

## **7.16 IBRUTINIB**

### **Oral capsule, 140 mg, Imbruvica®, Janssen-Cilag Pty Ltd.**

#### **1 Purpose of Application**

- 1.1 This was a minor re-submission which sought to address the following concerns raised by the PBAC for the November 2015 minor re-submission:
- the use of the rank preserving structural failure time (RPSFT) method to adjust the overall survival to account for patients crossing over from the comparator arm (ofatumumab) to ibrutinib;
  - the appropriate time horizon to inform the economic modelling; and
  - the request for a risk sharing arrangement.

#### **2 Requested listing**

- 2.1 The minor re-submission sought to list ibrutinib as a second-line therapy in patients with chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma (SLL) deemed unfit for further treatment with a purine analogue (i.e. fludarabine) as presented in the November 2015 re-submission.

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

#### **3 Background**

- 3.1 Ibrutinib is TGA registered for the treatment of (1) patients with CLL/SLL who have received at least one prior therapy or as first line in patients with CLL with 17p deletion and (2) patients with mantle cell lymphoma who have received at least one prior therapy.
- 3.2 The PBAC did not recommend the July 2015 major submission and deferred the November 2015 minor re-submission. In November 2015, the PBAC did not accept the overall survival results adjusted via the RPSFT method and considered that the overall survival results from the ITT population were the most appropriate for economic evaluation. The PBAC did not consider that ibrutinib was cost-effective at the price proposed. The PBAC recommended that the base case of the economic evaluation should be revised to obtain an incremental cost-effectiveness ratio (ICER) of \$45,000 - \$75,000 per quality-adjusted life year (QALY) or less with the following criteria: a ten-year time horizon; the use of three health states (which was considered appropriate over a ten-year time horizon); incremental overall survival based on the ITT population from the RESONATE trial; and, as modelled in the November 2015 minor re-submission, the assumption of a ■% improvement in the comparator arm to account for the lower efficacy of ofatumumab monotherapy compared to alternative therapies used in practice.
- 3.3 Table 1 provides a summary of the key differences between the July 2015 major submission, November 2015 minor re-submission and the current minor re-submission.

Table 1: Key differences between the July 2015 submission, the November 2015 minor re-submission and the March 2016 minor re-submission

	July 2015 submission	November 2015 minor re-submission	March 2015 minor re-submission
Requested PBS listing for:	Relapsed or refractory CLL and SLL, where the patient must have received $\geq 1$ prior therapy, and be considered unsuitable for treatment or retreatment with a purine analogue.	As per the July 2015 major submission. Additional criteria were included in the requested listing to define patients who are unsuitable for treatment or retreatment with a purine analogue based on the eligibility criteria in the RESONATE study.	No change
Requested restriction	Authority required (STREAMLINED)	Authority required (TELEPHONE)	No change
Effective ex-manufacturer price	\$ [REDACTED]	The minor re-submission offered a [REDACTED]% price reduction with a new effective ex-manufacturer price of \$ [REDACTED].  PBAC stated that the effective price should be such that the economic evaluation has an ICER of <\$ [REDACTED]/QALY with the criteria stated in Table 2.	No change, as new model resulted in ICER <\$ [REDACTED]/QALY
Main comparator	Rituximab plus chlorambucil	No change	No change
Clinical evidence	<u>Interim analysis (median follow-up 9.4 months)</u> <b>Median OS</b> Ibrutinib (N=195): not reached Ofatumumab (N=196): not reached HR: 0.43 (95% CI: 0.24, 0.79)  <u>Longer-term follow-up (median follow-up 16 months)</u> <b>Median OS</b> Ibrutinib (N=195): not reached Ofatumumab (N=196): [REDACTED] [REDACTED] [REDACTED] [REDACTED]	No change.  A comparison of ibrutinib to idelalisib + ofatumumab using ofatumumab as the common comparator was provided. This information was not pivotal to the minor re-submission.  The minor re-submission examined four methodologies to adjust for crossover. The preferred method was the RPFST.  The OS HR adjusted using the RPSFT method for the median follow-up of 16 months was [REDACTED]	Presentation of ITT (EOS), RPSFT methodology and ITT (amended), see paragraph 6.14-17 of this Minor Overview and Table 3.

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	July 2015 submission	November 2015 minor re-submission	March 2015 minor re-submission
Clinical claim	As evidenced by statistically significant and clinically relevant improvements in PFS, OS, and ORR, ibrutinib has a superior efficacy profile compared to ofatumumab (and by extension chlorambucil plus rituximab, the main comparator) and a different but acceptable safety and tolerability profile.	No change.  The minor resubmission did not identify any new evidence to determine the magnitude of benefit of ibrutinib over rituximab given in combination with chlorambucil.	No change
Economic model	Cost-utility analysis. 3-state model. 20-year time horizon. LYG and QALY outcomes. Markov model. Transition probabilities derived based on extrapolated PFS and OS KM estimates. Convergence applied at 24 months with full convergence to 25 years.	The structure of the economic model was unchanged.  The following relevant model inputs were revised: <ul style="list-style-type: none"> <li>• Discounted price for ibrutinib.</li> <li>• Time horizon truncated to 15 years (from 20 years).</li> <li>• █% reduction in the hazard of event in comparator arm (progression and death) to address the uncertainty in the magnitude of the treatment effect of ofatumumab versus rituximab plus chlorambucil.</li> </ul>	The following model inputs were revised: <ul style="list-style-type: none"> <li>• Time horizon truncated to 10 years (from 15 years).</li> <li>• Removal of the convergence factor.</li> </ul>
Base case ICER	Main submission: base case \$45,000/QALY – 75,000/QALY, with OS based on the unadjusted ITT analysis Pre-PBAC response: respecified base case \$45,000/QALY – 75,000/QALY, using RPSFT methodology.	\$45,000/QALY – 75,000/QALY The respecified ICER was based on the key assumptions and revisions shown in Table 2.	\$45,000/QALY – 75,000/QALY The respecified ICER was based on the key assumptions and revisions shown in Table 2.
Financial estimates	Incidence based approach.  Method was inappropriate, DUSC developed new estimates.	The financial estimates prepared by the DUSC for the July 2015 submission were accepted.	Unchanged

	July 2015 submission	November 2015 minor re-submission	March 2015 minor re-submission
Risk sharing arrangement	<p>The submission stated that a risk share arrangement should be based upon an assumption of 100% uptake in eligible patients with an appropriate financial buffer before any rebates apply.</p> <p>To reduce the risk of leakage, the submission stated willingness to work with the Department to negotiate a risk-sharing arrangement.</p>	<p>The minor re-submission has used the DUSC estimates to calculate caps for the proposed RSA. The proposed caps are based upon the assumption that all eligible patients as proposed by the DUSC's estimates will access ibrutinib.</p> <p>The minor re-submission acknowledges the potential for leakage to other populations (purine suitable, first-line CLL with 17p deletion and mantle cell lymphoma). An additional rebate of █% for all Commonwealth payments exceeding the subsidisation caps was proposed.</p> <p>The PBAC recommended that a RSA would be required consisting of a cap on expenditure with a █% rebate for budget certainty. The PBAC recommended that the RSA should be based on the DUSC estimates of the patient population representative of those included in the RESONATE trial.</p>	<p>The minor re-submission requested negotiations with the Department about the RSA.</p>

Source: compiled for the Minor Overview

CLL = chronic lymphocytic leukaemia; SLL = small lymphocytic lymphoma; PBS = pharmaceutical benefit scheme; DPMQ = dispensed price for maximum quantity; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years; PBAC = pharmaceutical benefit advisory committee; OS = overall survival; RPSFT = rank preserving structural failure time; HR = hazard ratio; EOS = end of study; ITT = intention to treat; PFS = progression free survival; ORR = overall response rate; LYG = life year gained; KM = Kaplan–Meier; DUSC = drug utilisation sub committee; RSA = risk sharing arrangement

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

#### 4 Clinical place for the proposed therapy

- 4.1 The clinical place for ibrutinib proposed in the July 2015 submission was unchanged in this minor re-submission.

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

## **5 Comparator**

- 5.1 The previous major submission considered by the PBAC in July 2015 nominated chlorambucil plus rituximab as the main comparator. This was unchanged in the November 2015 and current minor re-submission. The PBAC previously considered that the nominated comparator was appropriate for the requested restriction for patients unsuitable for treatment with a purine analogue.

*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 as it was a minor submission.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the two inputs from an individual and an organisation via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ibrutinib including a good response to therapy towards achieving remission.

### ***Clinical trials***

- 6.3 No new clinical trials were presented in the minor re-submission.

### ***Comparative effectiveness***

- 6.4 The trial results remain unchanged from the previous minor re-submission considered in November 2015.

### ***Comparative harms***

- 6.5 The adverse events results remain unchanged from the previous minor re-submission considered in November 2015.

### ***Clinical claim***

- 6.6 The November minor re-submission claimed superior comparative effectiveness and a different but acceptable safety and tolerability profile compared with ofatumumab monotherapy (and by extension chlorambucil plus rituximab). The current minor re-submission did not change the clinical claim.

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

### ***Economic analysis***

- 6.7 The current minor re-submission presented a revised cost-effectiveness analysis of

ibrutinib against ofatumumab with a base case ICER of \$45,000/QALY – 75,000/QALY calculated in the RPSFT population without convergence. Based on the criteria for the economic evaluation set by the PBAC in November 2015 the evaluation derived a base case ICER of \$75,000/QALY – 105,000/QALY based on the ITT (end of study) population with convergence applied to overall survival. The different ICERs resulting from the presented and the suggested parameters from the November 2015 PBAC recommendation are shown in the following table. The likely range of the true ICER was between \$45,000/QALY – 75,000/QALY and \$75,000/QALY – 105,000/QALY. In its Pre-PBAC response the sponsor offered a [REDACTED] % price reduction which reduced this ICER range to \$45,000/QALY – 75,000/QALY.

Table 4: Summary of modelled economic analysis

	Hazard Ratio	Time horizon (years)			
		10		15	
Convergence		yes	no	yes	no
<b>ICER</b>					
RPSFT	[REDACTED]	\$ [REDACTED]	\$ [REDACTED] <sup>b</sup>	\$ [REDACTED]	\$ [REDACTED]
ITT (EOS)	[REDACTED]	\$ [REDACTED] <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
ITT (amendment)	[REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
RPSFT – 5%	n.a.	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
RPSFT– 15%	n.a.	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
RPSFT–25 %	n.a.	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>QALY (LYG)</b>					
RPSFT	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ITT (EOS):	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ITT (amendment)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
RPSFT – 5%	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
RPSFT– 15%	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
RPSFT–25 %	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>COST</b>					
RPSFT	[REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
ITT (EOS)	[REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
ITT (amendment)	[REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 1.9, p30; Table 1.11, p33 of the minor re-submission and compiled during the evaluation

RPSFT = rank preserving structural failure time; ITT = intention to treat; EOS = end of study; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; LYG = life year gained; n.a. = not available.

<sup>a</sup> Based on November 2015 PBAC recommendation for the base case.

<sup>b</sup> Based on the current re-submissions revised base case.

6.8 The likely range of the true ICER was between \$45,000/QALY – 75,000/QALY and \$75,000/QALY – 105,000/QALY per QALY. In its Pre-PBAC response the sponsor offered a [REDACTED] % price reduction which reduced this ICER range to \$45,000/QALY – 75,000/QALY.

6.9 Table 2 shows the amendments made to the base case economic model over successive submissions.

Table 2: Economic model timeline

Base case approach	Jul-15 Sub	Jul-15 pre-PBAC	Nov-15 minor re-sub	Request PBAC in Nov 2015	Mar-16 minor re-sub
Time horizon	20 years	20 years	15 years	10 years	10 years
Population	ITT	RPSFT	RPSFT	ITT	RPSFT
Ibrutinib price <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	To result in ICER < \$ [REDACTED]	\$ [REDACTED]
Convergence	Starting at 2 years	Starting at 2 years	Starting at 2 years	Starting at 2 years (implicitly)	No
Other elements	-	-	ofatumumab efficacy increased by [REDACTED] %	ofatumumab efficacy increased by [REDACTED] %	ofatumumab efficacy increased by [REDACTED] %
ICER	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	< \$ [REDACTED]	\$ [REDACTED]

Source: Outcome 7.5 of the November 2015 PBAC meeting

<sup>a</sup> = effective ex-manufacturer

RPSFT = rank preserving structural failure time; ITT = intention to treat; ICER = incremental cost effectiveness ratio

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

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

- 6.10 The drug cost was not updated from the previous minor re-submission and remained \$ [REDACTED] per patient per course. The drug cost per patient per course was based on mean duration of treatment from the RESONATE trial of [REDACTED] months, an effective dispensed price of maximum quantity (DPMQ) of \$ [REDACTED] and a dose intensity of [REDACTED] % based on Table 11 of the Clinical Study Report. This was compared to \$ [REDACTED] for rituximab plus chlorambucil, over a mean duration of six months, using the listed prices for chlorambucil and rituximab as at October 2015.
- 6.11 In its Pre-PBAC response the sponsor offered a [REDACTED] % price reduction (ex-manufacturer price \$ [REDACTED]/DPMQ \$ [REDACTED]), resulting in a lower drug cost/patient/course than stated above.

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

**Estimated PBS usage & financial implications**

- 6.12 The minor re-submission did not present updated financial estimates. The November minor re-submission estimated a net cost to the PBS of \$60 - \$100 million in Year 5 of listing, with a total net cost to the PBS of more than \$100 million over the first 5 years of listing. These estimates in the previous minor re-submission were based on the methodology used by DUSC to revise the estimates for the July 2015 submission, using an effective DPMQ of \$ [REDACTED].
- 6.13 In its Pre-PBAC response the sponsor offered a [REDACTED] % price reduction, resulting in a lower drug cost/patient/course than stated above.

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

## 7 PBAC Outcome

- 7.1 The PBAC deferred its decision for the Authority Required listing of ibrutinib for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) to enable the Department to negotiate revisions to the eligibility criteria and the resulting patient estimates with the sponsor.
- 7.2 The PBAC recalled that for the November 2015 submission the Committee had recommended a respecified base-case for the economic modelling to obtain an incremental cost-effectiveness of \$45,000/QALY – 75,000/QALY based on the following parameters: a ten-year time horizon; the use of three health states (which was considered appropriate over a ten-year time horizon); incremental overall survival based on the ITT population from the RESONATE trial; and an assumption of a ■% improvement in the comparator arm to account for the lower efficacy of ofatumumab monotherapy compared to alternative therapies used in practice. The PBAC did not accept the revised base case ICER presented in the sponsor's minor re-submission and in the Pre-PBAC response, noting the proposed price reduction, as the economic evaluations were based on the RPSFT population without convergence in overall survival which was inconsistent with the criteria recommended in November 2015.
- 7.3 The PBAC recommended that ibrutinib should be restricted to relapsed/refractory CLL and SLL patients with genetic abnormalities in CLL and SLL who have the poorest outcomes to conventional treatment. The PBAC considered that the restriction should be based on the following eligibility criteria:
- a WHO performance status of less than 2.
  - used as monotherapy
  - relapsed/refractory CLL and SLL with either 17p deletion and/or 11q deletion and/or TP53 mutations (molecular markers that the PBAC considered indicated a poor prognosis for the patient);  
OR
  - relapsed/refractory CLL and SLL that is refractory to fludarabine, cyclophosphamide and rituximab (FCR): failure to achieve at least a partial response at the completion of FCR (a minimum of 3 cycles) or a progression-free interval of less than 1 year from completion of FCR treatment.
  - ongoing response would need to be demonstrated to obtain continuing access to ibrutinib.
- 7.4 The PBAC further recommended that ibrutinib should not be PBS-subsidised to treat the following patient groups where cost-effectiveness had not been demonstrated: first-line patients with CLL with 17p deletion; mantle cell lymphoma; or other B cell malignancies. The PBAC considered that under its revised eligibility criteria, ibrutinib would likely be cost effective in this high need patient population at the price proposed by the sponsor in its Pre-PBAC response.
- 7.5 The PBAC noted the estimates of the population who would be treated with ibrutinib under the sponsor's proposed restrictions which were prepared by its DUSC for the July 2015 submission. The PBAC estimated that around 15% of the current estimated population would meet the revised eligibility criteria but that this would

need to be further verified with the sponsor. The PBAC noted the sponsor's advice in its Pre-PBAC response that there were [REDACTED] patients enrolled in its named patient program. The PBAC noted that the revised estimate of the treated population would need to include the number of grandfathered patients from the sponsor's access program who would meet the Committee's proposed eligibility criteria. The PBAC considered that the sponsor's estimate for the cost of ibrutinib per patient per course of treatment was underestimated as it was based on the mean duration of treatment from the RESONATE trial of [REDACTED] months and the treatment duration in practice was likely to be longer. The PBAC noted the findings of a three-year follow-up study of ibrutinib (Byrd et al. (2015) Blood 125(16):2497-2506) where the estimated progression-free survival in previously treated patients with CLL/SLL was 69% at 30 months. The PBAC considered that the progression-free survival time from this longer-term study was an appropriate estimate of the likely time on ibrutinib treatment. The PBAC was of the view that an estimate of treatment duration in the poor prognosis patient group should be obtained using real world data and that this should be used to derive the financial estimates for ibrutinib.

- 7.6 The PBAC considered that there was a high risk of use outside its proposed eligibility criteria and that either or both a written Authority listing and a subsidisation cap would be necessary to manage this risk. When the size of the population who would meet the revised eligibility criteria was established, subsidisation caps would be recommended to reflect the final estimates balanced with the risk of leakage outside the restriction.
- 7.7 In including the presence of the molecular markers, namely 17p deletion, 11q deletion, and TP53 mutations in the proposed restriction for patients to receive ibrutinib, the PBAC requested that the Department write to the Medical Services Advisory Committee (MSAC) Executive for advice on whether the genetic tests for these mutations need to be assessed for inclusion in the Medicare Benefits Schedule, and whether there are any other relevant biomarkers which should also be considered.

**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**

Janssen are concerned by the PBAC's recommendation to restrict access to a narrow population. Ibrutinib has demonstrated superior and consistent efficacy in relapsed/refractory CLL or SLL in patients who are unsuitable for treatment or retreatment with fludarabine, regardless of whether they have genetic abnormalities such as 17p deletion, 11q deletion or TP53 mutation. The PBAC's proposed PBS restriction would create inequity by denying access to patients without genetic

abnormalities who have not received prior treatment with, or who cannot tolerate a fludarabine based regimen. Janssen will seek to work with the PBAC and Department of Health to address these issues as soon as possible in the interests of providing timely access for patients with relapsed or refractory CLL who are not suitable for treatment or retreatment with a fludarabine based regimen.