

4.02 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 issue raised by the EU and US drug regulatory agencies and identified to the TGA in relation to idelalisib. The submission aimed to clarify adverse events in the clinical area in which the listings for idelalisib 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 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 Tablet, 150 mg, 60 Tablet, 100 mg, 60	1	5	\$ [REDACTED] (published) \$ [REDACTED] (effective)	Zydelig [®] Gilead

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
PBS Indication:	Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment phase:	
Restriction Level / Method:	<input checked="" type="checkbox"/> 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	<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>A patient is inappropriate for chemo-immunotherapy because of one or more of the following:</p> <ul style="list-style-type: none"> - Severe neutropenia; or - Severe thrombocytopenia; or - Presence of 17p deletion; or - Presence of TP53 mutation.
Administrative Advice	<p>Severe neutropenia defined as absolute neutrophil count $\leq 1.0 \times 10^9/L$</p> <p>Severe thrombocytopenia defined as platelet count $\leq 50 \times 10^9/L$</p>

- 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 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 the March 2016 minor resubmission, the Sponsor indicated a willingness to work with the Department to finalise the restriction.

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

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, November 2015, and March 2016 PBAC meetings. 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.
- 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 that no consumer comments were received for this item.

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 SLL (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 the combination of idelalisib with rituximab for patients with relapsed/refractory indolent NHL.

4.6 The proposed PBS population is for patients with relapsed CLL after at least one prior therapy who are unfit for chemotherapy. As previously assessed by the PBAC, in the registration trial for this population, patients treated with or without idelalisib show relatively high rates of SAEs and mortality however no excess mortality signal specific to idelalisib was noted. The trial was stopped early due to demonstration of a significant survival benefit for treatment with idelalisib in combination with rituximab.

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 previously considered by the PBAC in support of the proposed listings. Therefore the sponsor considers that the safety data previously considered by the PBAC in November 2015 for the proposed PBS populations remains unchanged. The Sponsor has indicated that the overall benefit-risk evaluation for idelalisib remains positive for patients with relapsed CLL, including patients with 17p deletion of TP53 mutation.

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

- 4.8 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].

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

5 PBAC Outcome

- 5.1 The PBAC recommended the Authority Required listing of idelalisib in combination with rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic leukaemia (SLL). The PBAC was satisfied that idelalisib provides, for some patients, a significant improvement in efficacy over best supportive care.
- 5.2 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 trials that have been considered by the PBAC in the support of the proposed listing. However, noting the TGA is still undertaking an evaluation of the safety of idelalisib, the Committee considered that the concerns around toxicity remain and therefore considered that clinicians need to remain cautious of the risks relating to idelalisib use. In particular, the PBAC noted that a favourable benefit: risk ratio had not been established outside the population reflected by the clinical trial, and that use in combination with anti-CLL drugs other than rituximab was not appropriate. The PBAC suggested that restricting the use to this small, high need cohort would minimise the risk of unnecessary exposure to toxicity.
- 5.3 The PBAC agreed with the proposed restriction from the March 2016 PSD, 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 also noted that given the requirement for use with rituximab, use of idelalisib should be restricted to patients with CD20-positive CLL or SLL.
- 5.4 The PBAC reiterated 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 considered the price offered in the March 2016 submission, discounted from the price offered in November 2015, 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.
- 5.6 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 the utilisation estimates contained in the March 2016 submission's patient numbers.

- 5.7 The PBAC recommended that idelalisib should not be treated as interchangeable on an individual patient basis with any other drugs.
- 5.8 The PBAC advised that idelalisib is not suitable for prescribing by nurse practitioners.
- 5.9 The PBAC recommended that the Early Supply Rule should apply to idelalisib.
- 5.10 The PBAC noted the flow-on restriction changes to rituximab, with amendment of the clinical criteria to state that rituximab can be used with chemotherapy or idelalisib.
- 5.11 The PBAC noted that this submission is not eligible for an Independent Review as idelalisib has been recommended for listing.

Outcome:

Recommended

ADDENDUM

At its special meeting in August 2016, the PBAC recommended the PBS restriction for idelalisib for CLL and SLL include the requirement for patients to have evidence of a 17p deletion (noting that this test is yet to be considered by the Medical Services Advisory Committee). The PBAC also recommended including the TP53 mutation requirement for patients testing negative for the 17p deletion, if a test for TP53 mutation is made available through the Medicare Benefits Schedule.

6 Recommended listing

6.1 Add item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
IDELALISIB Tablet, 150 mg, 60 Tablet, 100 mg, 60	1	5	Zydelig® Gilead

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
PBS Indication:	Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment phase:	
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required – Written

Public Summary Document – July 2016 PBAC Meeting

Clinical criteria:	<p>The treatment must be in combination with rituximab;</p> <p>AND</p> <p>The condition must have relapsed or be refractory after at least one therapy;</p> <p>AND</p> <p>The condition must be CD20 positive;</p> <p>AND</p> <p>Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage);</p> <p>AND</p> <p>Patient must be inappropriate for chemo-immunotherapy</p>
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>A patient is inappropriate for chemo-immunotherapy because of one or more of the following:</p> <ul style="list-style-type: none"> - Severe neutropenia; or - Severe thrombocytopenia; or - Presence of 17p deletion; or - Presence of TP53 mutation.
Administrative Advice	<p>Severe neutropenia defined as absolute neutrophil count $\leq 1.0 \times 10^9/L$</p> <p>Severe thrombocytopenia defined as platelet count $\leq 50 \times 10^9/L$</p>

- 6.2 Amend current listing for rituximab (item codes 4615X & 7259C): Adding to the restriction that it can be used in combination with chemotherapy or idelalisib. Additions are in italics.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
RITUXIMAB			
Injection, 100mg/10ml, 2 X 10ml	1	5	Mabthera® Roche
Injection, 500mg/50ml, 1 X 50ml			

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
PBS Indication:	Chronic lymphocytic leukaemia (CLL)
Treatment phase:	
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required –Streamlined

Clinical criteria:	The condition must be CD20 positive-chronic lymphocytic leukaemia (CLL) AND The treatment must be in combination with chemotherapy <i>or idelalisib</i> .
Prescriber Instructions	-
Administrative Advice	-

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.