

4.03 IDELALISIB
Oral tablet, 100 mg, 150 mg
Zydelig[®], Gilead Sciences Pty Ltd

1 Purpose of Item

1.1 To provide the PBAC with information regarding an emerging safety signal raised by the EU and US drug regulatory agencies and identified to the TGA in relation to idelalisib, and to clarify adverse events in the clinical area in which the listings are being sought.

2 Requested listing

2.1 The resubmission did not request any changes to the wording of the listing from the March 2016 PBAC public summary document (PSD).

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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	Refractory
Severity:	-
Condition:	follicular B-cell non-Hodgkin's lymphoma
PBS Indication:	Refractory follicular B-cell non-Hodgkin's lymphoma
Treatment phase:	-
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Telephone
Treatment criteria:	-
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

Prescriber Instructions	<p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.</p> <p>The condition is considered refractory to both rituximab and an alkylating agent if the agents were administered together or in successive treatment regimens.</p> <p>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.</p>
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

- 2.2 At the November 2015 meeting, 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. In the March 2016 minor resubmission, the sponsor did not object to the implementation of a telephone authority and the restriction was updated accordingly at that time.

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, November 2015, and March 2016 PBAC meetings. At the November 2015 meeting, the PBAC deferred its decision for the Authority Required listing of idelalisib monotherapy in patients with follicular lymphoma, refractory to rituximab and an alkylating agent, as idelalisib was not considered to be cost-effective at the price proposed.
- 3.3 The decision to list for the aforementioned indication was again deferred at the March 2016 PBAC meeting to allow the committee to seek additional information from the Sponsor regarding emerging safety concerns in phase 3 clinical trials of idelalisib as identified by the EU and US drug regulatory agencies.

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 and welcomed the input from an organisation (1) via the Consumer Comments facility on the PBS website. The comment reiterated the lack of treatment options for patients with follicular lymphoma and highlighted the importance of providing another therapeutic option for these patients.

Clinical trials

- 4.3 As a minor resubmission, no new clinical trials were presented.
- 4.4 The resubmission provided information to clarify adverse events for the indication for which listing is being sought.
- 4.5 Serious adverse events for idelalisib were reported in three Phase 3 studies where idelalisib was added to standard therapies as first line treatment in either CLL (one study) or relapsed refractory indolent NHL, including follicular lymphoma (two studies). In these studies, a higher incidence of SAEs and increased risk of death (7.4% versus 3.5%) was observed among patients receiving idelalisib. The excess deaths were mainly caused by infections, including pneumocystis and cytomegalovirus. These studies included patients with different disease states and characteristics to those covered by the current authorised indications and studied patients who were less heavily pre-treated than in the trials considered by the PBAC. They also incorporated treatment combinations (bendamustine + rituximab) not currently approved for use as first line therapy for CLL or for second line therapy for indolent NHL. The trials studied the combination of idelalisib, rituximab and bendamustine in patients with previously untreated CLL and relapsed/refractory indolent NHL, and a combination of idelalisib with rituximab for patients with relapsed/refractory indolent NHL.
- 4.6 The proposed PBS population is as monotherapy for patients with Follicular Lymphoma (FL) that is refractory to both rituximab and an alkylating agent. Treatment options for this population are limited. Infectious complications were observed in the trial previously considered by the PBAC in support of this listing.
- 4.7 The new safety signals observed in the recently terminated Phase 3 studies were not identified in a re-analysis of the clinical trials in CLL and refractory follicular lymphoma previously considered by the PBAC in support of the proposed listings. Therefore the submission considered that the safety data previously considered by the PBAC in November 2015 for the proposed PBS populations remains unchanged and that the overall benefit-risk evaluation for idelalisib remains positive for patients with FL who are refractory to rituximab and alkylating agents.

Drug cost/patient/course: \$ [REDACTED]

- 4.8 This was based on a mean duration of treatment of 11.4 months (mean progression free survival duration estimated in the economic model, November 2015 resubmission), 92.7% dose intensity, and cost of \$ [REDACTED] per pack.

5 PBAC Outcome

- 5.1 The PBAC recommended the Authority Required listing of idelalisib as monotherapy for the treatment of follicular B-cell non-Hodgkin's lymphoma that is refractory to both rituximab and an alkylating agent. The PBAC was satisfied that idelalisib provides, for some patients, a significant improvement in efficacy over best supportive care.
- 5.2 The PBAC reiterated that there is a high unmet clinical need for an effective treatment for patients with double-refractory follicular lymphoma, considering that the

benefits are expected to outweigh the risks of significant toxicity in this patient population.

- 5.3 The PBAC acknowledged that the safety signals observed in the Phase 3 trials, resulting in the March 2016 submission deferral, were not identified in a re-analysis of the clinical trial in CLL and refractory follicular lymphoma that have been considered by the PBAC in the support of the proposed listing. However, it considered that the single arm nature of the follicular lymphoma trial made identification of an excess toxicity signal difficult. Further, the PBAC noted that the TGA is still undertaking an evaluation of the safety of idelalisib, and that there were more safety concerns with the use of idelalisib in follicular lymphoma than in chronic lymphocytic lymphoma. Consequently, the Committee considered that the concerns around toxicity remain. To address this concern, the PBAC recommended that PBS listing of idelalisib for this indication should not proceed until further safety advice from the TGA is available.
- 5.4 The PBAC agreed with the proposed restriction from the March 2016 submission, however considered it now appropriate for idelalisib listing to require a written authority as a mechanism to reduce the risk of patients being inappropriately exposed to potential toxicity. The PBAC reiterated that idelalisib should be used last-line in patients with follicular lymphoma, and should only be used as monotherapy.
- 5.5 The PBAC recalled that limitations in the data provided in the submissions meant that the comparative efficacy could not be estimated and the magnitude of any incremental benefit was highly uncertain. However, recognising the need for a treatment option for this cohort of patients, on balance the PBAC considered that idelalisib is clinically effective as a last-line treatment option.
- 5.6 The PBAC considered the reduced price offered in the March 2016 submission was acceptable and likely to be cost-effective. The PBAC maintained that the ICER remained high but considered this acceptable for this patient population for whom there are few treatment options. The PBAC also noted that the economic evaluation did not include the additional costs associated with the updated safety recommendations (*Pneumocystis jirovecii* pneumonia prophylaxis, regular screening for cytomegalovirus, and absolute neutrophil count monitoring), however considered that this would be unlikely to have a significant effect on the overall cost effectiveness.
- 5.7 The PBAC remained concerned that the total patient population is uncertain, considering that the Department should negotiate a risk sharing arrangement with a financial cap. The cap should be based on utilisation estimates contained in the March 2016 submission's patient numbers. The PBAC reiterated that due to the uncertainty in patient numbers, utilisation should be reviewed 3 years after listing.
- 5.8 The PBAC recommended that idelalisib should not be treated as interchangeable with any other drugs.
- 5.9 The PBAC advised that idelalisib is not suitable for prescribing by nurse practitioners.
- 5.10 The PBAC recommended that idelalisib should not be treated as interchangeable on an individual patient basis with any other drugs.

- 5.11 The PBAC recommended that the Early Supply Rule should apply to idelalisib.
- 5.12 The PBAC noted that this submission is not eligible for an Independent Review as idelalisib has been recommended for listing.

Outcome:

Recommended

6 Recommended listing

6.1 Add item:

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Condition:	follicular B-cell non-Hodgkin's lymphoma
PBS Indication:	Refractory follicular B-cell non-Hodgkin's lymphoma
Treatment phase:	
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Written
Treatment criteria:	
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
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.
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7 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.

8 Sponsor's Comment

The sponsor had no comment.