5.10 IDELALISIB
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 listing for idelalisib for the second-line treatment of chronic lymphocytic leukaemia (CLL).

2 Requested listing

2.1 The submission's requested restriction was for patients with CLL who have progressive disease despite previous treatment. This is outlined in the table below.

Name, form, and strength	Max. qty. packs	Max. qty. units	No. of rpts.	Proprietary name, manufacturer
IDELALISIB Oral tablet 150mg	1	60	5	Zydelig® Gilead Sciences Pty Ltd
IDELALISIB Oral tablet 100mg	1	60	5	Zydelig® Gilead Sciences Pty Ltd

Severity:	Relapsed disease
Condition:	Chronic Lymphocytic Leukaemia
Treatment phase:	Initial and continuing treatment
Restriction:	Section 85 Authority required (STREAMLINED)
Treatment criteria:	The patient must have progressive disease despite previous treatment for CLL
Clinical criteria:	Administer idelalisib in combination with rituximab. Discontinue PBS subsidised treatment with idelalisib in patients who experience disease progression whilst on treatment.

CLL = chronic lymphocytic leukaemia; PBS = Pharmaceutical Benefits Scheme

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

- it was inconsistent with the clinical evidence provided. Trial 312-0116 included patients who were less able to receive cytotoxic chemotherapy (refer to paragraph 2.5).
- it 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 a similar indication to that recommended by the ACPM. The TGA approved indication is:

  In combination with rituximab, for the treatment of patients with chronic lymphocytic leukaemia (CLL)/<u>small lymphocytic lymphoma (SLL) for whom chemo-immunotherapy is not considered suitable</u>, either:
  - <u>upon relapse after</u> at least one prior therapy; or
  - as first-line treatment in the presence of 17p deletion or TP53 mutation.

(Underlining indicates the proposed changes compared with the TGA indication originally requested by the sponsor.)

2.3 To address these issues, a revised restriction was proposed in the Pre-Sub-Committee Response (PSCR):
''Patients with CLL for whom chemo-immunotherapy is not considered suitable, upon relapse after at least one prior therapy'.

2.4 The PSCR and pre-PBAC response stated that the sponsor is "willing to work with the PBAC to finalise the PBS restriction for idelalisib".

2.5 The PBAC noted that the inclusion criteria for Trial 312-0116 included:
- Patients with CLL that warranted treatment.
- Patients who were less able to receive cytotoxic chemotherapy therapy based on the presence of:
    - ≥ grade 3 neutropenia or thrombocytopenia attributable to cumulative myelotoxicity from prior administration of cytotoxic agents (as documented by bone marrow biopsy obtained since last prior therapy);
    - Estimated creatinine clearance < 60 mL/min; or
    - Cumulative Illness Rating Scale (CIRS) score > 6.
- Patients who experienced CLL progression within 24 months of their last prior therapy.
- Previous treatment must have included either a CD20 antibody based regimen or at least two previous cytotoxic regimens.
- The trial excluded those who did not benefit from or, had experienced rapid progression following, prior anti-CD20 therapy.

2.6 The PBAC noted the criteria used in the key trial to define patients who are "less able" to receive cytotoxic chemotherapy. However, the PBAC noted that a CIRS score of > 6, low neutrophils, or low platelets alone would not necessarily preclude chemo-immunotherapy, and that creatinine clearance would not specifically identify patients who are unsuitable for chemo-immunotherapy. Therefore, the PBAC considered that narrower criteria would be required to restrict use to those patients who are truly unsuitable for chemo-immunotherapy.

2.7 The PSCR's revised restriction and the trial inclusion criteria are different to the TGA approved indication because the TGA indication includes:
- first-line treatment in the presence of 17p deletion or TP53 mutation, while patients in the trial had received previous treatment for CLL.
- patients with SLL, while patients with SLL were not enrolled in the trial.

2.8 The PBAC considered that the restriction should limit use in patients with 17p deletions to those who are relapsed or refractory. The PBAC noted that TP53 mutation testing is not yet routine or readily available in clinical practice. Further, the PBAC considered that it was appropriate for the restriction to enable use in SLL, due to the biological similarity between CLL and SLL.

2.9 The submission presented a cost-utility analysis of idelalisib plus rituximab compared with placebo plus rituximab.

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

3 Background

3.1 TGA status: The submission was made under TGA/PBAC Parallel Process. The TGA's Clinical Evaluation Report, Delegates Overview and ACPM recommendation were available during evaluation and at the time of ESC consideration. As outlined above, the ACPM recommended a narrower indication than that originally proposed by the sponsor. Idelalisib was TGA registered on 9 February 2015.

3.2 The TGA indication states that idelalisib is for use in combination with rituximab in CLL. The pivotal trial used eight doses of rituximab. However the PBS subsidises up to six doses in this setting. It was unclear to the evaluator how patients would obtain subsidised access to the two additional doses of rituximab.

3.3 This medicine has not been considered by the PBAC previously. At the March 2015 PBAC meeting, idelalisib was also considered for the treatment of patients with refractory indolent non-Hodgkin lymphoma.

4 Clinical place for the proposed therapy

4.1 Idelalisib was evaluated as a second-line treatment for patients with relapsed CLL, which is a haematological B-cell malignancy.

4.2 The evidence provided in the submission and the approved TGA indication suggest that the place in therapy for idelalisib will be in patients deemed unfit for further treatment with cytotoxic agents. The ESC noted that the revised restriction proposed in the PSCR would help limit use to this patient population.

4.3 The ESC considered that the treatment algorithm for CLL is evolving, noting two recent changes. In November 2014, the PBAC recommended ofatumumab + chlorambucil for the first-line treatment of CLL in patients who are inappropriate for fludarabine based therapy. On 1 December 2014, rituximab was listed for use in CLL in combination with chemotherapy. PBS-subsidised rituximab had previously been restricted to use in combination with fludarabine plus cyclophosphamide.

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

5 Comparator

5.1 The submission proposed rituximab monotherapy as the comparator. The evaluator considered that this was not the appropriate comparator because rituximab monotherapy is not routinely used as a second-line treatment for CLL. The submission's proposed listing was not limited to patients who are unsuitable for chemotherapy and as such, the evaluation considered that an appropriate comparator could have been rituximab in combination with chemotherapy. The PBAC agreed that chemo-immunotherapy was the appropriate comparator for the broader population originally requested in the submission.

5.2 The ESC considered that rituximab monotherapy was not the appropriate comparator because rituximab monotherapy is neither PBS-listed nor TGA-approved for use in

CLL. Further, expert opinion was that rituximab is not routinely used as monotherapy in CLL in Australian clinical practice.

5.3 While the PSCR revised the restriction to limit idelalisib use to patients in whom chemo-immunotherapy is not considered suitable, the ESC considered that this would be interpreted in clinical practice as patients less able to tolerate chemo-immunotherapy. Expert opinion was that low doses of chemotherapy are often added to rituximab in patients less able to tolerate chemotherapy. Should use of idelalisib be restricted to patients truly unable to tolerate further chemotherapy, rituximab monotherapy and/or best supportive care may become more important comparators.

5.4 The IPSOS Oncology Monitor dataset (quarter 4 2012 - quarter 3 2013) found that fludarabine + cyclophosphamide + rituximab (FCR, which would include FCR-lite) was the most commonly used regimen in second and later lines of therapy (used in 30% of patients), while rituximab monotherapy (± prednisone) was the second most commonly used regimen (used in 27% of patients). A range of other treatments also appeared to be used in this setting, including chlorambucil ± prednisone (11%) and cyclophosphamide ± prednisone (10%). However, the submission provided limited information regarding the survey methodology and thus the ESC considered that the reliability of this source was unclear. While additional information was included in the pre-PBAC response, detailed information on the survey methodology and data collection were not provided. The ESC noted that the IPSOS data may not reflect current Australian practice given the rapidly evolving nature of the CLL treatment algorithm.

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 and welcomed the input from individuals (5) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with idelalisib including that it prolongs remission, improves quality of life and provides another treatment option while patients await the development of a potential cure.

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 or CLL.

- 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 progression-free survival (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 a 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 head-to-head trial comparing idelalisib plus rituximab to placebo plus rituximab (n = 220).

6.5 Details of the trial presented in the submission are provided in the table below.

The direct randomised trial presented in the submission

Trial ID	Protocol title/Publication title	Publication citation
Direct randomised trial		
312-0116	A phase III, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with rituximab for previously treated chronic lymphocytic leukemia.	23 November 2013; Second interim clinical study report; Study No: GS-US-312-0116
Furman	Idelalisib and rituximab in relapsed chronic lymphocytic leukemia.	N Eng J Med; 2014;370(11):997-1007.

Source: Table B.3, p44 of the submission

6.6 The key features of the direct randomised trial are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ Duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Idelalisib plus rituximab vs. placebo plus rituximab						
312-0116	220	R, DB, MC, PC Approx. 6 months	Low	Relapsed Less able for chemotherapy	PFS, OS	Yes

Source: compiled during the evaluation

DB = double blind; MC = multi-centre; OS = overall survival; PC = placebo controlled; PFS = progression-free survival; R = randomised

6.7 The trial was stopped after a median duration of follow-up of 6.1 months for the idelalisib plus rituximab arm and 4.4 months for the placebo plus rituximab arm due to meeting predefined efficacy criteria.

6.8 Patients with disease progression were eligible to enrol in the follow-up 312-0117 study, which was a double-blind continuation study, where patients in the idelalisib plus rituximab group received a higher idelalisib dose and patients in the placebo plus rituximab group received the standard idelalisib dose. However, the clinical trial report of 312-0117 was not provided in the submission.

6.9 Whilst cross-over was permitted in the follow-up 312-0117 study (46.4% of patients in the rituximab monotherapy comparator arm of 312-0116 progressed, and 80% of these patients crossed-over to receive the standard idelalisib dose in combination with rituximab), the truncated trial duration meant there was very little cumulative follow-up in subjects who crossed-over. No analysis with statistical adjustment for cross-over was provided.

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

Comparative effectiveness

6.10 Results of the primary outcome, progression-free survival, are presented in the table below.

6.11 The submission used data from the second interim analysis of Trial 312-0116 (6.1 months median duration of follow-up in the idelalisib plus rituximab arm). The final analysis included an additional two months of follow-up data. Extracts of data from the final analysis were provided in the PSCR and Pre-PBAC response. However, the Clinical Study Report was not provided and therefore this data could not be evaluated and verified.

Table 3: Results of progression-free survival from Trial 312-0116 (second interim analysis)

Trial ID	Idelalisib + rituximab (n = 110)	Placebo + rituximab (n = 110)
Median duration of follow-up (months)	6.1	4.4
Patients with events; n/N (%)	16 (14.5%)	59 (53.6%)
Patients censored; n/N (%) Ongoing Discontinued without event	94 (85.5%) 82 (74.5%) 12 (10.9%)	51 (46.6%) 46 (41.8%) 5 (4.5%)
KM estimates (months); median (95% CI)	NR (10.7, NR)	5.5 (3.8, 7.1)
Adjusted HR (95% CI)	**0.18 (0.10, 0.32)**	

Source: Table B.17, p65 of the submission: Table B.6.1 of the evaluation report
CI = confidence interval; HR = hazard ratio; KM = Kaplan Meier; NR = not reached. **Bold** = significant result

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

Comparative harms

6.12 The incidence of treatment emergent adverse events occurring in at least 10% of participants was similar across both treatment arms of Trial 312-0116. Idelalisib plus rituximab resulted in significantly increased rates of pyrexia.

Idelalisib has a FDA boxed warning based on longer term analyses stating that treatment can result in fatal and serious toxicities including hepatotoxicity, severe diarrhoea or colitis, pneumonitis and intestinal perforation. The ACPM recommended that pharmacovigilance was required for anaphylaxis, intestinal perforation and progressive multifocal leukoencephalopathy.

6.13 A comparison of the incidence of adverse events (≥ Grade 3) at the second interim and final analyses is presented in the table below. The additional two months of follow-up data indicated that longer term use of idelalisib resulted in an increase in some adverse events such as diarrhoea and colitis (noting these data could not be verified).

Adverse events (≥ Grade 3) in Trial 312-0116: a comparison between the 2nd interim and the final analyses

	Idelalisib + rituximab		Placebo + rituximab	
	2nd interim analysis	Final analysis	2nd interim analysis	Final analysis
Neutropenia	21.8%	22.7%	12.0%	16.7%
Febrile neutropenia	4.5%	4.5%	3.7%	4.6%
Anaemia	4.5%	7.3%	6.5%	6.5%
Thrombocytopenia	2.7%	3.6%	4.6%	3.7%
Pneumonia	10.9%	13.6%	10.2%	10.2%
Sepsis	3.6%	5.5%	2.8%	2.8%
Diarrhoea	3.6%	9.1%	0	0
Colitis	2.7%	4.5%	0	0

Source: Table 4 of the Pre-Sub-Committee Response

[a]*The source documentation was not provided with the PSCR and therefore the information could not be verified.*

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

Benefits/harms

6.14 A summary of the comparative benefits and harms for idelalisib plus rituximab versus placebo plus rituximab is presented in the table below (based on the second interim analysis results).

Summary of comparative benefits and harms for idelalisib plus rituximab and placebo plus rituximab from Trial 312-0116 (based on the second interim analysis results)

BENEFITS					
	Idelalisib + rituximab		**Placebo + rituximab**	**Absolute Difference**	**HR (95% CI)**
Progression free survival *					
Progressed disease; n/N (%)	16/110 (14.5%)		59/110 (53.6%)	-	**0.18 (0.10, 0.32)**
Median (months)	NR (10.7, NR)		5.5 (3.8, 7.1)	NC	-
Overall survival *					
Died; n/N (%)	6/110 (5.5%)		20/110 (18.2%)	-	**0.28 (0.11, 0.69)**
HARMS					
Treatment emergent harms	**Idelalisib + rituximab**	**Placebo + rituximab**	**RR (95% CI)**	**Event rate/100 patients ***	**RD (95% CI)**
				Idelalisib + rituximab / **Placebo + rituximab**	
Neutropenia	30/110	18/108	1.64 (0.97, 2.75)	27.3 / 16.7	0.11 (-0.00, 0.22)
Diarrhoea	21/110	16/108	1.29 (0.71, 2.33)	19.1 / 14.8	0.04 (-0.06, 0.14)
Pyrexia	38/110	18/108	**2.07 (1.26, 2.40)**	34.5 / 16.7	**0.18 (0.07, 0.29)**

* Median duration of follow-up: idelalisib plus rituximab = 6.1 months; placebo plus rituximab = 4.4 months

Source: Tables B.16, p64 and B.23, p75 of the submission.

CI = confidence interval; HR = hazard ratio; NC = not calculated; NR = not reported; RD = risk difference; RR = relative risk; **Bold** = significant result

6.15 On the basis of direct comparison evidence presented by the submission, over a median duration of follow-up of 6.1 months, for every 100 patients treated with idelalisib plus rituximab in comparison to placebo plus rituximab:

- Approximately 39 fewer patients would have progressed disease.
- Approximately 13 fewer patients would have died.
- Approximately 18 additional patients would have fever (pyrexia).

6.16 For every 100 patients treated with idelalisib plus rituximab, over a median duration of follow-up of 8.3 months, approximately 9 will experience significant diarrhoea and 4 or 5 will develop colitis, two side effects that were not seen in patients treated with rituximab alone

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

Clinical claim

6.17 The submission described idelalisib plus rituximab as having superior comparative effectiveness and non-inferior comparative safety over rituximab monotherapy.

6.18 The evaluator considered that the claim of superior comparative effectiveness was adequately supported by data from Trial 312-0116.

- Idelalisib plus rituximab showed superior progression-free survival and overall survival benefits compared with placebo plus rituximab.

However the evaluator considered that:

- The claim of superiority was only valid in patients who were less able to tolerate additional chemotherapy; and
- The claim of superiority is only valid if rituximab monotherapy (and the rituximab dosing regimen used in Trial 312-0116) is considered to be an appropriate comparator.

6.19 The ESC considered that the claim of superior comparative effectiveness may not have been adequately supported because:

- The results presented are compared with rituximab monotherapy. For the population requested in the submission (i.e. patients who may have been suitable for chemo-immunotherapy), the relative efficacy of idelalisib plus rituximab was likely to have been overestimated compared with rituximab plus low-dose chemotherapy; and
- The duration of follow-up of Trial 312-0116 was short (approximately six months, with an additional two months provided in the PSCR) and overall survival results were premature (5.5% and 18.2 % of patients had died in the idelalisib plus rituximab, and the rituximab plus placebo arm, respectively).

6.20 The evaluator considered that the claim of non-inferior comparative safety may not have been reasonable because:

- The short duration of follow-up meant the identification of long term adverse events with idelalisib was not possible;
- The dosing regimen of rituximab in the trial differed to the approved Australian dosing regimen, making safety comparisons with the wider CLL rituximab population difficult; and
- Longer term idelalisib treatment has resulted in fatal and/or serious hepatotoxicity, severe diarrhoea or colitis, pneumonitis and intestinal perforation.

6.21 The ESC agreed that the claim of non-inferior comparative safety was not adequately supported and further considered that:

- the results presented are compared with rituximab monotherapy. For the population requested in the submission (i.e. patients who may have been suitable for chemo-immunotherapy), the comparative harm of idelalisib plus rituximab was

likely to have been overestimated compared with rituximab plus low dose chemotherapy;

- the short duration of the pivotal trial made it difficult to identify potential long term safety effects. The PSCR stated that 'severe diarrhoea is typically a late-onset event, and may not have occurred by the time of the second interim analysis of study 312-0116' (that is, the data-set provided in the submission). The additional two months of follow-up data provided in the PSCR indicated that longer term use of idelalisib resulted in an increase in some adverse events, as shown in paragraph 6.13. The ESC concluded that the longer term safety outcomes were not known.

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

Translation issues

6.22 The submission claimed that because the trial patients were sicker, less fit and more heavily pre-treated than the proposed PBS population, they represented the most pessimistic outcomes and that PBS-funded patients would experience better outcomes. However, the ESC considered that the impact of this difference on the incremental effectiveness of idelalisib is unknown and not necessarily biased against idelalisib as argued in the submission. Further, the submission's claim that PBS-funded patients would experience better outcomes was based on a comparison between patient characteristics in the trial and the intended Australian population; however the data used to characterise Australian CLL demographics were for all "drug-treated" CLL patients, not for those patients who were unable to tolerate chemotherapy. The ESC concluded that it was difficult to determine the applicability of the trial results to the intended Australian population.

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

Economic analysis

6.23 The submission presented a trial-based cost utility analysis, based on the results of Trial 312-0116. The model structure is summarised in the table below.

Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case versus 6.1 months (idelalisib plus rituximab) and 4.4 months (placebo plus rituximab) in the trial
Outcomes	LYG and QALYs
Methods used to generate results	Trial based + extrapolation; Markov model; cohort or expected value analysis; deterministic sensitivity analyses
Health states	Alive with stable disease; alive with progressed disease; dead
Cycle length	7 days
Utilities	From the literature stable disease: 0.71 progressed disease: 0.59[a]
Transition probabilities	Markov trace

Source: compiled during the evaluation. [a] *EQ 5D 3L collected in the trial but utilities not reported and data post-progression not collected therefore deemed to be unusable in the model*
LYG = life years gained; QALY = quality adjusted life year

6.24 The time horizon and the model structure were the key drivers of the model, and appeared to favour idelalisib (see table below).

Key drivers of the economic model

Description	Method/Value	Impact
Time horizon	10 years; assumed from ~ 6 month trial duration	High; favoured idelalisib
Model structure	Literature based; three health states	High; favoured idelalisib
Resource use and costs	MBS and AR-DRG costs; use based on literature	Low; favoured comparator

Source: compiled during the evaluation
AR-DRG = Australian refined diagnosis-related groups; MBS = Medicare Benefits Schedule

6.25 The results of the economic evaluation are presented in the table below.

Results of the economic evaluation (discounted at 5%)

	Idelalisib + rituximab	Placebo + rituximab	Increment
Costs	$ [redacted]	$42,383	$ [redacted]
QALYs	3.76	1.96	1.80
Incremental cost/extra QALY gained			**$** [redacted]

Source: Table D.8, p153 of the submission
QALY = quality adjusted life year

6.26 The economic evaluation resulted in an ICER of $45,000/QALY – $75,000/QALY for idelalisib plus rituximab versus placebo plus rituximab. The evaluation and the ESC considered that the ICER was unreliable due to:

- Questions surrounding the accuracy and appropriateness of the parametric modelling used to estimate progression-free survival and overall survival given the short duration of follow-up in Trial 312-0116. In the case of the overall survival estimate, sparse event data were available from the trial (approximately six months) and were extrapolated over a comparatively long time period (10 years). This resulted in unrealistic overall survival estimates for idelalisib plus rituximab, i.e. 52.0% of the idelalisib plus rituximab patients were alive after 10 years, compared with 9.0% of the placebo plus rituximab patients.

- The inappropriate model inputs and structure which did not incorporate post-progression treatment benefits, age adjusted all-cause mortality or long term adverse events.
  - The ESC considered that all-cause mortality was important given the age of the likely cohort, and that the inclusion of all-cause mortality would be likely to reduce the overall size of benefit.
  - The rates of adverse events were based on the relatively short duration of Trial 312-0116 and were unlikely to reflect the true rates of adverse events for idelalisib over the model period (10 years). The ESC considered that this is likely to have under-estimated the cost of idelalisib, but acknowledged that longer term adverse events are unknown.

Overall, the ESC considered that the estimated proportion of people alive at the end of 10 years appeared to be implausibly high (double the estimated current observed survival for the Australian CLL population). The ESC further noted that sensitivity analyses demonstrated that the model was most sensitive to changes in time horizon, extrapolation curve choice and model structure. Therefore, the ESC

concluded that the model did not provide a realistic estimate of the true incremental cost-effectiveness of idelalisib in this treatment setting.

6.27 The ESC considered that resource use and costs of treating serious adverse events may have been underestimated. The PSCR provided additional sensitivity analyses using rates of adverse events from the final analysis of Trial 312-0116. The ESC noted that the updated adverse event rates made little difference to the ICER, and considered this would also be the case for revised estimates of the cost of treating adverse events.

6.28 The submission presented univariate sensitivity analyses that indicated that the model was most sensitive to the time horizon and changes in the survival parameters (see table below).

Results of sensitivity analyses (discounted at 5%)

	Δ costs	Δ QALY	ICER
Base case	**$**	**1.80**	**$**
Time horizon (base case = 10 years)			
1 year	$	0.28	$
3 years	$	0.67	$
5 years	$	1.07	$
7 years	$	1.46	$
Joint PFS and OS models (base case = independent)	$	1.70	$
HR PFS and OS models (base case = parametric)	$	1.76	$
HR - lower 95% CI	$	2.67	$
HR - upper 95% CI	$	0.55	$

Source: Table D.10, p155 of the submission; Section D Excel workbook; and calculated during evaluation.
[a]Note this uses the updated costs of rituximab.
CI = confidence interval; ICER = incremental cost-effectiveness ratio; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; QALY = quality adjusted life year;

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

Drug cost per patient per course: $

6.29 The drug cost per patient per course was based on a median duration of treatment of 17 months, a monthly cost of $, and a dose intensity of 95.2%. This was compared to $ for rituximab monotherapy, using the 1 December 2014 listed price.

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

Estimated PBS usage & financial implications

6.30 This submission was not considered by the Drug Utilisation Sub-Committee. The submission combined epidemiological and market share approaches to assess the utilisation and costs of idelalisib over a five year period (see table below).

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to hospitals	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated total net cost					
Total net cost	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

[a] Assuming [redacted] prescriptions per year as estimated by the submission.
Source: Section E Excel workbook

6.31 The net cost to Government of idelalisib was estimated to be $30 - $60 million per year over the first five years of listing. At year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be $10 - $20 million.

6.32 The evaluation considered that there was potential for the submission's estimate of the overall costs to Government to be over or under estimated because:

- The number of eligible patients was likely to be inaccurate due to:
  - The percentage of actively treated CLL patients was based on US market data which, though in line with UK data, was lower than values for five European countries and might not have reflected the Australian situation (potential under estimate),
  - The assumption that idelalisib would only replace second-line treatments for patients currently on non-cytotoxic treatments (under estimate);
- The proposed PBS restriction did not limit treatment to patients who could not tolerate further cytotoxic treatments. The assumption that the 35% of patients who received non-cytotoxic second-line treatment represented the eligible population may have under estimated the eligible PBS population. The ESC acknowledged that the PSCR's revised PBS restriction may help address this issue;
- The inappropriate estimates used to calculate initiating and continuing patients suggested a much longer treatment duration per patient than what was predicted in the economic evaluation;
- Changes in the CLL market as a result of the amended rituximab PBS listing (1 December 2014) and the PBAC recommendation for listing ofatumumab in the first-line setting (unclear); and
- The submission only considered cost off-sets for rituximab monotherapy and this would not be appropriate if idelalisib replaces other therapies (under estimation).

6.33 The evaluation and ESC considered that the submission had inappropriately assumed that in year 5 of listing approximately one in ten patients would be new (initiating) patients, while the remainder would be continuing patients. The evaluation considered that this did not reflect the treatment duration of idelalisib which is until disease progression and was estimated to be 17 months. The evaluation considered that this assumption would result in an overestimation of the number of scripts per patient.

6.34 The submission's financial estimates were based on idelalisib plus rituximab replacing rituximab monotherapy, and the submission included financial offsets from reduced use of rituximab monotherapy, including drug costs and administration costs. However, such use of rituximab is not in line with its PBS restriction.

6.35 Sensitivity analyses suggest that the cost was impacted by the proportion of patients eligible for idelalisib (as per table below).

Sensitivity analyses of the total net cost to Government

	Year 1	Year 2	Year 3	Year 4	Year 5
Base case	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
Actively treated CLL (base case = 23%)					
30%	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
15%	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
% 2nd-line patients eligible for idelalisib (base case = 35%)					
55%	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
75%	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
100%	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]

Source: Table E.12, p177 of the submission; and calculated during evaluation
CLL = chronic lymphocytic leukaemia

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

6.36 The redacted table above shows that increasing the proportion of patients eligible for idelalisib would increase the net cost to Government to less than $10 million in year 1 to $10 - $20 million per year 5.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of idelalisib for the treatment of patients with chronic lymphocytic leukaemia (CLL) because the patient population was not adequately defined, the nominated comparator was inappropriate and the economic evaluation required amendment. 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 idelalisib is an active drug that provides an additional avenue of therapy for patients with relapsed CLL for whom chemo-immunotherapy is not suitable.

7.2 The PBAC agreed that there is a high unmet clinical need for an effective treatment for this patient population. The PBAC welcomed the input received from individuals and at the consumer hearing. The comments highlighted that idelalisib prolongs remission and improves quality of life.

7.3 The PBAC agreed with the PSCR's proposal to restrict use to patients who are unsuitable for chemo-immunotherapy. The PBAC recommended the restriction be further refined to target those patients with the highest clinical need and for whom there is adequate evidence from the trial.

7.4 Therefore, per paragraphs 2.6 and 2.8, the PBAC considered that a revised

restriction should be based on:

- Treatment of CLL or SLL that is relapsed or refractory after at least one therapy in patients with a CIRS score of > 6 AND in whom chemo-immunotherapy is contraindicated because of one or more of the following:
  - (i) severe neutropenia; OR
  - (ii) severe thrombocytopenia; OR
  - (iii) presence of 17p deletion.
- Administrative note: severe neutropenia is defined as absolute neutrophil count < 1.0 x 10^9/L, severe thrombocytopenia is defined as platelet count < 50 x 10^9/L; presence of 17p deletion must be detected by FISH or cytogenetics.

7.5 The PBAC considered that rituximab monotherapy was not the appropriate comparator for the specific subgroup of patients who are unsuitable for chemo-immunotherapy because rituximab monotherapy is neither PBS-listed nor TGA approved for use in CLL. Further, the PBAC noted that patients in the placebo plus rituximab arm of Trial 312-0116 had generally poor outcomes with high rates of progression and low overall survival. The PBAC considered that best supportive care, which does not include rituximab, is the appropriate comparator for the specific subgroup of patients who are unsuitable for chemo immunotherapy.

7.6 The PBAC noted the gains in PFS and OS with idelalisib plus rituximab compared with rituximab monotherapy reported in Trial 312-0116. However, the PBAC noted that the trial data were immature with respect to overall survival and long term safety.

7.7 The PBAC considered that the trial data indicated that idelalisib plus rituximab is inferior to rituximab monotherapy for some short term safety outcomes. The PBAC agreed with the ESC that, given the relatively short trial duration it was difficult to identify potential long term safety effects, and as such long term toxicities are unknown. The PBAC noted the high rates of late colitis, as outlined paragraphs 6.13 and 6.16.

7.8 The PBAC considered that the data from Trial 312-0116, which compared idelalisib plus rituximab to placebo plus rituximab, would only be applicable if rituximab monotherapy is considered as a surrogate for best supportive care. The PBAC considered that this assumption was reasonable with respect to survival outcomes given the absence of evidence of a survival benefit associated with rituximab monotherapy. The PBAC considered that the submission's use of comparative data from the placebo plus rituximab arm may have led to an underestimation of both the incremental benefit with regard to progression events, and the comparative harms of idelalisib plus rituximab compared with best supportive care alone.

7.9 While the inclusion criteria for Trial 312-0116 do not specifically align with the revised restriction outlined in paragraph 7.4, the PBAC noted the trial was enriched for patients with CIRS score of > 6, neutropenia, thrombocytopenia, and/or 17p deletion. As such the PBAC considered that the trial results were applicable to the patient population who would be eligible under the revised restriction.

7.10 The PBAC noted the ESC's concerns that the model structure did not include post-progression treatment benefits. However, the PBAC considered that in view of the poor prognosis of the patient population (i.e. patients who progress are likely to transition quickly to end-of-life care), a simple model structure that does not include

post-progression benefits and costs would be appropriate for this specific population.

7.11 The PBAC considered that the model should include age adjusted all-cause mortality, as outlined in paragraph 6.26. Further, the PBAC considered that a 7 year time horizon would be appropriate for the patient population included in the revised restriction, and that a sensitivity analysis with a 5 year time horizon would be informative. In addition, the PBAC considered that the choice of extrapolation method would need to align with the observed data reported in the final Clinical Study Report (i.e. modelled PFS and OS would need to be consistent with the trial-based data).

7.12 The PBAC noted the issues with the estimated usage and financial implications, as outlined in paragraphs 6.32 and 6.33. In particular, the PBAC considered that the submission's assumption, that in year 5 of listing approximately one in ten patients would be new (initiating) patients while the remainder would be continuing patients, was inappropriate. Given the rapidly evolving treatment algorithm for CLL, the PBAC considered that it is imperative that robust estimates of the numbers of patients requiring second or subsequent line therapy for CLL are generated.

7.13 The PBAC considered that the financial estimates should not include any cost-offsets for the use of rituximab as monotherapy because such use is outside the PBS restriction for rituximab.

7.14 The PBAC considered that the estimated number of patients would need to be revised to reflect the patient population who would be eligible under the revised restriction.

7.15 The PBAC considered that the following would need to be addressed in a major resubmission: present a revised restriction that targets patients with the highest clinical need and for whom there is adequate evidence from the trial; use of the appropriate comparator; present adequate evidence of comparative efficacy and safety in this group; update the economic evaluation; and revise the financial estimates.

7.16 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 of Zydelig for patients with chronic lymphocytic leukemia that has progressed despite prior treatment.