7.03 IDELALISIB
oral tablet, 100mg, 150mg
Zydelig®, Gilead Sciences Pty Ltd

1 Purpose of Application

1.1 The resubmission requested Section 85, Authority Required (STREAMLINED) listing of idelalisib for the treatment of follicular lymphoma that is refractory to both rituximab and an alkylating agent. The first submission was considered at the March 2015 PBAC meeting.

1.2 The resubmission also requested that the PBAC consider whether the 'rule of rescue' is applicable.

2 Requested listing

2.1 The requested PBS listing is presented below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IDELALISIB				Zydelig® Gilead
Tablet, 150mg, 60	1	5	$[redacted] (published) $[redacted] (effective)	
Tablet, 100mg, 60				

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	*Refractory*
Severity:	~~Refractory disease~~
Condition:	follicular *B-cell non-Hodgkin's* lymphoma
PBS Indication:	Refractory follicular *B-cell non-Hodgkin's* lymphoma
Treatment phase:	~~Initial and continuing treatment~~
Restriction Level / Method:	☒Streamlined

Treatment criteria:	~~The condition must be refractory to both rituximab and an alkylating agent.~~ ~~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.~~
Clinical criteria:	*The condition must be refractory to rituximab* *AND* *The condition must be refractory to an alkylating agent* *AND* *The treatment must be as monotherapy* ~~PBS subsidised treatment with idelalisib must be discontinued in patients who experience disease progression whilst on treatment~~
Prescriber Instructions	*A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.* *The condition is considered refractory to both rituximab and an alkylating agent if the agents were administered together or in successive treatment regimens.* *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.*
Administrative Advice	*No increase in the maximum quantity or number of units may be authorised.* *No increase in the maximum number of repeats may be authorised.* *Special Pricing Arrangements apply.*

2.2 The resubmission presented a cost-utility analysis of idelalisib compared with best supportive care.

2.3 In comparison with the previous submission, listing was only sought for patients with follicular lymphoma rather than all sub-types of indolent non-Hodgkin's lymphoma. This was appropriate and addressed the PBAC's concerns from March 2015 that the restriction should align with the TGA indication (Paragraph 7.9, March 2015 PBAC Minutes).

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

3 Background

3.1 Idelalisib was TGA registered on 9 February 2015 as monotherapy for the treatment of patients with refractory follicular lymphoma, who have received at least two prior systemic therapies.

3.2 This item was previously considered at the March 2015 PBAC meeting.

Table 1: Summary of the previous submission and current resubmission

	Idelalisib, iNHL, March 2015	Current resubmission
Requested PBS listing	iNHL that is refractory to both rituximab and an alkylating agent (as requested in PSCR). **PBAC Comment**: restriction should align with the final TGA indication (Para 7.9).	FL that is refractory to both rituximab and an alkylating agent.
DPMQ	Effective DPMQ: $[redacted] (for 150 mg and 100 mg)	Unchanged.
Main comparator	BSC which included a mix of therapies (anti-cancer, investigational, unfunded). In the economic evaluation, 20% of BSC patients were assumed to receive anti-cancer drugs. **PBAC Comment:** BSC was the appropriate comparator (Para 7.4).	Unchanged, except that 30% (rather than 20%) of BSC patients were assumed to receive anti-cancer drugs.
Clinical evidence	Idelalisib evidence Study 101-09. Data-cut from 25 June 2013. Data from 11 June 2014 data-cut was provided in abstract form in the pre-PBAC response. Supplementary evidence: Two Phase I dose-ranging studies. **PBAC Comment:** The median PFS of idelalisib in Study 101-09 was 11 months, indicating that idelalisib is an active treatment. (Para 7.5).	Same 3 studies. Study 101-09 data-cut from 11 June 2014, which included FL subgroup results.
	To inform comparator arm (BSC): "Contextual efficacy": Two open-label Phase II studies of other therapies. Economic model: 'non-responder analysis'. Last line of prior therapy was used to support the approach. **PBAC Comment:** 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 BSC in this patient population. (Para 7.6).	Same data to inform BSC, plus: - Time to progression on the last line of prior therapy was used to derive PFS in the economic model. *This was supportive data in the previous submission, but the resubmission used the FL subgroup in the base case.* - Post-progression survival following idelalisib was used to derive OS in the economic model. - A survival analysis using PBS 10% sample data (Prospection analysis) was used to support the OS results.
Key effectiveness data	Idelalisib: Study 101-09 (25 June 2013), median follow-up 9.7 months. Median PFS, ITT: 11.0 months (8.1, 13.8) Median OS, ITT: 20.3 months (16.4, NR) BSC (proxy) Median PFS, all non-responders: 3.9 months Median OS, all non-responders: 13.1 months **PBAC Comment:** The comparative efficacy and safety of idelalisib could not be estimated (Para 7.6).	Idelalisib: Study 101-09 (11 June 2014), median follow-up 19.4 months, FL subgroup Median PFS, FL: 11.0 months (8.0, 14.0) Median OS: FL: NR (NR, NR) BSC (proxy) PFS (last line of prior therapy): 5.1 months OS (post-progression survival): NR (0.21, NR)
Key safety data	Idelalisib: Study 101-09 (25 June 2013). ITT study population: Death due to AE: 8% (10/125) Any Grade 3/4 AE: 70% (68/125) Neutropenia Grade 3 or higher: 21% (26/125) Diarrhoea Grade 3 or higher: 13% (16/125)	Idelalisib: Study 101-09 (11 June 2014), FL subgroup: Death due to AE: 8% (6/72) Any Grade 3/4 AE: 65% (47/72) Neutropenia Grade 3 or higher: 19% (14/72) Diarrhoea Grade 3 or higher: 14% (10/72)

	Idelalisib, iNHL, March 2015	Current resubmission
Clinical claim	Superior efficacy and safety compared with BSC for the treatment of patients with iNHL. **PBAC Comment:** "The comparative efficacy and safety of idelalisib could not be estimated" (Para 7.6, March 2015).	Superior efficacy and inferior safety of idelalisib compared with BSC.
Economic evaluation	Cost-utility model with cost/QALY $[redacted] ITT population from Study 109-09, June 2013 data-cut (idelalisib), and the non-responders from this study (BSC). **PBAC Comment:** "In the absence of suitable data to inform the effectiveness of BSC, a reliable economic evaluation could not be conducted" (Para 7.7).	Cost-utility model with cost/QALY $[redacted]. FL subgroup from Study 109-09, June 2014 data-cut (idelalisib). To inform BSC: - PFS from the last line of prior therapy analysis; and - OS from the post-progression survival analysis.
Economic evaluation – model structure	Time horizon: 10 years. **PBAC Comment:** Not adequately justified (Paras 6.42 and 7.9) Dose Intensity: 72.6% **PBAC comment:** The ESC considered 92.7% would be more reliable (Para 6.44).	Time horizon: 5 years. Dose intensity: 92.7%
Number of patients	[redacted] in Year 1 increasing to [redacted] in Year 5 (iNHL patients). **PBAC Comment**: The utilisation and financial impacts were underestimated (Para 7.8). The eligible population should have been calculated more directly, and the treated prevalence and uptake rate were underestimated (Para 6.46).	[redacted] in Year 1 increasing to [redacted] in Year 5 (FL patients only).
Estimated cost to PBS	$[redacted] million in Year 5 $[redacted] million over the first 5 years of listing. **PBAC Comment:** Underestimated (as above).	$[redacted] million in Year 5 $[redacted] million over the first 5 years of listing.
PBAC decision	Reject.	-

Source: *compiled during the evaluation*

AE = adverse event; BSC = best supportive care; DPMQ = dispensed price for maximum quantity; ESC = Economics Sub-Committee; FL= follicular lymphoma; iNHL = indolent non-Hodgkin's lymphoma; ITT = intention-to-treat; NR = not reached; OS = overall survival; Para = paragraph; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression free survival; PSCR = Pre-Sub-Committee Response; QALY = quality-adjusted life year; TGA = Therapeutic Goods Administration

3.3 A second resubmission, requesting listing of idelalisib for the second-line treatment of chronic lymphocytic leukaemia and small lymphocytic lymphoma, will also be considered at the November 2015 PBAC meeting.

4 Clinical place for the proposed therapy

4.1 The resubmission proposed that the place in therapy was for the treatment of follicular lymphoma that is refractory to both rituximab and an alkylating agent ("double-refractory").

5 Comparator

5.1 The resubmission nominated best supportive care as the comparator. The PBAC considered this to be the appropriate comparator in its previous consideration.

5.2 As per the previous submission, the resubmission assumed that best supportive care included a mixture of symptom management, re-treatment with chemotherapy despite low and unknown efficacy, and use of investigational and unfunded treatments. For the economic evaluation, the resubmission assumed that 30% of patients who received best supportive care would be given anti-cancer drugs such as low-dose fludarabine, cyclophosphamide and rituximab (FCR). This was increased from 20% in the previous submission. The proportion of use of these treatments was not adequately justified in the resubmission. Use of anti-cancer treatments would be less likely in patients with double-refractory disease given there is a risk of harms but low or unknown efficacy.

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.

Clinical trials

6.3 The resubmission was based on one single-arm Phase II study of patients with indolent non-Hodgkin's lymphoma treated with idelalisib, Study 101-09. This was the same study as presented in the previous submission. However, the resubmission was based on a more recent data-cut that provided an additional 12 months of follow-up and information on the subgroup of patients with follicular lymphoma. The resubmission also presented a survival analysis that was based on a 10% sample of PBS claims data (Prospection analysis).

6.4 The resubmission provided two supportive Phase I safety studies of idelalisib, and two open-label studies of other therapies to provide what the submission called "contextual efficacy". These were unchanged from the previous submission, and no additional justification was provided for their inclusion. The PBAC did not consider these studies to be informative in its previous consideration. Therefore, these studies are not further discussed.

6.5 Details of the studies presented in the resubmission are provided in the table below.

Table 2: Studies and associated reports presented in the resubmission

Trial ID/ First Author	Protocol title/ Publication title	Publication citation
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 Aug 2013
	Gopal AK, Kahl BS, de Vos S, *et al.* PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma.	*N Engl J Med* 2014 370(11): 1008-1018
	Salles G, Schuster S, de Vos S, *et al*. Idelalisib Efficacy and Safety in Follicular lymphoma Patients From a Phase 2 Study.	J Clin Oncol 33, 2015 (suppl; abstr 8529)
	Applicant's Response for Post-Authorisation Measures (PAM002), Study 101-09. Gilead Submission Reference Number 1101-14-268.	101-09, 19 Nov 2014
Prospection Pty Ltd	Follicular Lymphoma Market Analysis, Time on Therapy	Unpublished, 18 June 2015

Source: Table B-7, pp61-62 of the resubmission

6.6 The key features of the included evidence are summarised in Table 3.

Table 3: Key features of the included evidence

Study	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
101-09	125	OL, single arm idelalisib Median follow-up: 19.4 months	High	iNHL, refractory to both RIT and alkylating agent median prior tx: 4	OS, PFS, ORR	FL subgroup (n=72) used for idelalisib efficacy. Also used to derive BSC efficacy (see below).
Prospection analysis	*unclear* [a]	Retrospective analysis of PBS claims database [a]	High	FL, based on PBS item and authority codes. Prior tx: 2 or 3	Time to death	No

Source: compiled during the evaluation

BSC = best supportive care; FL = follicular lymphoma; iNHL = indolent non-Hodgkin's lymphoma; OL = open-label; ORR = overall response rate; OS = overall survival; PBS = Pharmaceutical Benefits Scheme; PFS = progression free survival; RIT = rituximab; tx = treatment; yr = year

[a] The number of patients and duration of follow-up for the Prospection 'FL Market Analysis, Time on Therapy' was not clear. The Study Methodology stated that patient numbers were scaled, while the Summary of Results stated that they were not scaled. The Study Methodology stated that data from January 2010 to December 2014 were used, while the Summary of Results stated that data from 2006 to 2014 were used.

6.7 The resubmission used data from Study 101-09 to derive the efficacy of both idelalisib and best supportive care (referred to as "conceptual best supportive care") for the economic evaluation. The resubmission also provided supportive data to substantiate the estimates of best supportive care efficacy. The data used in the resubmission are outlined in Table 4.

Table 4: Summary of the data used in the resubmission

	Idelalisib	"Conceptual BSC"		
		Base case of economic model	Supportive data	
			Sensitivity analysis [a]	Other
PFS	Study 101-09, FL subgroup n=72 PFS	Study 101-09, FL subgroup n=72 Time to progression on the last line of prior therapy	Study 101-09, iNHL n=54 Non-responders to idelalisib	-
OS	Study 101-09, FL subgroup n=72 OS	Study 101-09, FL subgroup n=56 Post-progression survival following idelalisib	Study 101-09, iNHL n=54 Non-responders to idelalisib	Prospection analysis (n= unclear [b]) Time to death

Source: compiled during the evaluation

BSC = best supportive care; FL = follicular lymphoma; iNHL = indolent non-Hodgkin's lymphoma; OS = overall survival; PFS = progression free survival

[a] Used in previous submission, and presented as a sensitivity analysis in the economic evaluation

[b] The number of patients and duration of follow-up for the Prospection 'FL Market Analysis, Time on Therapy' were not clear (see Table 3 table note a).

6.8 For the base case of the economic model, the efficacy of "conceptual best supportive care" was based on the following:

- Time to progression on the last line of prior therapy before starting idelalisib in Study 101-09 (follicular lymphoma subgroup) was used to derive progression free survival.
- Post-progression survival following idelalisib in Study 101-09 (follicular lymphoma subgroup) was used to derive overall survival. In the study, idelalisib was ceased at progression. Patients receiving best supportive care were assumed to experience only the post-progression survival outcomes from Study 101-09. That is, patients treated with best supportive care were assumed to have no pre-progression period (for the overall survival analysis only).

6.9 The non-responders analysis, which was used as the base case in the previous submission, was re-presented as supportive data. However, the PBAC did not consider this to be reliable in its previous consideration.

6.10 A Prospection analysis was also used as supportive data for overall survival with best supportive care. This was based on a 10% sample of PBS claims data. Patients who were dispensed PBS items for follicular lymphoma (based on streamlined authority codes for rituximab, where applicable) were followed up over time. Patients were considered to be on their first "line of therapy" when they received their first PBS-subsidised item for follicular lymphoma. The next line of therapy was defined based on a break of more than 84 days between PBS items for follicular lymphoma, or more than six months for rituximab monotherapy (to account for rituximab maintenance therapy). These data were used to estimate the time between a "line of treatment" for follicular lymphoma and death. The ESC suggested a more meaningful analysis of the 10% sample would be informative in the absence of concurrent comparator arm in the pivotal study.

Comparative effectiveness

6.11 Comparative effectiveness data for idelalisib versus the base case assumptions for "conceptual best supportive care" are presented in Table 5.

Table 5: Results of progression free survival and overall survival in Study 101-09

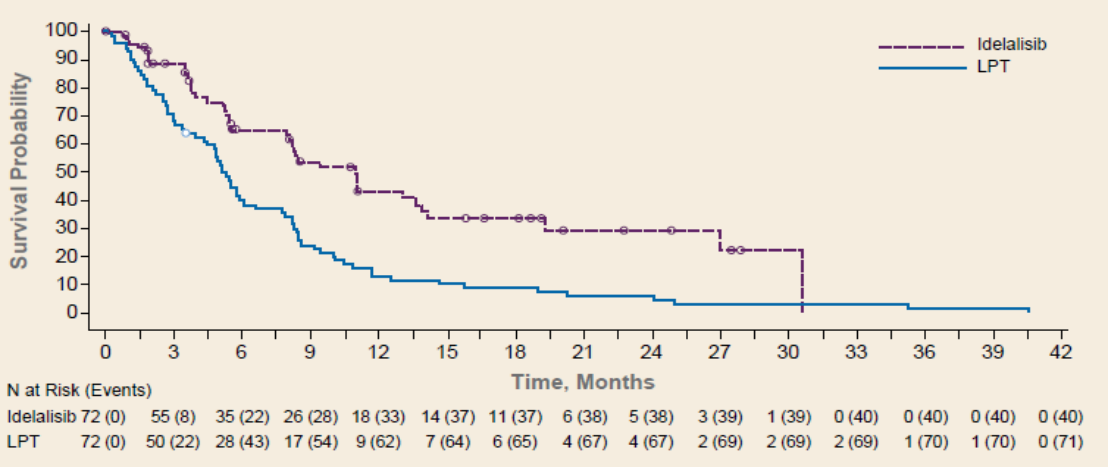
Study ID	Idelalisib Study 101-09		"Conceptual BSC" data from Study 101-09		
	Longer-term follow-up (11 June 2014 data-cut)		Last line of prior therapy		Post-progression survival
Population	ITT	FL	ITT	FL	FL
N/n	125	72	125	72	56
Median follow-up, months	NA	19.4	-	-	*~3 to 4*
Progression free survival					
Median PFS, months (95% CI)	11.0 (8.3, 13.8)	11.0 (8.0, 14.0)	3.9 (range 0.7, 41.4)	5.1 (4.4, 6.0)	-
Overall survival					
Died, n (%)	42 (34%)	19 (26%)	-		*8 (14.3%)*
Median OS, months (95% CI)	30.8 (26.8, NR)	NR (NR, NR)	-		*NR (0.2, NR)*
KM estimate of % surviving at 24 weeks (%)		96.5%			*86.1% (74.8, 99.1)*

Source: Table B-31, p94; Table B-32, p98 of the resubmission; *Salles* et al. *(2015)*; Table 3, p20; Table 4, p29; Table 2.4.1, p82; Table 2.4.2, p92; Table 2.7.2, p128 of the PAM002 response; Tables 8-10, p70 of the CSR of 101-09; and *data provided by the Sponsor during the evaluation*

BSC = best supportive care; CI = confidence interval; FL = follicular lymphoma; ITT = intention-to-treat; KM = Kaplan-Meier; NA = not available; NR = not reached; OS = overall survival; PFS = progression free survival

6.12 Figures 1 and 2 present the Kaplan-Meier curves for progression free survival and overall survival, respectively, for idelalisib and "conceptual best supportive care".

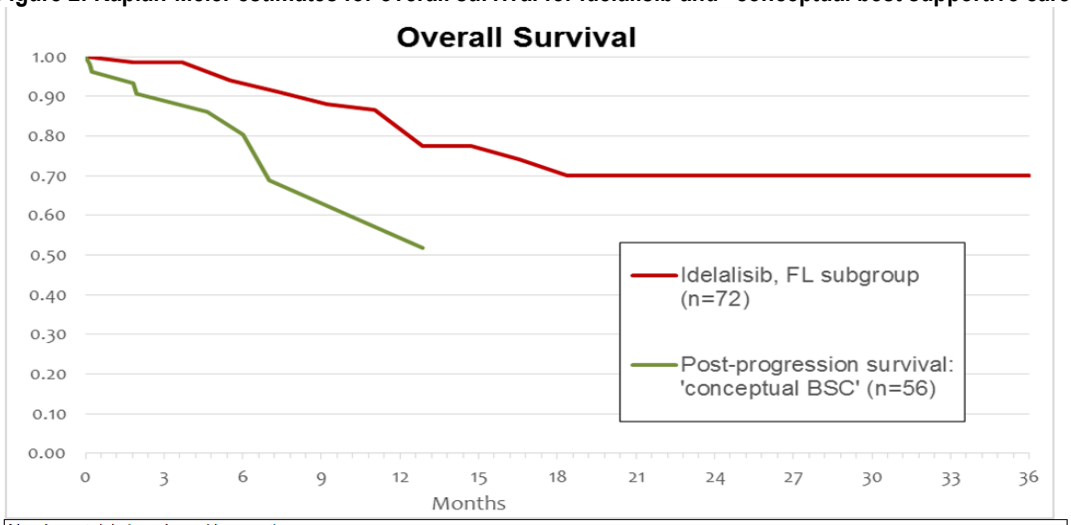
Figure 1: Kaplan-Meier estimates for progression free survival for idelalisib and "conceptual best supportive care"



Source: Figure B-5, p94 of the resubmission

LPT = last line of prior therapy

Figure 2: Kaplan-Meier estimates for overall survival for idelalisib and "conceptual best supportive care"



Number at risk (number with event)													
Ide	72(0)	67 (1)	63(4)	59 (7)	57 (9)	50 (15)	41 (17)	27 (19)	14 (19)	9 (19)	5 (19)	1 (19)	0 (19)
BSC	*56 (0)*	*26 (4)*	*17 (5)*	*6 (7)*	*6 (7)*	-	-	-	-	-	-	-	-

Source: Figure C-3, p 170 of the submission.
BSC = best supportive care; FL = follicular lymphoma; Ide = idelalisib

6.13 At a median follow-up of 19.4 months, the median progression free survival for idelalisib in Study 101-09 was estimated to be 11 months (95% confidence interval (CI): 8 to 14 months). Median progression free survival for "conceptual best supportive care" using the last line of prior therapy analysis was 5.1 months (95% CI: 4.4 to 6.0). The median overall survival had not been reached for idelalisib or for "conceptual best supportive care" using the post-progression survival analysis. The resubmission did not present a hazard ratio to estimate the comparative effectiveness of idelalisib versus "conceptual best supportive care".

6.14 Using the Prospection analysis data set, the median time to death for patients with follicular lymphoma was estimated to be 7.6 months after initiating second-line treatment and 8.0 months after initiating third-line treatment. This analysis did not provide a reliable estimate of overall survival in double-refractory follicular lymphoma (see Clinical claim).

6.15 There were limitations with all the methods used to derive the efficacy of "conceptual best supportive care" (see Clinical claim). These data did not form a good proxy for a comparable population treated with best supportive care. Therefore, the comparative effectiveness of idelalisib versus best supportive care could not be established. The Pre-Sub-Committee Response (PSCR, p1) acknowledged the limitations of these approaches but considered that there are no available alternatives. The ESC considered that the validity of the various control groups used in the analysis remained an important issue.

Comparative harms

6.16 The incidence of Grade 3 or higher adverse events did not change markedly between the June 2013 and June 2014 data-cuts.

6.17 Most patients with follicular lymphoma who were treated with idelalisib reported at least one Grade 3 or higher adverse event (65%). The most frequent of these were neutropenia (19%), diarrhoea (14%), increased alanine aminotransferase (7%), pneumonia (7%), and increased aspartate aminotransferase (7%). Six (8%) patients with follicular lymphoma died due to adverse events. Idelalisib was the probable cause of adverse events leading to death in thirteen patients (10.4%) in Study 101-09 (intention-to-treat population). The PSCR (p2) confirmed that none of the patients who experienced an adverse event leading to death were included in the post progression survival data.

6.18 Idelalisib has an FDA boxed warning stating that treatment can result in fatal and serious toxicities including hepatotoxicity, severe diarrhoea or colitis, pneumonitis and intestinal perforation.

6.19 The Australian Product Information does not have a black box warning but recommended precaution in hepatic infection, anaphylaxis, intestinal perforation, progressive multifocal leukoencephalopathy and use in special patient populations. The ESC noted that differences in US and Australian safety recommendations may reflect registration approval timelines, the availability of additional safety data and the updated risk-benefit relationship at the time of respective registration.

6.20 The resubmission did not provide information on the safety of best supportive care.

Benefits/harms

6.21 A summary of the comparative benefits and harms for idelalisib versus best supportive care (as opposed to "conceptual best supportive care") is presented in the table below.

Table 6: Summary of comparative benefits and harms for idelalisib and best supportive care

Benefits								
	Idelalisib		**BSC**	**Absolute difference**	**HR (95% CI)**			
Study	Study 101-09, FL Longer term follow-up							
N/n	72		*No data*					
Median follow-up, months	19.4		*No data*					
Progression free survival								
Progressed	40 (55.6%)		*No data*	-	-			
Median (months)	11.0 (95% CI: 8.0, 14.0)		*No data*	-				
Overall survival			*No data*	-				
Died	19 (26.4%)		*No data*	-				
Median (months)	NR (95% CI: NR, NR)		*No data*	-	-			
KM estimate of % surviving at 24 weeks	96.5%		*No data*	-	-			
Harms								
	Idelalisib Study 101-09 Longer term follow-up		**BSC**	**RR (95% CI)**	**Event rate/100 patients**			**RD (95% CI)**
					Idelalisib		**BSC**	
	ITT	**FL**			**ITT**	**FL**		
Adverse event, Grade ≥3								
Death due to AE	13/125	6/72	*No data*	-	10%	8%	*No data*	-
Any Grade 3/4	90/125	47/72	*No data*	-	72%	65%	*No data*	-
Neutropenia	27/125	14/72	*No data*	-	22%	19%	*No data*	-
Diarrhoea	19/125	10/72	*No data*	-	15%	14%	*No data*	-
Colitis	5/125	2/72	*No data*		4%	3%	*No data*	

Source: compiled during evaluation; and Table B-28, p87; Table B-31, p94; Table B-32, p98; Table B-42, p112 of the resubmission; and *extracted from Table 3.7.1, pp632-637; Table 3.7.2, pp650-653 of the PAM002 response*

AE = adverse event; BSC = best supportive care; CI = confidence interval; FL = follicular lymphoma; HR = hazard ratio; ITT = intention-to-treat; KM = Kaplan-Meier; NR = not reached; RD = risk difference; RR = relative risk

[a] This was reported as the range in the PAM002 response, but it appears to be a 95% confidence interval

6.22 The resubmission did not present reliable evidence of the efficacy or safety of best supportive care. Therefore a meaningful comparison of the benefits and harms of idelalisib versus best supportive care could not be conducted.

Clinical claim

6.23 The resubmission claimed that idelalisib was superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care. This differed from the claim of superior comparative safety made in the previous submission.

6.24 The claim of superior efficacy was not supported by clinical evidence. The methods used to derive the efficacy of best supportive care were considered to be inappropriate because:

- Time to progression on the last line of prior therapy before starting idelalisib in Study 101-09, which was used to derive progression free survival, compared patients at different stages of disease.
- The use of post-progression survival to derive overall survival was based on data from those patients who progressed earliest on idelalisib and who were thus likely to be sicker (favoured idelalisib).
- The non-responder analysis from Study 101-09, which was used as supportive evidence, was not considered appropriate by the PBAC in its previous consideration.
- The Prospection data analysis did not provide results that could be compared with the other methods to estimate overall survival for best supportive care:
  - Time to death was only based on those patients who had died. Data from surviving patients were not included and therefore comparisons against overall survival data were not meaningful.
  - The PBS claims database included year of death, and assumptions needed to be made to approximate date of death. Therefore time to death might not have been accurately measured.

6.25 The resubmission did not present any comparative evidence to inform the safety of idelalisib compared with best supportive care. In March 2015, the PBAC considered that idelalisib was generally well tolerated but associated with some toxicities including late colitis (Paragraph 7.5, March 2015 Public Summary Document).

Economic analysis

6.26 The resubmission presented a modelled cost-utility analysis, using the data as presented in the comparative effectiveness section, that is:

- Idelalisib:
  - Follicular lymphoma subgroup from Study 101-09;
- Best supportive care:
  - Progression free survival: time to progression on last line of prior therapy; and
  - Overall survival: post-progression survival.

6.27 A comparison between the model presented in the resubmission and the previous submission is presented in Table 7.

Table 7: Summary of model structure and rationale

Component	Previous submission			Resubmission		
Model structure	3 health states 28-day cycles			Unchanged		
Time horizon	10 years			5 years		
Methods used to generate results	Single patient expected value analysis			Unchanged		
Health state costs	Stable disease – BSC = $48 Stable disease – idelalisib = $[redacted] Progressive disease = $201			Stable disease – BSC = $2,427 Stable disease – idelalisib = $[redacted] Progressive disease = $94		
Adverse event costs	BSC: $0 Idelalisib: $[redacted] applied in the first cycle			BSC: $0 Idelalisib: $[redacted] applied in the first cycle		
Idelalisib cost/patient	$[redacted] (72.6% dose intensity)			$[redacted] (92.7% dose intensity)		
Comparator and costs per patient	20% use of anti-cancer drugs in BSC $6,025 (i.e. $30,125 per BSC patient treated with anti-cancer drugs)			30% use of anti-cancer drugs in BSC $9,685 (i.e. $32,283 per BSC patient treated with anti-cancer drugs)		
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.			Unchanged		
Extrapolation	All Weibull				**PFS**	**OS**
				Idelalisib	Weibull	Weibull
				BSC	Weibull	Gompertz
Utilities	Stable disease= 0.805 Progressive disease = 0.618 Disutility for AE = 0.002			Unchanged		
	Idelalisib	**BSC**	**Increment**	**Idelalisib**	**BSC**	**Increment**
Cost	$[redacted]	$8,044	$[redacted]	$[redacted]	$30,135	$[redacted]
QALYs	1.34	0.83	0.51	1.31	0.91	0.40
ICER			**$[redacted]**			**$[redacted]**

Source: compiled during the evaluation

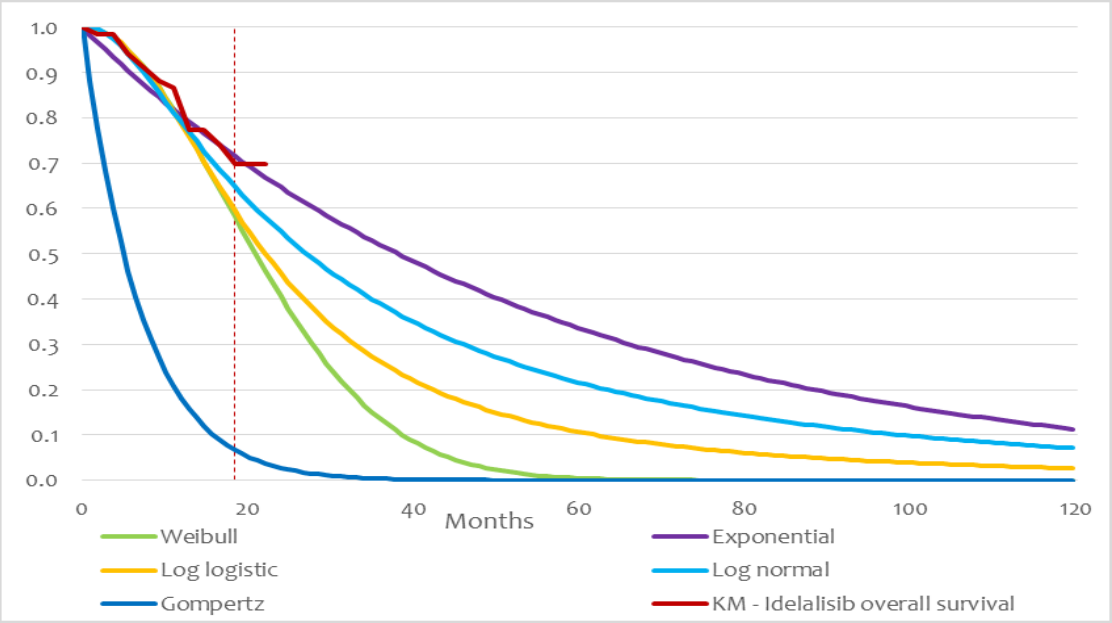
AE = adverse event; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life year

6.28 The resubmission used a three health state model, comprising the following health states: stable disease; progressive disease; and death. The structure was unchanged from the previous submission. The use of a three health state model might be reasonable in this patient population who have a late stage of the disease (double-refractory patients) and given the short time horizon of the model (5 years).

6.29 The ESC considered that the change from a 10 year to 5 year time horizon was more realistic for this condition.

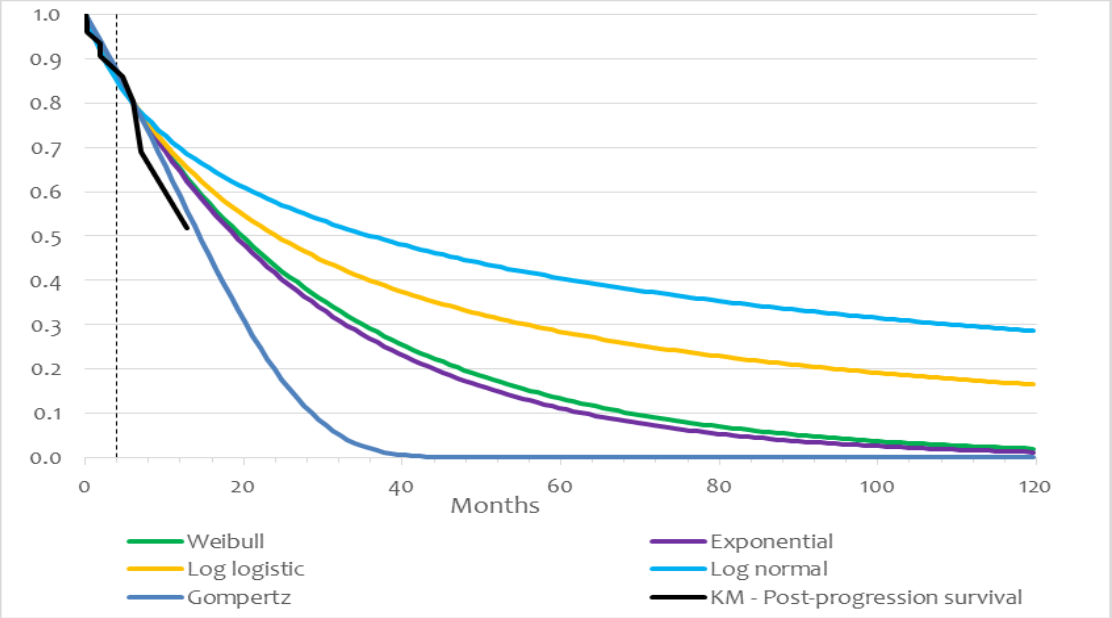
6.30 The ESC noted that the projected overall survival was highly sensitive to the choice of extrapolation method, as demonstrated in Figures 3 and 4 below. The ESC noted that the accuracy of progression free survival predictions may be reliable, however the accuracy of overall survival predictions may have been compromised as the tail was informed by a small proportion of patients. The pre-PBAC response (p1) acknowledged the ESC concerns regarding the lack of confidence in survival estimates, expressing a willingness to negotiate on the proposed treatment cost of idelalisib in this population to account for uncertainty in the estimated survival benefit.

Figure 3: Parametric extrapolations for overall survival with idelalisib from Study 101-09



Source: Figure C-4, p183 of the resubmission
Dotted vertical line represents median duration of follow-up for Study 101-09
KM = Kaplan-Meier

Figure 4: Parametric extrapolations for overall survival for best supportive care



Source: Figure C-4, p183 of the resubmission
Dotted vertical line represents median duration of follow-up for the post-progression survival analysis
KM = Kaplan-Meier

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

Table 8: Key drivers of the model

Description	Method/Value	Impact
Efficacy of BSC	Use of *post hoc* analyses of idelalisib study o Last line of prior therapy for PFS o Post-progression survival for OS	High, values were unreliable
Choice of parametric distribution	Gompertz for BSC OS, Weibull for the other curves	High, favoured idelalisib
Health state resource costs	Differential costs for idelalisib and best supportive care in the stable disease health state	Moderate, favoured idelalisib
Use of anti-cancer treatments in BSC	30%, assumed to continue for every month of PFS	Moderate, favoured idelalisib

Source: *compiled during the evaluation*

BSC = best supportive care; OS = overall survival; PFS = progression free survival

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

Table 9: Results of the modelled economic evaluation

Modelled evaluation	Idelalisib	BSC	Increment
Costs	$ [redacted]	$30,135	$ [redacted]
QALYs	1.31	0.91	0.40
LYs	1.84	1.29	0.55
Incremental cost/extra QALY gained			**$ [redacted]**
Incremental cost/extra LY gained			**$ [redacted]**

Source: Table D-8, p216 of the resubmission

BSC = best supportive care; LYs = life years; QALYs = quality-adjusted life years

6.33 The economic evaluation resulted in an incremental cost-effectiveness ratio (ICER) of $45,000 – $75,000 per quality-adjusted life year (QALY) for idelalisib versus best supportive care. The ICER was $45,000 – $75,000 per QALY in the previous submission. The ESC considered that this is likely to be optimistic and represent the lower bounds of the ICER. The ESC considered a stepped economic evaluation including the ITT population results to the point of follow up prior to extrapolation would be informative.

6.34 The ICER presented was uncertain due to:

- inappropriate methods were used to inform the efficacy of "conceptual best supportive care";
- the choice of extrapolation method for overall survival with best supportive care appeared to be influenced by the tail of the Kaplan-Meier curve, which was informed by a small number of patients. Overall survival projections varied significantly across different parametric functions. The ESC noted that there were only 6 patients in the BSC arm informing the curve, making it difficult to rely on the extrapolated comparator. The ESC considered that OS should be extrapolated from an earlier time point, where patient numbers are greater. Use of the more flexible Royston & Parmar models would overcome this issue, by fitting curves to the KM curve using multiple points of inflexion[1]. The Pre-PBAC response (p2) acknowledged this alternative approach but noted that they were unable to explore this methodology prior to PBAC consideration to ascertain whether the alternative method of extrapolation would materially have an impact on the ICER;
- health resource use costs, which were changed significantly compared with the previous submission. The costs of the stable disease health state increased

[1] Latimer N. Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data: inconsistencies, limitations and a practical guide. Med Decis Making. 2013 Aug;33(6):743-54

substantially, while those for the progressive disease health state decreased. Additionally, differential costs were used for the two treatment arms in the stable disease health state. The cost of the stable disease health state for best supportive care was three times higher than for idelalisib treatment. The costs were not adequately justified. Further, the same costs were used in the resubmission for idelalisib in chronic lymphocytic leukaemia, and some of the costs were based on a survey of patients with chronic lymphocytic leukaemia. The resubmission did not justify the use of the same resource costs for the two different conditions. The ESC considered that the validity of such a cost differential between who groups who are both in the stable disease health state appears implausible, but noted that this did not substantially alter the ICER; and

- overestimation of the cost of best supportive care. The duration of treatment with anti-cancer therapies in best supportive care was overestimated. In the model, patients were assumed to continue on chemotherapy for every month of stable disease. This resulted in an average of 7.5 months of treatment, while in clinical practice treatment would be given for 3 or 4 months, depending on the regimen. Further, the proportion of use of anti-cancer treatments in best supportive care was not adequately justified. The pre-PBAC response (p2) acknowledged that this could overestimate the cost for an average patient and reduced the cost to assume that patients receiving BSC only receive one course of chemotherapy.

6.35 The PSCR provided a revised economic base case to address the cost of chemotherapy and the cost of thrombocytopenia. The impact on the ICER was small, increasing from $[redacted] to $[redacted]/QALY. The ESC noted that the revised base case did not adjust for the cost of chemotherapy.

6.36 The resubmission presented univariate sensitivity analyses and additional analyses were performed during evaluation (see Table 10).

Table 10: Results of selected sensitivity analyses

	Δ costs	Δ QALY	ICER
Base case	**$[redacted]**	**0.397**	**$[redacted]**
Non-responders analysis – Sensitivity analysis for BSC efficacy	$[redacted]	0.340	$[redacted]
Time horizon (base case = 5 years)			
1 year	$[redacted]	*0.112*	$[redacted]
3 year	$[redacted]	*0.355*	$[redacted]
10 years	$[redacted]	0.398	$[redacted]
Extrapolation OS (base case = Weibull distribution for idelalisib, Gompertz for BSC)			
BSC OS – exponential; and idelalisib – log-logistic	$[redacted]	*0.178*	$[redacted]
Idelalisib OS extrapolation – exponential [a]	$[redacted]	*1.037*	$[redacted]
Use of anti-cancer medicines in BSC (base case = 30%)			
0%	$[redacted]	0.397	$[redacted]
20% (previous submission)	$[redacted]	*0.397*	$[redacted]
Time on BSC anti-cancer therapy base case = avg 8 months tx)	$[redacted]	*0.397*	$[redacted]
Limited to one course (3 or 4 months, depending on regimen)			
Other monthly healthcare costs (base case = SD: $2,427 [BSC], $795 [Idel]; PD = $94)	$[redacted]	*0.397*	$[redacted]
As per previous submission (SD: $48 both arms; PD: $201)			
Multivariate analyses			
Multivariate sensitivity analysis	$[redacted]	*0.397*	$[redacted]
Health state resource costs per previous submission; and			

	Δ costs	Δ QALY	ICER
Anti-cancer therapy in BSC limited to one course (3 or 4 months)			

Source: Table D-10, p218 of the resubmission; *and extracted from Section D workbook. Figures in italics were calculated during evaluation*

avg = average; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; Idel = idelalisib; OS = overall survival; PD = progressive disease; PFS = progression free survival; QALY = quality-adjusted life year; SD = stable disease; tx = treatment

[a] The resulting survival projection was that 34% of idelalisib patients would be alive at 5 years

6.37 The sensitivity analyses indicated that the ICER was sensitive to the choice of best supportive care efficacy, extrapolation method for overall survival with best supportive care, health care resource costs and use of anti-cancer medicines in best supportive care. The multivariate sensitivity analysis indicated that when the health state resource costs from the previous submission were used and anti-cancer therapy in best supportive care was limited to one course, the ICER would be $105,000/QALY – $200,000/QALY. The PSCR (p3) argued that the sensitivity analysis of the extrapolation method was not informative as it did not take into account the distribution fit and clinical paucity. The ESC considered that the overall survival projections were highly sensitive to the choice of extrapolation method.

Drug cost/patient/course*: $[redacted]*

6.38 This was based on a mean duration of treatment of 11.4 months (mean progression free survival duration estimated in the economic model), 92.7% dose intensity, and cost of $[redacted] per pack (60 tablets).

Estimated PBS usage & financial implications

6.39 This resubmission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the prevalent follicular lymphoma population. The financial estimate method was not altered from the previous submission.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated – March 2015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate – March 2015	35%	55%	65%	70%	80%
Uptake rate	35%	55%	65%	70%	80%
Scripts – March 2015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS – March 2015	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS – March 2015	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to hospitals – March 2015	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to hospitals	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS/MBS – March 2015	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Net cost to PBS/RPBS/MBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Source: Table 8, p11 of the previous commentary; and Section E Excel workbook
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
[a] Assuming 11.3 prescriptions per year as estimated by the resubmission

6.40 The net cost to government of idelalisib was estimated to be $10 – $20 million over the first five years of listing, compared with $20 – $30 million in the previous submission. This reduction was mainly due to limiting the treatment to patients with follicular lymphoma.

6.41 A number of issues raised in the February 2015 DUSC advice were not addressed, such as:

- The proportion of indolent non-Hodgkin's lymphoma that is treated was based on the opinion of three haematologists in the UK and was unlikely to be applicable to the Australian population. DUSC considered that this was highly uncertain and could be underestimated.
- The assumed uptake rate was not justified and could be underestimated.
- The prevalence of non-Hodgkin's lymphoma is rising due to the increasing incidence and decreasing mortality.
- The assumption that all patients prescribed idelalisib would cease receiving ineffective anti-cancer treatments might have been unreasonable.

Therefore, DUSC's previous concerns that the utilisation was underestimated remained. The overall cost to government might be higher than estimated.

6.42 The PSCR (p5) provided revised financial estimates to correct dose-intensity, patient co-payments and category distribution, and the public/private hospital split. The net cost to the PBS/RPBS/MBS over five years is $10 – $20 million using the PSCRs revised base case. The PSCR also provided a sensitivity analysis of the financial estimates, which was based on a 20% increase in the number of patients with treated refractory disease. This increased the net cost to the PBS/RPBS/MBS over five years to over $20 – $30 million.

Quality Use of Medicines

6.43 The resubmission requested the PBAC consider whether the 'rule of rescue' would apply. This was not requested in the previous submission. The resubmission stated that there is a high unmet clinical need, the condition is progressive and life-limiting, and the anticipated number of patients and cost is small. Table 12 assesses idelalisib against the four factors that must apply for the rule of rescue to be relevant.

Table 12: Rule of rescue

Rule of rescue factor	Comments
No alternatives exist	While the resubmission stated in Section F that no alternative treatments are available, for the remainder of the resubmission it assumed alternatives were available. Cost offsets were included in the economic evaluation and financial estimates. The PBAC previously considered that there is a high and unmet clinical need for an effective treatment option in this patient group (Para 7.2, March 2015 PBAC Minutes).
Condition is severe, progressive and expected to lead to premature death	The resubmission did not provide sufficient information on the natural history of the condition in current Australian practice.
Very small number of eligible patients	There was limited epidemiological evidence to reliably determine the prevalence of double-refractory follicular lymphoma. There would be potential for idelalisib to be used by more than a very small number of patients.
Drug provides a worthwhile clinical improvement sufficient to qualify as a rescue from the condition	The resubmission did not adequately justify the extent of clinical improvement, compared with best supportive care.

Source: Section F.1, pp247-251 of the resubmission; and Section F.3, p258 of the PBAC Guidelines version 4.4
Para = paragraph; PBAC = Pharmaceutical Benefits Advisory Committee

6.44 The submission did not adequately establish that rule of rescue would apply.

Financial Management – Risk Sharing Arrangements

6.45 The resubmission proposed an effective price of $[redacted], and published price of $[redacted]. The resubmission did not propose any risk-sharing arrangements.

7 PBAC Outcome

7.1 The PBAC deferred its decision for the Authority Required listing of idelalisib for the treatment of follicular lymphoma as idelalisib was not considered to be cost-effective at the price proposed. The PBAC therefore considered that the submission should be deferred to enable the Department to negotiate a reduced price, adopting a pragmatic approach that would reduce the base-case ICER as presented in the multivariate sensitivity analysis to a more appropriate range.

7.2 The PBAC accepted the restriction as proposed by the Secretariat, but considered that a telephone authority would be more appropriate than a streamlined authority. The PBAC considered that leakage into Waldenstrom's Macroglobulinemia was likely.

7.3 The PBAC reiterated that there is a high unmet clinical need for an effective treatment for patients with double-refractory follicular lymphoma. The PBAC also noted with caution the significant toxicities that can be experienced by patients using this drug, and considered that the incidence of these in Australian practice should be closely monitored.

7.4 The PBAC noted the limitations in the data provided meant that comparative efficacy and safety of idelalisib could not be estimated, but accepted that no further data is likely to become available to inform this consideration.

7.5 The PBAC considered that idelalisib is clinically effective as a last-line treatment for follicular lymphoma, however considered that the magnitude of any incremental benefit is not robustly supported and highly uncertain.

7.6 The PBAC noted that harms, particularly relating to severe diarrhoea and colitis, are likely to be significant for many patients.

7.7 The PBAC agreed with the ESC that a five-year time horizon in the economic model was appropriate and more realistic for this condition

7.8 The PBAC considered that the multivariate sensitivity analysis performed during the evaluation that resulted in an ICER of $105,000/QALY – $200,000/QALY, whilst requiring acceptance of an uncertain extrapolation of overall survival, provided the most realistic estimate of cost effectiveness and should be used as the base-case. The Committee considered that this ICER was unacceptably high, and that a significant price reduction would be required in order to reduce the ICER to less than $45,000 – $75,000/QALY.

7.9 The PBAC considered that the total patient population is uncertain and as such, a risk sharing arrangement with a cap based on the patient numbers as presented in the resubmission should be adopted once financial estimates are updated in line with the Committee's requested changes. The PBAC considered that due to the uncertainty in patient numbers, utilisation should be reviewed following listing.

7.10 The PBAC considered that idelalisib did not meet the criteria for the rule of rescue as the extent of clinical improvement over best supportive care is not adequately justified.

Outcome:
Deferred

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

The sponsor had no comment.