7.18 IDELALISIB
Oral tablet, 100 mg, 150 mg
Zydelig®, Gilead Sciences Pty Ltd

1 Purpose of Application

1.1 The minor re-submission requested a Section 85, Authority Required listing of idelalisib for the treatment of relapsed/refractory chronic lymphocytic leukaemia (CLL)/small lymphocytic leukaemia (SLL).

2 Requested listing

2.1 The re-submission does not request any changes to the wording of the listing as described in November 2015 PBAC Public Summary Document (PSD).

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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment phase:	
Restriction Level / Method:	☒Authority Required - Telephone
Clinical criteria:	The treatment must be in combination with rituximab; AND The condition must have relapsed or be refractory after at least one therapy; AND Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage); AND Patient must be inappropriate for chemo-immunotherapy

Prescriber Instructions	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. A patient is inappropriate for chemo-immunotherapy because of one or more of the following: - Severe neutropenia; or - Severe thrombocytopenia; or - Presence of 17p deletion; or - Presence of TP53 mutation.
Administrative Advice	Severe neutropenia defined as absolute neutrophil count ≤ 1.0 x 10^9/L Severe thrombocytopenia defined as platelet count ≤ 50 x 10^9/L

2.2 At the November 2015 meeting, the PBAC advised that the Department should work with the sponsor to finalise an appropriate telephone Authority restriction. The PBAC agreed with the ESC that patients should be treated until progression and that this should be incorporated into the restriction wording. The Secretariat has updated the restriction to include Authority required (Telephone) and the Prescriber Instruction: A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. In this minor re-submission, the sponsor is willing to work with the Department to finalise the restriction.

3 Background

3.1 Idelalisib was TGA registered on 9 February 2015 for the indication:
In combination with rituximab, for the treatment of patients with chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma (SLL) for whom chemo-immunotherapy was not considered suitable, either:
- upon relapse after at least one prior therapy; or
- as first-line treatment in the presence of 17p deletion or TP53 mutation.

3.2 This item was previously considered at the March 2015 and November 2015 PBAC meeting. At the November 2015 meeting, the PBAC deferred its decision for the Authority Required listing of idelalisib in combination with rituximab for the second-line treatment of relapsed chronic lymphocytic leukaemia (CLL) and small lymphocytic leukaemia (SLL) in patients who are unfit for chemotherapy as idelalisib was not considered to be cost-effective at the price proposed.

Table 1: Summary of previous submission and current resubmission:

	Idelalisib, November 2015, recommendations	**Idelalisib, March 2016, response**
Requested Listing	The PBAC advised that, once a price is negotiated, the Department should work with the sponsor to finalise an appropriate telephone Authority restriction.	The sponsor is willing to work with the Department to finalise the restriction.
Requested Price	The PBAC deferred its decision for listing idelalisib it was considered to be not cost-effective at the price proposed. Previous requested price: **Effective DPMQ**	In the resubmission, the sponsor proposed an effective price of $[redacted], requesting a [redacted]% reduction of the proposed published price ($[redacted]). The pre-PBAC response proposed a new effective DPMQ of $[redacted]. The listing of the 100 mg strength, at the same price as the 150 mg strength, is requested only for facilitation of dose reduction for adverse even

	Idelalisib, November 2015, recommendations	Idelalisib, March 2016, response
	Oral tablet 150mg/ 100 mg — $[redacted]	management. Current requested price: Oral tablet 150mg /100 mg — Effective DPMQ (proposed in the pre-PBAC response): $[redacted]
Economic evaluation	The PBAC considered that the most realistic estimate of cost-effectiveness could be calculated using the assumptions in the PBAC base case. This resulted in the ICER being $105,000/QALY - $200,000/QALY. The PBAC considered the ICER per QALY to be unacceptably high and a significant price reduction would be required in order to reduce this base case ICER to less than $45,000/QALY - $75,000/QALY. Given that the incremental overall survival (OS) is likely underestimated by its reliance on the ITT analysis, the PBAC requested that the consequence of this price reduction be presented in the lower bound sensitivity analysis generated using the RPSFT analysis. [7.13, Nov 2015 PSD]	The respecified base-case economic evaluation was presented with the following assumptions: • A price reduction of [redacted]% at effective DPMQ • ITT analysis using parametric extrapolation •Accepting an 8 year time horizon •Removing costs of rituximab in the BSC arm •Removing costs and disutilities for rituximab treatment in the BSC arm (by setting proportion of rituximab users to zero) •Adjusting the cost of anaemia and thrombocytopenia •Corrected rate of pneumonia in idelalisib plus rituximab arm of 10% •Costs of stable and progressive disease as per original submission. When the base case is respecified the ICER is; $45,000/QALY - $75,000/QALY (RPSFT-adjusted crossover) and $75,000/QALY - $105,000/QALY (ITT). These ICERs were independently verified. In the pre-PBAC response, applying the requested price to the PBAC-specified base case economic model brought the ICER/QALY for idelalisib in the treatment of CLL to; $45,000/QALY - $75,000/QALY (RPSFT-adjusted crossover) and $45,000/QALY - $75,000/QALY (ITT).
Number of patients and financial estimates	The PBAC considered that the total patient population was uncertain, but that the alternative approach presented by the evaluation including both the incident and prevalent populations is more reasonable and should be the basis for any risk sharing arrangement. [7.15, Nov 2015 PSD] The PBAC agreed that cost offsets for rituximab monotherapy should not be included in the estimated cost to the PBS. [7.16, Nov 2015 PSD]	The re-submission updates the estimate provided in the PSCR in October 2015 (including both the incident and prevalent populations) with the revised pricing. These estimates differ from those in the November 2015 PBAC PSD [paragraph 6.50], as they allow 20% market growth in response to the listing of an effective treatment where none exists. From the PSCR (p4, 7.04 Nov 2015): The Sponsor could also not ascertain why the [alternative approach in the Commentary] had elected to omit the assumption that listing of idelalisib could be expected to grow the number of patients receiving treatment by 20% (i.e. market growth 120%). The numbers presented in this minor re-submission are the same as presented in Table

	Idelalisib, November 2015, recommendations	Idelalisib, March 2016, response
		5 of the Nov 2015 PSCR. This growth assumption was not specifically raised in the Nov 2015 ESC ADV. Cost offsets for rituximab have been removed from the financial estimates.
Main Comparator	Unchanged from November PBAC submission	
Clinical evidence		
Key effectiveness data		
Key safety data		
Clinical claim		

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

4.2 The PBAC noted that no consumer comments were received for this item.

For more detail on PBAC's view, see section 5 "PBAC outcome"

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

4.3 This was based on a mean duration of treatment of 21.6 months (mean progression free survival duration estimated in the economic model), 92.7% dose intensity (calculated from Trial 312-0116), and a pack DPMQ of $[redacted].

Estimated PBS usage & financial implications

4.4 Applying the requested price from the pre-PBAC response, the net cost of idelalisib (CLL) to government is estimated to be $30 - $60 million per year over the first five years of listing. The previous November 2015 PBAC submission was approximately $30 - $60 million per year. In year 5, the cost to the PBS/RPBS was estimated to be less than $10 million, with less than 10,000 patients estimated to be treated.

Table 2: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated – Mar 2015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number treated – Nov 2015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number treated – Nov 2015 alternate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS – Mar 2015	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS – Nov 2015	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS- Nov 2015 alternate	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS- pre-PBAC response price proposal	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Net cost to MBS – Mar 2015	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS – Nov 2015	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS – Nov 2015 alternate	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Net cost to hospitals – Mar 2015	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to hospitals – Nov 2015	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to hospitals – Nov 2015 alternate	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to hospitals	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

For more detail on PBAC's view, see section 5 "PBAC outcome"

The redacted table shows that at year 5, the estimated range of patients was less than 10,000 per year and the net cost to the PBS would be less than $10 million per year.

5 PBAC Outcome

5.1 The PBAC recalled that the Committee at its November 2015 meeting deferred its decision for the Authority Required listing idelalisib for the second-line treatment of chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) 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.

5.2 The PBAC noted the modifications to the economic model and the price proposed in the pre-PBAC response of this resubmission which resulted in ICERs of $45,000/QALY - $75,000/QALY (based on RPSFT-adjusted crossover) and $45,000/QALY - $75,000/QALY (based on ITT analysis). The PBAC considered that this range of ICERs were high but may be acceptable in the context of a tight restriction.

5.3 The PBAC noted the modification in patient utilisation, including both the incident and prevalent populations, the methodology preferred by the PBAC, with 20% market growth. The PBAC considered this estimate to be more reasonable, but remained concerned that the total patient population is uncertain and likely underestimated if idelalisib is added to the currently available treatments on the PBS. The PBAC reiterated that a risk sharing arrangement should be adopted.

5.4 The PBAC recalled that during the November 2015 meeting, the Committee:

- reiterated that there is a high unmet clinical need for an effective treatment for this patient population, and that an oral medication is likely to be preferred for this group. 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.
- reiterated as in the March 2015 consideration that there were statistically significant efficacy results indicating gains in OS and PFS for idelalisib in combination with rituximab over the comparator, noting that this is balanced against significant harms particularly in relation to diarrhoea and colitis which may occur late.

5.5 The PBAC noted recent global concerns about an increased rate of serious adverse events, including deaths, mostly due to infections in current on-going clinical trials studying idelalisib in combination with other medicines. The PBAC noted that, while these on-going trials are being carried out in different diseases or in different patient populations compared to the patient population for which listing is being sought, these serious adverse events represent harms in addition to those raised in clinical data provided in the submission.

5.6 The PBAC deferred the listing of idelalisib for the treatment of follicular lymphoma that is refractory to both rituximab and an alkylating agent to seek additional information regarding safety given the recent concerns raised by regulators. The PBAC requested the sponsor to update the PBAC on adverse events in the clinical areas in which listing is being sought, and if, or how, the recent emergence of additional serious adverse events in the current trials may impact patients if idelalisib becomes available in the broader PBS population. The PBAC was also mindful that these additional harms associated with idelalisib may have an impact on the evaluation of cost-effectiveness.

5.7 Further, the PBAC noted that the sponsor agreed with an Authority required (Telephone) listing. If idelalisib for this condition was listed, the PBAC were of a mind to recommend that:

- The Early Supply Rule should apply to idelalisib as the requested maximum quantity is sufficient supply for 30 days of treatment.

- Idelalisib is not suitable for prescribing by nurse practitioners as antineoplastic agents are currently considered to be out of scope for prescribing by nurse practitioners.
- Under Section 101 (3BA) of the National Health Act, idelalisib would not be treated as interchangeable with any other drug(s) or medicinal preparation(s) on an individual patient basis.

Outcome:
Deferred

6 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.

7 Sponsor's Comment

The sponsor had no comment.