of idelalisib in treatment of CLL relapsed/refractory patients and treatment-naïve patients who carry the 17p deletion or *TP53* mutation. On one hand, there were some concerns that the toxicity might be higher in first-line treatment; on the other it was considered that unauthorised use of idelalisib and rituximab in combination with bendamustine treatment may have accounted for the additional toxicity. Some SAG members agreed that the new data added to the overall uncertainty about benefits and risks in this indication which would impact the clinical decision-making since an alternative treatment is authorised in this indication (ibrutinib). However, other SAG members argued that idelalisib + rituximab (with appropriate risk minimisation measures) is still a valid treatment option as in some situations only potentially suboptimal treatment options are available (e.g. in case of contraindication to ibrutinib and when the only alternative treatment was dexamethasone). The SAG agreed that conclusive evidence on the benefits and risks of idelalisib in this subset and line of treatment would require a randomised study in this setting. However, the feasibility and appropriateness of such trial is questioned due to the small number of patients and the availability of suitable alternative treatment.

Regarding mortality and serious adverse events in the studies of idelalisib in combination with rituximab and that with ofatumumab in relapsed/refractory CLL patients, the experts discussed a number of factors that could have led to the observed differences between these studies and considered these added complexity to any comparison.

The SAG also agreed that these results do not add concerns of a detriment in the currently approved third-line monotherapy indication in FL considering the different combination likely resulting in increased toxicities compared to monotherapy and as the risk of infection can be further minimised with the new measures. A confirmatory trial in a third-line FL indication would be informative but the feasibility of such study was questioned, due to the observed effect of idelalisib monotherapy (e.g. approximately twice longer PFS compared to prior treatment), heterogeneity associated with many different possible comparators and approaches, the heterogeneity of the patient population also with respect to prior treatments, the increasing practice of maintenance treatment and response-adapted treatment approaches, the changing landscape with new active agents, and the interest to explore this drug in combination if toxicity does not become limiting. Nevertheless, it would be interesting to obtain data from an observational study with a representative sample of institutions to gain further information on the safety and efficacy in clinical practice; registry data could also be considered.

In view of the unexpected increased risk of CMV infection observed particularly in association with treatment combinations and based on analogies with post-transplant patient management, the experts considered that regular monitoring of CMV using reverse transcription-PCR should be recommended and the frequency adapted depending on change in viraemia compared to baseline and clinical manifestations. In case of negative CMV serology at baseline, monitoring is not recommended. Interruption of idelalisib treatment should be considered in case of observation of CMV reactivation with clinical manifestations, balancing the severity of the clinical manifestations with the urgent need

for idelalisib treatment. Once CMV with clinical manifestations has been observed, subsequent CMV prophylaxis should be recommended if continuing/restarting treatment with idelalisib is considered.

When asked for its views on potential practical or clinical implications of recommending *Pneumocystis* prophylaxis throughout treatment with idelalisib, the SAG considered this measure appropriate and was of the view that prophylaxis should be prolonged beyond end of treatment in view of the reported cases. The appropriateness of prolonged prophylaxis should be considered in the context of subsequent therapies. The SAG considered the risk minimisation measures proposed appropriate.

4. Benefit-risk balance

Zydelig (idelalisib) is a centrally authorised product and is currently 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. Idelalisib is also indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment. The CHMP recently adopted a positive opinion to also authorise the use of idelalisib in CLL in combination with another anti CD20 monoclonal antibody, ofatumumab.

This review was initiated due to a reported increased risk of death and higher incidence of serious adverse events (SAE) among subjects receiving idelalisib compared to the control groups observed in three clinical trials (GS-US-312-0123, GS-US-313-0124, GS-US-313-0125). The PRAC considered the new interim safety data and very limited efficacy data from three studies (-0123, -0124, -0125), that have been terminated, evaluating the addition of idelalisib to standard therapies in first line CLL and relapsed indolent non-Hodgkin lymphoma (iNHL)/small lymphocytic lymphoma (SLL) as well as the results of all other relevant trials including those that supported the above listed indications. The PRAC noted that in study -0123, idelalisib was administered in combination with rituximab and bendamustine (an unauthorised combination) in previously untreated CLL patients with and without 17p deletion/*TP53* mutation, which is not the same population as the one in the current CLL indication in first line. Similarly, in studies -0124 and -0125 idelalisib was not used as monotherapy as currently authorised but in combination with rituximab or rituximab and bendamustine, respectively. Further, these two studies included patients with earlier disease characteristics than the population for which idelalisib is authorised.

Idelalisib is known to cause very commonly infections and neutropenia and these risks are reflected in the product information. While these risks were considered acceptable due to the demonstrated beneficial effect observed in the studies that supported the initial marketing authorisation and later extension of indication, these three new studies indicate that in patients with early disease (CLL or iNHL) the risks (particularly of serious infection) are not outweighed by benefit. There was however no indication that treatment-naïve CLL patients constitute a population more at risk of developing idelalisib-related adverse events compared to relapsed/refractory patients. These results highlight nonetheless the importance of ensuring that the risk of serious infection is adequately minimised in the authorised indications, in line with the measures employed in studies that demonstrated the positive benefit-risk balance of idelalisib. In particular an increased incidence of PJP, carrying a high risk of morbidity and mortality, was observed in the idelalisib treatment arms compared to controls in all the studies, and appeared to be significantly lower in patients administered PJP prophylaxis. No low-risk population or risk-free period could be identified and the risk may persist after end of therapy, therefore, taking into account current guidelines on PJP prophylaxis and in line with the advice from

experts consulted during the review (SAG), the PRAC recommended that PJP prophylaxis should be administered to all patients throughout idelalisib treatment and prolonged afterward for up to 6 months based on clinical judgement. CMV infections were also notably reported in the idelalisib treatment arms, however, in controlled studies where idelalisib was administered in combination with rituximab or ofatumumab and not bendamustine, the reported rate was low. Nonetheless, considering the seriousness of those events, and following the SAG advice, the PRAC recommended that patients with evidence of prior CMV infection should undergo regular clinical and laboratory monitoring and patients with CMV viremia should be carefully monitored. If clinical signs of CMV infection appear, consideration should be given to interrupting idelalisib until the infection has resolved. If the benefits of resuming idelalisib are judged to outweigh the risks of CMV, consideration should be given to administering pre-emptive CMV therapy. While CMV and PJP are important risks, in the studies they accounted for a relatively small proportion of the serious infections observed, therefore the PRAC considered that more general measures to minimise the risk of serious infections as implemented as part of the provisional measures were justified. In particular, PRAC recommended that treatment should not be initiated in patients with evidence of ongoing systemic infection, that patients should be monitored for respiratory signs and symptoms throughout treatment and advised to report new respiratory symptoms promptly. Patients' blood counts should also be monitored during the first 6 months of treatment, adapting the frequency to the ANC. In case of very low ANC (<500/mm^3), treatment should be interrupted and may be resumed, at a lower dose, once this has resolved. These recommendations should be reflected in the product information together with a description of the infectious events and the MAH should conduct a study to assess healthcare practitioners' awareness to these risk minimisation measures.

The results of study -0123 are considered of limited relevance to the benefit-risk balance of idelalisib in the authorised CLL indication, due to the added toxicity of bendamustine. In addition, the data suggest that these results reflect the fact that the known toxicity of the treatment was not outweighed by its benefits due to the good prognosis and therefore low disease-related mortality of previously untreated CLL patients. However as patients with 17p deletion or *TP53* mutation have a poor prognosis, the extrapolation of the positive results observed in relapsed/refractory subjects with 17p deletion or *TP53* mutation that supported the initial granting of the indication in patients unsuitable for chemoimmunotherapy is not questioned. Nevertheless, in view of the limited data available in this subset and considering availability of other options for first line treatment for CLL patients, the PRAC was of the view that as a precaution, idelalisib should only be used in patients with 17p deletion or *TP53* mutation if they are not eligible for any other therapies. The benefit-risk balance of idelalisib in combination with rituximab in treatment naïve and relapsed/refractory CLL is therefore considered to remain positive provided the recommended risk minimisation measures are applied. The wording of the indication in first line CLL should be amended to reflect the above recommendation and it should be specified that this is linked to the limited data available in this setting.

For the same reasons, the relevance of the results of study -0123 is considered limited for the benefit-risk balance of idelalisib in combination with ofatumumab in the same types of CLL patients. The PRAC concluded that the same risk minimisation measures should be applied. Following the same precautionary principle, in view of the limited data available in treatment naïve patients with 17p deletion or *TP53* mutation it was also considered that idelalisib in combination with ofatumumab should be only be used first-line in CLL patients with 17p deletion or *TP53* mutation who are not eligible for any other therapies.

The unfavourable results of studies -0124 and -0125 reflect the use of the additional treatment related toxicity, which is not the same as that of the authorised use in monotherapy. Characteristics of patients in those studies are compatible with a good prognosis, including slow disease progression,

hence leading as in study -0123 to an unmasking of the idelalisib toxicity. Therefore while the relevance of these results are also limited for the authorised use in patients refractory to two prior lines of follicular lymphoma treatment, where idelalisib has been demonstrated to be effective and no other effective treatment options exist, they highlight the importance of minimising the risk of serious infection. The PRAC considered that the benefit-risk balance in this indication remained positive provided the risk minimisation measures are implemented. In addition as no controlled study was conducted in this indication, in view of the importance of the risk of serious infections, the MAH should conduct a post-authorisation safety study to collect additional safety data in those patients.

The PRAC concluded that the benefit-risk balance in the authorised indications remained positive, provided that first line treatment with idelalisib is only used in patients with 17p deletion or *TP53* mutation that are not eligible for any other therapies and that changes are implemented in the product information to minimise the risk of serious infections. The PRAC considered that these measures should be applied for the use of idelalisib in combination with ofatumumab in CLL patients.

5. Risk management

The MAH should operate a risk management system described in a risk management plan which has been endorsed as part of the current review procedure. The PRAC considered that “serious infections including opportunistic infections such as PJP and CMV” should be added as an important identified risk as well as “off label use” in first line CLL therapy in patients without 17p deletion or *TP53* mutation and early line iNHL therapy.

5.1. Pharmacovigilance activity

5.1.1. Specific adverse reaction follow-up questionnaires

The PRAC considered that targeted questionnaires to collect additional follow-up information on reported serious infections and PJP cases should be implemented. Their results should be discussed in future periodic safety update reports (PSURs).

5.1.2. Non-interventional studies

A survey of European HCPs was proposed by the MAH to measure the effectiveness of the risk minimisation measures implemented in this procedure. The MAH is required to submit the protocol of this category 3 study to the EMA for assessment by the PRAC, within 3 months of adoption of the European Commission decision.

In addition, in view of the results of studies GS-US-313-0124 and -0125 and as the study supporting the initial marketing authorisation in treatment of refractory FL did not include a control arm, the MAH is required to collect more safety data on these patients through an observational study. To this end, the MAH should consider establishing a registry or collaborating with an established one. The protocol of this category 3 study should also be submitted to the EMA for assessment by the PRAC, within 3 months of adoption of the European Commission decision.

5.2. Risk minimisation activities

5.2.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the risk of serious infections associated with the use of idelalisib. These changes refined those implemented in the provisional measures in March 2016[8] and include amendments to sections 4.1, 4.4 and 4.8 of the SmPC.

The indication in first line treatment of CLL was revised to only allow treatment of adult patients with 17p deletion or *TP53* mutation who are not eligible for any other therapies. It was further explained that this is linked to the limited availability of data in this patient population.

Warnings and precautions of use relating to the PJP and CMV risks associated with the use of idelalisib were also refined. The risk of serious infection was described and further qualified.

The Package Leaflet was amended accordingly. In addition, the opportunity was taken to correct the local representatives of Slovakia and Slovenia in the Package Leaflet of the 100 mg strength in the English and Croatian languages.

5.2.2. Direct Healthcare Professional Communications/Communication plan

A DHPC was disseminated in March 2016 based on the very limited and preliminary data available, to inform about the recommended temporary precautionary restrictions in the use of idelalisib and the additional monitoring requirements. A DHPC with updated information further to this thorough review was considered needed and the PRAC therefore adopted the wording of a Direct Healthcare Professional Communication to inform healthcare professionals of additional information identified during the review, including the indication in combination with rituximab for the first-line treatment of adult patients with CLL in the presence of 17p deletion or *TP53* mutation who are not eligible for any other therapies, the prolonged need for PJP prophylaxis and more adapted CMV monitoring requirements. The PRAC also agreed on a communication plan.

6. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Zydelig (idelalisib).
- The PRAC reviewed the preliminary data provided by the marketing authorisation holder on the interim results of studies GS-US-312-0123, GS-US-313-0124, GS-US-313-0125 that suggested an increased risk of death and serious infection with idelalisib. The PRAC also reviewed all the other relevant data presented by the MAH and the views expressed by the oncology scientific advisory group.
- The PRAC noted that studies -0123, -0124 and -0125 involved patient groups and treatment combinations different from those of the authorised indications of Zydelig. The PRAC considered the results of these studies of limited relevance for the benefit-risk balance of

[8] More information is available in the published assessment report on provisional measures

idelalisib in its authorised indications and ongoing extension of indication in combination with ofatumumab for the treatment of CLL. Nevertheless, as a precaution and in view of the fact that limited data are available in treatment-naïve CLL patients with 17p deletion or *TP53* mutation, the PRAC recommended that idelalisib should only be used in this group of patients if they are not eligible for any other therapies.

- The PRAC noted that most of the serious adverse events reported in studies -0123, -0124 and -0125 were related to infections. The PRAC considered that further minimisation measures of the known risk of infection related to the use of idelalisib were necessary. To this effect, the PRAC recommended that treatment with idelalisib should not be initiated in patients with evidence of systemic infections, that patients should be monitored for respiratory symptoms and that they should be administered *Pneumocystis jirovecii* pneumonia prophylaxis throughout and after idelalisib treatment. Regular clinical and laboratory monitoring for cytomegalovirus infection is also recommended in patients with evidence of prior infection. In addition, neutrophil count monitoring is recommended. In the event of severe neutropenia, treatment should be interrupted and may be restarted at a lower dose upon resolution.

In view of the above, the Committee considers that the benefit-risk balance of Zydelig remains favourable subject to the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Zydelig.