

## 5.11 IDELALISIB

### oral tablet, 100 mg tablet, 60; 150 mg tablet, 60; Zydelig®; Gilead Sciences Pty Ltd.

#### 1 Purpose of Application

- 1.1 The submission requested Section 85, Authority Required (STREAMLINED) listing for the treatment of indolent subtypes of B-cell non-Hodgkin's lymphoma (NHL) in patients with progressive disease despite previous treatment.

#### 2 Requested listing

- 2.1 The submission's requested restriction was for the treatment of adult patients with relapsed or refractory indolent NHL (iNHL) who had received at least two prior therapies as shown below.

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IDELALISIB				
Oral tablet 150 mg	60	5	DPMQ: \$ [REDACTED] Effective: \$ [REDACTED]	Zydelig Gilead Sciences Pty Ltd
Oral tablet 100 mg	60	5	DPMQ: \$ [REDACTED] Effective: \$ [REDACTED]	
Severity	Relapsed disease			
Condition	Indolent subtypes of B-cell non-Hodgkin lymphoma			
Treatment phase	Initial and continuing treatment			
Restriction	Section 85 Authority required (STREAMLINED)			
Treatment criteria	Patients must have progressive disease despite previous treatment for this condition; previous treatment must include at least two prior therapies.			

- 2.2 The commentary had identified a number of issues with the submission's requested restriction including that:

- it was not consistent with the pivotal study because patients in the study were refractory (not relapsed) to both rituximab and an alkylating agent; and
- "two prior therapies" is ambiguous, for example, it could be interpreted to include R-CHOP and rituximab maintenance.

These two issues were addressed in a revised restriction that was proposed in the Pre-Sub-Committee Response (PSCR):

Severity	Refractory
Condition	Indolent B-cell non-Hodgkin lymphoma
Treatment criteria	The condition must be refractory to both rituximab and an alkylating agent.
Definitions	The condition is considered refractory if the patient experiences less than a partial response or progression of disease within 6 months after completion of a prior therapy. The condition is considered refractory to both rituximab and an alkylating agent if the agents were either administered together or in successive treatment regimens.

- 2.3 However the revised restriction did not align with the indication proposed in the Advisory Committee on Prescription Medicines (ACPM) resolution, which was

provided during the evaluation. Idelalisib was TGA registered on 9 February 2015 for the same indication as recommended by the ACPM. The TGA approved indication is: as monotherapy for the treatment of patients with refractory follicular lymphoma, who have received at least 2 prior systemic therapies. (Underlining indicates the proposed changes compared to the requested indication.)

The ACPM recommended approval in follicular NHL but not other types of indolent NHL because it considered that there was insufficient evidence for indolent NHL, as the data were immature with only a surrogate endpoint, overall response rate, supporting the efficacy.

- 2.4 The PSCR's revised restriction does not align with the indication that was approved by the TGA because the proposed restriction would allow subsidised access in all indolent sub-types of B-cell NHL, while the TGA indication restricts use to follicular lymphoma.
- 2.5 The basis for the requested PBS listing was a cost-utility analysis using best supportive care as the comparator.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **3 Background**

- 3.1 TGA status: The submission was made under the TGA/PBAC Parallel Process. At the time of ESC consideration, the ACPM resolution was available. As outlined above, idelalisib was TGA registered on 9 February 2015.
- 3.2 The PBAC had not previously considered a submission for idelalisib. Idelalisib was also considered at the March 2015 PBAC meeting for use in patients with chronic lymphocytic leukaemia in combination with rituximab.

### **4 Clinical place for the proposed therapy**

- 4.1 Indolent NHL refers to a broad group of slow-growing NHLs. In approximately 50% of cases, the disease is asymptomatic. Indolent NHL can be B-cell or T-cell lymphomas. B-cell indolent subtypes of NHL include follicular lymphoma, small lymphocytic lymphoma, marginal-zone lymphoma, and lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinaemia. They are not generally considered curable.
- 4.2 The ESC noted that NHL represents a heterogeneous condition that has a variable natural history, including spontaneous regression.<sup>1</sup>
- 4.3 The submission described the current treatment algorithm as follows: Under current arrangements, patients with symptomatic indolent NHL would be treated with rituximab plus chemotherapy. A proportion would receive rituximab maintenance therapy (almost all patients with follicular lymphoma and 30% of the patients without

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<sup>1</sup> Horning S, Rosenberg S. The Natural History of Initially Untreated Low-Grade Non-Hodgkin's Lymphomas. N Engl J Med 1984; 311:1471-1475

follicular lymphoma). Patients who relapsed while receiving rituximab maintenance therapy, or who relapsed within 6 months of receiving rituximab therapy ('refractory' patients) would not be eligible for further rituximab treatment. Rather they could receive a stem cell transplant if physically fit, localised radiotherapy, experimental treatments in a clinical trial, or palliative care. Patients who relapsed more than 6 months after finishing rituximab (maintenance therapy and/or first-line rituximab + chemotherapy) would receive a second line of rituximab plus chemotherapy. The submission proposed that if these patients had a further relapse they would not be eligible for further rituximab treatment. The evaluation considered that this does not appear to reflect current clinical practice where patients who relapse may receive more than two lines of rituximab treatment.

- 4.4 The submission proposed that the only difference between the current treatment algorithm and that proposed would be the insertion of idelalisib as a third line treatment after failing two cycles of rituximab treatments (either one induction cycle and one maintenance cycle or two induction cycles), before localised radiotherapy, experimental treatments in a clinical trial, or palliative care.
- 4.5 The PSCR's revised restriction would limit use to patients who have disease that is refractory to both rituximab and an alkylating agent, rather than relapsed disease as proposed in the submission. Refractory was defined as less than a partial response or disease progression within 6 months after completion of a prior therapy.
- 4.6 The ESC considered that the treatment algorithm for iNHL is evolving. On 1 December 2014, rituximab was listed as maintenance therapy in follicular NHL following a partial or complete response to the induction phase of treatment. Further, bendamustine (an alkylating agent) was also considered by the PBAC in March 2015 for the treatment of patients with iNHL.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **5 Comparator**

- 5.1 The submission nominated best supportive care as the comparator. Best supportive care represented a mix of ill-defined therapies, for which no comprehensive clinical data was available. This was not considered to be the appropriate comparator by the evaluator for the population requested in the submission.
- 5.2 For the population requested in the submission, i.e. progressive disease despite previous treatment with at least two prior therapies, the evaluator considered that rituximab could be used as a comparator, as some patients may receive more than two lines of rituximab treatment.
- 5.3 Bendamustine (an alkylating agent) was also considered by the PBAC in March 2015 for the treatment of patients with indolent NHL. The evaluator had considered that this could also be a comparator, and efficacy between the two treatments could be compared using a naïve indirect comparison.

- 5.4 The PSCR's revised restriction would limit use to patients who are refractory to both rituximab and an alkylating agent, and therefore the ESC considered that best supportive care was the appropriate comparator.
- 5.5 The ESC noted that the submission considered "best supportive care" to include a mix of therapies (anti-cancer, investigational, unfunded). The economic evaluation estimated that 20% of patients who received best supportive care would be given anti-cancer drugs such as low dose FCR and rituximab monotherapy. The cost (but not benefit) of these treatments was included in the model's base case.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **6 Consideration of the evidence**

### **Sponsor hearing**

- 6.1 There was no hearing for this item.

### **Consumer comments**

- 6.2 The PBAC noted that no consumer comments were received for this item through the consumer comments facility of the PBS website.
- 6.3 Representatives of the PBAC met with Lymphoma Australia prior to the PBAC meeting, and reported the following key points to the PBAC in relation to the agenda items for CLL and indolent NHL:
- Consumers place high importance on having access to the best available treatments. Where cure is not possible, the eventual goal would be to enable indolent lymphomas and CLL to be treated as chronic diseases. Ultimately patients may die of conditions unrelated to their lymphoma.
  - Patients may relapse multiple times in the course of the disease, and will be treated on relapse. As PBS subsidy may influence the choice of treatment, subsidising the most clinically effective treatments is critical to ensure the best value for the taxpayer.
  - Patients may be diagnosed at a young age and live for years after diagnosis, and therefore place a high value on PFS. Patients who are well during the progression-free period can resume day-to day functions including participating in the workforce and family life. In this context, the decision for the patient rests on a balance of the PFS gained against the quality of life impacts of drug toxicity. The psychological impact of patients' fear of relapse can have a highly detrimental effect on their quality of life.

The PBAC noted and welcomed this input. The PBAC recognises that a drug may be useful even when it does not provide a survival advantage, but does provide quality of life benefits. In terms of using PFS to value the benefits of a drug, the PBAC recalled that some of the most informative submissions seen to date have presented economic models that incorporate the impacts on quality of life when patients are in a

PFS state, capturing the fact that PFS is not an homogenous state. It was noted that exploring how patients could provide more input to rigorous measurement of Quality of Life would be valuable in future consumer submissions.

## Clinical trials

- 6.4 The submission was based on one open-label Phase II study of patients treated with idelalisib, and two supportive Phase I safety studies of idelalisib. Two open label studies of patients on other therapies were reviewed to provide what the submission called “contextual efficacy.” The submission considered the latter to overestimate the efficacy of the nominated comparator, best supportive care. This evidence was provided in lieu of a formal comparison. The evaluation performed a comparison of idelalisib and bendamustine, as the evaluation considered that bendamustine could have been a comparator.
- 6.5 Studies 101-09 and 101-02 were part of the TGA’s consideration of idelalisib in NHL. These studies were also the basis for the Food and Drug Administration’s (FDA) approval of idelalisib under the agency’s accelerated approval program for use in relapsed follicular B-cell NHL or small lymphocytic lymphoma in patients who have received at least two prior systemic therapies. The FDA’s approved indication for these conditions states:  
 “Accelerated approval was granted for follicular lymphoma and small lymphocytic lymphoma based on overall response rate. Improvement in patient survival or disease related symptoms has not been established. Continued approval for these indications may be contingent upon verification of clinical benefit in confirmatory trials”.
- 6.6 Details of the trials presented in the submission are provided in the table below.

### Studies and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
<b>Idelalisib studies</b>		
101-09	A Phase 2 Study to Assess the Efficacy and Safety of Idelalisib in Subjects with Indolent B-Cell Non-Hodgkin Lymphomas Refractory to Rituximab and Alkylating Agents.	Clinical study report 101-09, 12 August 2013
Gopal	PI3K $\delta$ Inhibition by idelalisib in Patients with Relapsed Indolent Lymphoma.	<i>N Engl J Med</i> 2014 370(11): 1008-1018
101-02/99	A Phase 1 Sequential Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of CAL-101 (GS-1101 [idelalisib]) in Patients with Selected, Relapsed or Refractory Hematologic Malignancies.	Clinical Study Report 101-02/99, 24 July 2013
101-07/99	A Phase I Study to Investigate the Safety and Clinical Activity of CAL-101 in Combination with Chemotherapeutic Agents and Anti-CD20 mAb in Patients with Relapsed or Refractory Indolent B-cell Non-Hodgkin Lymphoma, Mantle Cell Lymphoma or Chronic Lymphocytic Leukaemia.	Clinical Study Report 101-07/99, 18 June 2013
<b>Comparator efficacy studies – according to the submission less pretreated</b>		
Witzig	Treatment With Ibritumomab Tiuxetan Radioimmunotherapy in Patients With Rituximab-Refractory Follicular Non-Hodgkin’s Lymphoma.	<i>J Clin Onc</i> 2002. 20(15): 3262-3269
Kahl	Bendamustine Is Effective Therapy in Patients With Rituximab-Refractory, Indolent B-cell Non-Hodgkin Lymphoma.	<i>Cancer</i> 2010 116(1): 106-114

Source: Table B-7, pp55-56 of the submission

6.7 The key features of the non-randomised studies are summarised in the table below.

**Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Idelalisib</b>						
101-09	125	OL, single arm idelalisib Median follow-up: 9.7 months	High	iNHL, refractory to both RIT and alkylating agent median prior tx: 4	OS,PFS, ORR	ITT: idelalisib NR: BSC
101-02/99	64	OL, dose ranging, subgroup of patients with iNHL 48 weeks, or disease progression	High	iNHL, refractory to or relapsed after ≥1 prior chemotherapy regimen and having received RIT, and not eligible for transplantation	ORR,PFS, OS	Not used
101-07/99	79	OL, dose ranging, idelalisib in combination with other treatments 48 weeks, or disease progression	High	iNHL Previously treated with relapsed or refractory disease	ORR,PFS, OS	Not used
<b>Comparator efficacy studies – according to the submission less pretreated</b>						
Witzig (2002)	54	P, OL, single arm Y-ibritumomab tiuxetan + rituximab Median follow-up: NR	High	FL, prior treatment with RIT, and either did not respond or had a TTP of <6 months median prior tx: 4	ORR, TTP, DOR,	Not used
Kahl (2010)	100	P, OL, single arm Bendamustine Median follow-up 11.8 months	High	indolent B-cell lymphoma and RIT-refractory median prior tx: 3	ORR, PFS, DOR, safety	Not used

Source: compiled during the evaluation

DOR = duration of response; FL = follicular non-Hodgkin's lymphoma; iNHL = indolent non-Hodgkin's lymphoma; ITT = intention to treat; NR = not reached; OL=open label; ORR=overall response rate; OS=overall survival; P = prospective; PFS=progression-free survival; RIT = rituximab; TTP = time to progression;

6.8 The two supportive phase 1 idelalisib studies (101-02, 101-07) differed from Study 101-09 and each other with regard to inclusion criteria, distribution of iNHL sub-types and disease status. Patients in the Phase I studies (101-02/99 and 101-07/99) were not similar to those included in Study 101-09, and are therefore not further discussed below.

Exchangeability of studies

6.9 The inclusion criteria in Study 101-09 were more stringent than those in the comparator studies, however heavily pretreated patients were not excluded from the comparator studies. The PSCR's revised restriction may result in use in a more heavily pretreated population.

6.10 The patients in Kahl (2010) were reasonably similar to those in Study 109-09, although there were differences between the two study populations with regard to age, sex, number of prior treatments and lymphoma histology. Furthermore, as outlined in the PSCR, patients in the Kahl study were not required to be refractory to

an alkylating agent. It is unclear whether these differences would impact on the efficacy and safety outcomes.

- 6.11 The Witzig study differed from both of the single-arm studies, Study 101-09 and the Kahl study in terms of age, sex and lymphoma histology, limiting its use as 'supportive context' or corroboration for idelalisib efficacy.

On-going Phase III trials of idelalisib in NHL

- 6.12 There are two on-going phase III randomised controlled trials of idelalisib in patients with previously treated iNHL listed on [clinicaltrials.gov](http://clinicaltrials.gov).
- Trial GS-US-313-0125 will assess the efficacy and safety of idelalisib in combination with bendamustine and rituximab in previously treated patients with iNHL.
  - Trial GS-US-313-0124 (NCT01732913) will assess the efficacy and safety of idelalisib in combination with rituximab in patients with previously treated iNHL who are not refractory to rituximab.
- 6.13 The Pre-PBAC response outlined that these trials are investigating the use of idelalisib in combination with rituximab or bendamustine-rituximab in patients at earlier stages of treatment. The PBAC agreed with the Pre-PBAC response that these trials will inform the future place of idelalisib in combination therapy for patients with NHL, but that these trials will not inform the role of idelalisib monotherapy in the patient group requested in this submission.
- 6.14 The Pre-PBAC response incorrectly stated that “the decision question (is): efficacy and safety of idelalisib” in the requested patient population. The PBAC noted that the decision question for the PBAC is comparative effectiveness and cost-effectiveness.

*For more detail on PBAC's view, see section 7 “PBAC outcome”*

**Comparative effectiveness**

- 6.15 The table below presents evidence from the idelalisib study alongside two other single arm studies of alternative treatments: radioimmunotherapy (Witzig 2002), and bendamustine (Kahl 2010). The submission described the comparison to radiotherapy and bendamustine as providing “contextual efficacy”.
- 6.16 For Study 101-09, the sub-group of patients with follicular lymphoma is presented in addition to the ITT results given the TGA registration for idelalisib is in follicular lymphoma only.

**Results of clinically relevant indicators across the non-randomised studies**

Study ID	Idelalisib 101-09		Comparator studies	
			Y-ibritumomab tiuxetan Witzig (2002)	Bendamustine Kahl (2010)
N	125 (ITT)	72 (FL)	54 <sup>a</sup>	100
Median duration of follow-up, months	9.7	NA	NA	11.8
<b>Progression-Free Survival</b>				
Patients with event, n (%)	57 (46%)	35 (49%)	NA	57 (57%)
Censored, n (%)	68 (54%)	37 (51%)	-	43 (43%)
Discontinued study	36 (29%) <sup>d</sup>	20 (28%)	-	-
Data cut-off	32 (26%)	17 (24%)	-	-
Median PFS, months (95% CI)	11.0 (8.1, 13.8)	8.5 (5.7, 13.1)	6.8 (range 1.7, >25.9) <sup>b</sup>	9.3 (8.1, 11.9)
<b>Overall survival</b>				
Died n (%)	28 (22%) <sup>c</sup>	NA	2 (4%)	11 (11%)
Median OS, months (95% CI)	20.3 (16.4, NR)	NA	NA	NA

Source: Table B-28, p79, Table B-29, p80, Table 30, p83, text p84, Table B-31, p85, Table B-39, p95, text, pp95-98, Table B-40, p97, and extracted from Table 2.5.1.4, p1110 of the CSR and the publications of Witzig (2002) and Kahl (2010).

CI = confidence interval; FL = follicular lymphoma; ITT = intention to treat; NA = not available; NR = not reached; OS = overall survival; PFS = progression-free survival;

<sup>a</sup> Efficacy data was presented for patients with follicular lymphoma only

<sup>b</sup> Time to progression, the publication noted that 30% of the patients were censored.

<sup>c</sup> This value was for the median duration of follow-up

<sup>d</sup> 20% due to adverse events, 6% at the investigator's request, 3.2% withdrew consent.

- 6.17 The submission did not provide any comparative data to inform the comparison with best supportive care. Instead, the submission used non-responders in the single arm study (101-09) to approximate outcomes for best supportive care. The ESC considered that this approach was inappropriate because it is inherently biased and confounded. This is further discussed in the 'Economic Analysis' section.
- 6.18 The PSCR provided information from the most recent data cut-off of Study 101-09 (June 2014).<sup>2</sup> This represented an additional 12 months of data.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

**Comparative harms**

- 6.19 Most patients treated with idelalisib reported at least one adverse event that was grade 3 or higher (70%). The most frequent grade 3 or higher adverse events were neutropenia (21%), diarrhoea (13%), increased alanine aminotransferase (9%), pneumonia (7%), and increased aspartate aminotransferase (6%). Ten (8%) patients died due to adverse events. No formal statistical comparison was presented by the submission. No attempt was made to establish that idelalisib was superior in safety to best supportive care. The FDA had the following black box warning on its prescribing information for idelalisib; "warning: fatal and serious toxicities: hepatic, severe diarrhoea, colitis, pneumonitis and intestinal perforation".
- 6.20 The ESC noted that idelalisib was the probable cause of adverse events leading to death in four patients in Study 101-09.

<sup>2</sup> Gopal, Ajay K., et al. "Mature Follow up from a Phase 2 Study of PI3K-Delta Inhibitor Idelalisib in Patients with Double (Rituximab and Alkylating agent)-Refractory Indolent B-Cell Non-Hodgkin Lymphoma (iNHL)." Blood 124.21 (2014): 1708-1708

For more detail on PBAC's view, see section 7 "PBAC outcome"

## Benefits/harms

- 6.21 A summary of the comparative benefits and harms for idelalisib versus best supportive care is presented in the table below.

**Summary of comparative benefits and harms for idelalisib and best supportive care**

Benefits						
	Idelalisib	BSC	Absolute Difference	HR (95% CI)		
<b>PFS</b>	Study 101-09					
Median follow-up, months	9.7	No data	-	-		
Progressed	57/125 (46%)	No data	-	-		
Median (months)	11.0 (8.1, 13.8)	No data	-	-		
<b>Overall survival</b>						
Died	28/125 (22%)	No data	-	-		
Median (months)	20.3 (16.4, NR)	No data	-	-		
Harms						
	Idelalisib	BSC	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Idelalisib	BSC	
<b>Adverse event</b>						
Death due to AE	10/125	No data	-	8	-	-
Death probably due to idelalisib	4/125	No data	-	3	-	-
Any grade $\geq$ 4	68/125	No data	-	54	-	-
Neutropenia	34/125	No data	-	27	-	-
Diarrhoea	16/125	No data	-	13	-	-

<sup>a</sup> Median duration of follow-up/Median duration of exposure: Study 101-09 = 9.7 months/6.6 months.

CI = confidence interval; NA = Not available; NR = not reached; OS = overall survival; PBO = placebo; PFS = progression-free survival; RD = risk difference; RR = relative risk; BSC = best supportive care

Source: Compiled for the ESC advice.

- 6.22 The submission did not present comparative evidence for idelalisib versus best supportive care, and the ESC considered that no information had been provided that would enable a reliable comparison of idelalisib and best supportive care.
- 6.23 A summary of the comparative benefits and harms for idelalisib versus the contextual efficacy comparison studies is presented in the table below.

**Summary of comparative benefits and harms for idelalisib and two comparator studies**

<b>Benefits</b>						
	<b>Idelalisib</b>	<b>Y-ibritumomab tiuxetan</b>	<b>Bendamustine</b>	<b>Absolute Difference Bendamustine</b>	<b>HR (95% CI)</b>	
<b>PFS</b>	Study 101-09	Witzig 2002	Kahl (2010)			
Median follow-up, months	9.7	NA	11.8			
Progressed	57 (46%)	NA	57 (57%)	-		
Median (months)	11.0 (8.1, 13.8)	6.8 (range 1.7, >25.9) <sup>b</sup>	9.3 (8.1, 11.9)	1.7 (-1.7, 5.1)	NR	
<b>Overall survival</b>						
Died	28 (22%) <sup>c</sup>	2 (4%)	11 (11%)			
Median (months)	20.3 (16.4, NR)	NA	NA		NR	
<b>Harms</b>						
	<b>Idelalisib</b>	<b>Bendamustine</b>	<b>RR (95% CI)</b>	<b>Event rate/100 patients*</b>		<b>RD (95% CI)</b>
				<b>Idelalisib</b>	<b>Bendamustine</b>	
<b>Adverse event</b>						
Death due to AE	10/125	7/100	1.14 (0.45, 2.89)	8	7	1.0 (-5.9, 7.9)
<i>Death probably due to idelalisib</i>	4/125					
Any grade $\geq$ 4	68/125	39/100	<b>1.39 (1.04, 1.87)</b>	54	39	<b>15 (3, 28)</b>
Neutropenia	34/125	61/100	<b>0.45 (0.32, 0.62)</b>	27	61	<b>-34 (-46, -22)</b>
Diarrhoea	16/125	5/100	2.56 (0.97, 6.8)	13	5	<b>8 (1, 15)</b>

<sup>a</sup> Median duration of follow-up/Median duration of exposure: Study 101-09 = 9.7 months/6.6 months ; Witzig (2002) = not available/not available; Kahl (2010) = 11.8 months/not available.

CI = confidence interval; NA = Not available; NR = not reached; OS = overall survival; PBO = placebo; PFS = progression-free survival; RD = risk difference; RR = relative risk

Source: Compiled during the evaluation

6.24 Based on a naïve indirect comparison, the comparison of idelalisib and bendamustine did not result in a significant difference in overall survival or progression-free survival.

On the basis of a naïve indirect comparison, for every 100 patients treated with idelalisib in comparison to bendamustine over a median duration of follow up of approximately 10 months:

- approximately 15 additional patients would have a grade 3 or higher adverse event;
- approximately 34 fewer patients would have severe neutropenia;
- approximately 8 additional patients would have severe diarrhoea.

6.25 Based on a naïve indirect comparison, the comparison of idelalisib and Y-ibritumomab tiuxetan did not result in a significant difference in overall survival or progression-free survival

## Clinical claim

- 6.26 The submission claimed that idelalisib had superior efficacy and safety compared to best supportive care for the treatment of patients with indolent NHL. No appropriate comparative evidence was provided in the submission to support this. Therefore the ESC concluded that the submission's claim was not adequately supported. The ESC further noted:
- Naïve comparisons were made between the single arm idelalisib study 101-09, and two other single arm studies which did not precisely represent best supportive care. The only comparable outcome was progression-free survival, and this did not indicate major differences. Other key issues were:
    - The patient characteristics differed, which made the comparison difficult;
    - There were no common treatment arms to allow for assessment of the exchangeability of the studies;
    - A large proportion of patients were censored due to adverse events.
- The ESC considered that the naïve comparisons did not represent comparative evidence against best supportive care.
- The adverse event profiles between the studies were different, with bendamustine having higher rates of neutropenia, while idelalisib was associated with higher rates of diarrhoea and pneumonia. No statistical evidence was presented for the increased safety of idelalisib.
  - The superior efficacy and safety claim was inconsistent with the claim presented for the economic evaluation. In the economic evaluation a claim of superior efficacy but inferior safety was made.
  - The TGA registration is for follicular lymphoma only.
- 6.27 The ESC considered that the information provided was not an appropriate basis for informing the comparative effectiveness and safety of idelalisib versus best supportive care.
- 6.28 Patients in Study 101-09 patients had a median of four prior lines of treatment. The ESC noted that the applicability with regard to the number of prior therapies in the revised PBS population was not assessed.
- 6.29 The PBAC considered that the claim of superior comparative efficacy and safety was not adequately supported by the data.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## Economic analysis

- 6.30 The submission presented a modelled cost-utility analysis, using the ITT population from Study 109-09 to inform idelalisib efficacy (i.e. the entire study cohort was used to inform idelalisib efficacy) and the non-responders from this study to inform best supportive care.

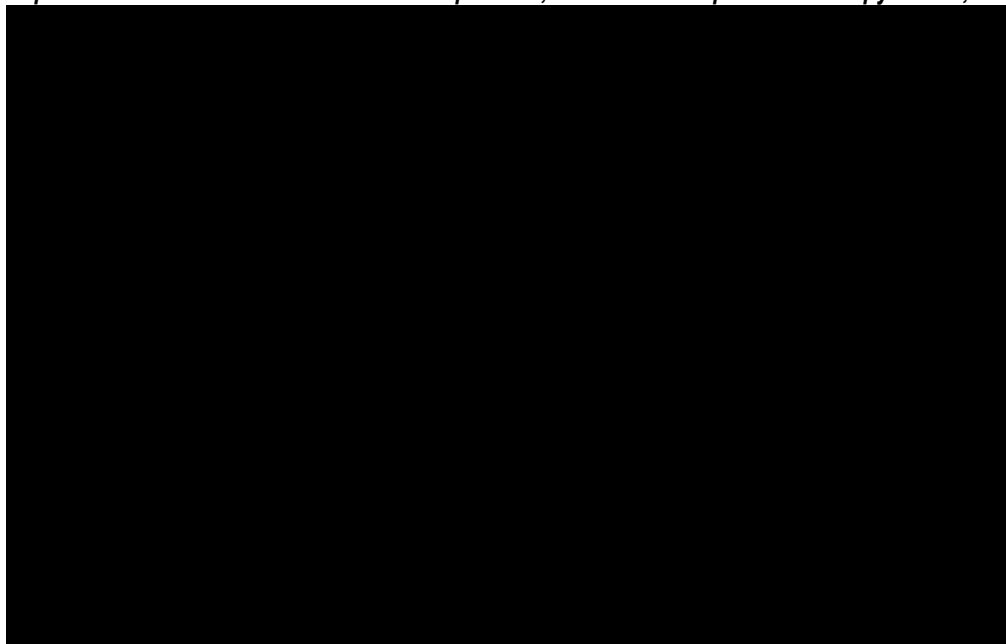
### Use of non-responders from the single arm study to inform best supportive care

- 6.31 The ESC considered that the use of non-responders as a proxy for best supportive care was inappropriate. Overall survival among the non-responders was probably

lower due to adverse events potentially associated with idelalisib treatment, i.e. 10/125 (8%) patients died in Study 101-09 due to adverse events. Further, non-responders to any active intervention tend to have inherently poorer prognoses than the average patient and confounding cannot be ruled out. Finally, it was not reasonable to assume idelalisib given to non-responders would have the same treatment effect as best supportive care given to average patients.

- 6.32 Whilst non-responders were similar to the ITT population with regard to age, sex, baseline disease stage and prior exposure to antineoplastic agents, the ESC considered that it was unclear how comparable the non-responders were with regard to other potential confounders of outcome including performance status and baseline cytopenias, as well as other confounders of treatment effect that were unknown or not observed.
- 6.33 Non-responders may have experienced drug-related toxicities that may have affected their outcomes. The commentary noted that ten patients in Study 101-09 died due to adverse events, and it was not clear how these patients were handled in the analysis. The PSCR outlined that idelalisib was the probable cause of an adverse event leading to death in four patients in Study 101-09. Three of these patients were classed as non-responders. As idelalisib may have been a cause of death in these patients, the ESC considered that it was unreasonable to include them in a group meant to simulate the “no idelalisib” arm. This may have underestimated the overall survival of best supportive care.
- 6.34 As shown in Figure 1, the submission supported this approach by comparing the PFS of non-responders with the estimated PFS that patients had achieved with their previous line of therapy before entering Study 101-09. The submission concluded that the PFS of the non-responders was similar to that observed with the last line of previous therapy, and that the similarities in the PFS patterns support the approach applied in the economic evaluation.
- 6.35 The ESC considered that the analysis was unreliable. In addition to the concerns outlined above regarding the submission’s approach to estimating the comparator arm, the ESC also noted:
- This analysis compared patients at different stages of disease, which was unreasonable even considering the large number of prior treatments that patients received before entering Study 101-09.
  - a large proportion of the patients on idelalisib were censored due to adverse events. These patients were more likely to be in the non-responder arm of Study 101-09.
  - By their very nature both groups included in the analysis presented in the figure below were “non-responders”. To enter the trial 101-09 participants had to be “non-responders” and the assumption is that without idelalisib everyone will be non-responders to BSC following the same trajectory of outcome as the non-responders in trial 101-09. This assumption is unreasonable as it is subject to high chance of confounding and potential bias.

**Kaplan Meier estimates for PFS for non-responders, and last line of previous therapy for ITT, 101-09**



Source: Table C-3, p 138 of the submission, Figure C.2.1.1 of commentary, Figure 1 of PSCR.  
 PFS = progression-free survival, ITT = intention to treat, LLPT = last line of previous therapy

6.36 The ESC concluded that the outcomes of non-responders were not an appropriate basis to inform the outcomes of best supportive care.

Economic model

6.37 Details of the model structure are presented below.

**Summary of model structure and rationale**

Component	Summary
Time horizon	10 years in the model base case versus 9.7 months in study (median duration of follow-up)
Outcomes	LYs and QALYs
Methods used to generate results	Single patient expected value analysis
Health states	3: Stable disease, progressed disease, dead. <i>Utilities were sourced from the literature.</i>
Cycle length	28 days
Transition probabilities	Formal Markov transition probabilities were not used. The population of health states was determined by parametric curve fitting of observed progression-free survival and overall survival curves. For the intervention (idelalisib) arm, the whole ITT population of study 101-09 was used. For the comparator (best supportive care) arm, the subgroup of non-responders in study 101-09 was used. <i>The ESC considered this to be unreasonable.</i>

Source: compiled during the evaluation.  
 LY = life year; QALY = quality adjusted life year

- 6.38 A summary of the key drivers of the model is presented in the table below.

**Key drivers of the model**

Description	Method/Value	Impact
Efficacy BSC	Use of non-responder of idelalisib study	High, values are unreliable
Time horizon	10 years; assumed from 6 month trial duration	High, favours idelalisib
Dose intensity	72.6%, calculated indirectly from study 101-09	Moderate, favours idelalisib
Use of anti-cancer treatments in BSC	20%, assumed	Moderate, favours idelalisib

Source: compiled during the evaluation.  
BSC = best supportive care.

- 6.39 The results of the cost-utility analysis are presented below.

**Results of the stepped economic evaluation**

modelled evaluation	idelalisib	Best supportive care	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	1.344	0.831	0.513
Life Years	1.878	1.181	0.697
<b>Incremental cost/extra QALY gained</b>			<b>\$ [REDACTED]</b>
<b>Incremental cost/extra LY gained</b>			<b>\$ [REDACTED]</b>

Source: Table D-8, p 174 of the submission.  
QALYs = quality-adjusted life years

- 6.40 The submission stated that idelalisib compared to best supported care resulted in an incremental cost effectiveness ratio (ICER) of \$45,000/QALY – \$75,000/QALY per quality adjusted life year (QALY). The ESC considered that this estimate was not informative for decision making because the model was underpinned by the inappropriate assumption that non-responders to idelalisib were a proxy for best supportive care. As it was unclear what the appropriate efficacy was for best supportive care, this could not be tested in sensitivity analyses.
- 6.41 The ICER was sensitive to the model duration, idelalisib dose intensity, use of anti-cancer medicines in BSC, utilities, and the choice of parametric distribution.
- 6.42 The model's time horizon was 10 years, based on a median duration of follow-up of 9.7 months in Study 101-09. The ESC noted that the model was sensitive to this parameter, and considered that the submission had not adequately justified the use of a time horizon that was 10 times longer than clinical study's median duration of follow-up.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

**Drug cost/patient/course: \$ [REDACTED] (dose intensity of 93%)**

- 6.43 The drug cost/patient/course was based on the submission's assumption that patients would receive treatment until disease progression, with a median duration of 11 months (per the economic model). The drug cost/patient/course presented above was also based on a dose intensity of 93%.
- 6.44 Using the dose intensity assumed by the submission, which was 73%, the cost per patient would be \$ [REDACTED]. The evaluation considered that the submission's estimation

of dose intensity was unreasonable as it included patients who were censored because they discontinued from the study. The dose intensity of 93% was derived by the evaluator using a more direct method of dividing the number of days on active treatment by the number of days on treatment.

- 6.45 The ESC considered that the evaluation's estimation of dose intensity (93%) was reliable and did not consider this to be an upper estimate of dose intensity, as suggested in the PSCR. The ESC noted that the model is sensitive to this parameter and if a dose-intensity of 93% is used the ICER increases to \$75,000/QALY – \$105,000/QALY (compared to \$45,000/QALY – \$75,000/QALY if 73% is used per the submission's base case).

### **Estimated PBS usage & financial implications**

- 6.46 The DUSC considered that the submission had underestimated the potential utilisation and financial impacts of listing idelalisib. The main issues identified by the DUSC were:

- The eligible population was underestimated. The DUSC considered that the submission could have calculated the eligible population more directly. Since idelalisib was proposed as a third line treatment, the proportion of treated patients who received third + line treatment reported by IPSOS (18%) would be more appropriate.
- The treated prevalence based on UK market research was underestimated.
- The uptake rate used by the submission was not justified and may have been underestimated. The DUSC noted that no evidence provided to justify the uptake rate. DUSC agreed with the Commentary that, as the eligible population could be underestimated and the uptake rate is uncertain, the submission is likely to have underestimated the treated population.
- The number of prescriptions was underestimated due to a problematic methodology to estimate the dose intensity.
- The number of MBS monitoring tests was based on a formula that was not justified.

- 6.47 The DUSC noted that, due to an increasing prevalent pool of patients in Australia, even a small percentage increase in the number of patients could make a large difference to the total cost of idelalisib.

- 6.48 The DUSC did not agree with the Sponsor that the revised listing addresses concerns about the underestimated patient population.

- 6.49 As shown in the table below, at year 5, the estimated number of patients was [REDACTED] and the net cost to the PBS /RPBS would be \$ [REDACTED].

**Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated					
Market share	35%	55%	65%	70%	80%
Scripts <sup>a</sup>					
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to MBS	-\$	-\$	-\$	-\$	-\$
<b>Estimated total net cost</b>					
<b>Net cost to PBS/RPBS/MBS</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>

Source: Commentary Table 8, p11; Submission Tables E-7 and E-12, pp 194 and 199

MBS = Medicare Benefits Schedule; PBS = pharmaceutical benefits scheme; RPBS = repatriation pharmaceutical benefits scheme

<sup>a</sup> Assumed [redacted] scripts per year as estimated by the submission.

6.50 The redacted table above shows that the estimated net cost to government would be less than \$10 million per year in years 1-5

6.51 The PBAC noted that the pre-PBAC response acknowledged the advice of DUSC and provided revised estimates, resulting in a slightly higher number of patients than presented in the submission.

**Financial Management – Risk Sharing Arrangements**

6.52 The submission did not state that the sponsor would be willing to undertake a risk sharing arrangement.

**7 PBAC Outcome**

7.1 The PBAC did not recommend the listing of idelalisib for the treatment of patients with indolent NHL on the basis that the comparative effectiveness could not be established because the submission had not provided information about a comparable population treated with best supportive care. Therefore the cost-effectiveness could not be estimated, in the context of a drug with a high cost compared with current care. The PBAC considered that the application was fundamentally deficient, because the data were of poor quality and did not provide a reliable basis for decision-making.

7.2 The PBAC agreed that there is a high unmet clinical need for an effective treatment for patients with 'double-refractory' indolent NHL (i.e. refractory to both rituximab and an alkylating agent). The PBAC welcomed the input received at the consumer hearing. The comments highlighted the sense of hope that an active treatment can provide.

7.3 The PBAC noted that the proposed restriction was revised in the PSCR to limit use to patients whose disease is refractory to both rituximab and an alkylating agent, which is consistent with the pivotal study. The PBAC considered that this revision was appropriate. However, the proposed restriction would allow use in patients with all indolent sub-types of NHL, while the final TGA registration would allow use only in follicular lymphoma.

- 7.4 The PBAC considered that best supportive care was the appropriate comparator for the patient population with double-refractory indolent NHL.
- 7.5 The PBAC noted that the median PFS of idelalisib in the pivotal phase 2 study (Study 101-09) was 11 months, indicating that idelalisib is an active treatment. The PBAC also noted that idelalisib was generally well tolerated but was associated with some toxicities including late colitis.
- 7.6 However, for the reasons outlined in Paragraphs 6.9 to 6.36, the PBAC considered that neither the non-responder group, nor the data from single arm studies of alternative agents provided an acceptable basis for estimating the efficacy and safety of best supportive care in this patient population. Therefore the comparative efficacy and safety of idelalsib could not be estimated.
- 7.7 In the absence of suitable data to inform the effectiveness of best supportive care, the PBAC concluded that a reliable economic evaluation could not be conducted. Therefore the cost-effectiveness of idelalisib in iNHL could not be determined.
- 7.8 The PBAC considered that the utilisation and financial impacts were underestimated in the submission, as outlined by the DUSC (refer to Paragraphs 6.46 to 6.49).
- 7.9 The PBAC considered that a re-submission should: include a restriction that aligns with final TGA indication; and provide a reliable estimate of the comparative effectiveness and safety of idelalisib, based on a dataset that adequately demonstrates outcomes with best supportive care in the population requested. The PBAC acknowledged that there would be limitations with such a dataset. Should such a dataset become available, the PBAC considered that the other concerns raised by the evaluation and the ESC would also need to be addressed in the re-submission.
- 7.10 The PBAC considered that a major re-submission would be required to seek listing of idelalisib for iNHL.
- 7.11 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**  
Rejected

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

Gilead looks forward to working with the Department in order to achieve PBS listing for Zydelig for patients with refractory/relapsed disease.