

7.09 IBRUTINIB

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

1 Purpose of Application

- 1.1 The minor resubmission requested a Section 85, Authority Required (TELEPHONE) listing for ibrutinib for the second-line treatment of chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL).
- 1.2 The July 2015 PBAC minutes stated: ‘The PBAC considered that the following would need to be addressed in a major resubmission: present a revised restriction targeting CLL and SLL patients with relapsed or refractory disease with the highest clinical need; use against the appropriate comparator(s); present evidence to demonstrate the comparative efficacy and safety; and an updated economic evaluation and revised financial estimates. The PBAC considered that an ICER should be between \$50,000 and \$60,000/QALY in order for ibrutinib to be acceptably cost-effective’.
- 1.3 This was a resubmission which sought to address the following concerns raised by the PBAC for the July 2015 submission: (1) an inadequate definition of the patient population and clinical place in therapy for ibrutinib; (2) the size of the comparative clinical benefit over the nominated comparator (i.e. rituximab + chlorambucil) could not be quantified; and (3) an unacceptably high ICER of \$45,000/QALY – \$75,000/QALY and an underestimation of the financial cost.
- 1.4 Additional information was provided in the minor resubmission, and in a further response requested by the PBAC Secretariat, on the methodology that was used to adjust the overall survival estimates for patients in the comparator arm of the trial crossing over to start ibrutinib following a progression event.
- 1.5 The base case ICER presented in the minor resubmission was based on an overall survival estimate that had been adjusted for patient cross-over in the RESONATE trial using the rank preserving structural failure time (RPSFT) methodology. The PBAC considered whether it was appropriate to re-specify the base case ICER using the RPSFT-adjusted overall survival estimate because: (1) the base case ICER is generally informed by the overall survival results from an intention-to-treat (ITT) analysis; and (2) there were several uncertainties with the results of the RPSFT analysis. These include: (i) the RPSFT-adjusted ICER (\$45,000/QALY – \$75,000 per QALY) was substantially less than the ICER based on an ITT analysis (\$45,000/QALY – \$75,000/QALY); (ii) the RPSFT method relies on the assumption of a common treatment effect (i.e. ibrutinib will result in the same overall survival gain in both patients randomised to ibrutinib initially and those patients in the ofatumumab arm who crossed over to receive ibrutinib). This is an untestable assumption and it was uncertain if it had been met in the analysis presented in the minor resubmission; (iii) the comparator was an active agent – this is problematic given that the RPSFT requires that patients are either “on treatment” or “off treatment”. (iv) whether the additional treatment multiplier effect (i.e. acceleration factor on survival gain) of ██████ for ibrutinib estimated from the RPSFT analysis was reasonable. This acceleration factor assumes that, had patients not crossed over to ibrutinib and

continued to receive ofatumumab, they would have only had █% of the actual survival time while on treatment with ibrutinib.

2 Requested listing

2.1 The resubmission requested the following new listings:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IBRUTINIB Capsule 140 mg, 90	1	5	Published \$ █ Effective \$ █	Imbruvica Janssen

Authority required (TELEPHONE)

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:	Relapsed or refractory chronic lymphocytic leukaemia
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria: (To be finalised)	The patient must have received at least one prior therapy for this indication AND The patient must be considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following: a. Failure to respond (stable disease or disease progression on treatment), or a progression free interval of less than 3 years from treatment with a purine analogue based therapy and anti-CD20 containing chemoimmunotherapy regimen after at least two cycles OR b. Age ≥ 70 years OR c. Age ≥ 65 and the presence of comorbidities (Cumulative Illness Rating Scale ≥ 6 or creatinine clearance <70 mL/min) that might place the patient at an unacceptable risk for treatment related toxicity with purine analogue based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent based (or purine analogue based) anti-CD20 antibody containing chemoimmunotherapy regimen. OR d. History of purine analogue associated autoimmune anaemia or autoimmune thrombocytopenia OR e. del17p AND Patient must have a WHO performance status score of less than 2.

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Prescriber Instructions (To be finalised)	Treatment must be discontinued in patients who experience disease progression while on treatment
Administrative Advice (To be finalised)	<p>A patient is considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following:</p> <ul style="list-style-type: none"> a. Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles b. Age ≥ 70 years c. Age ≥ 65 years and the presence of comorbidities (Cumulative Illness Rating Scale ≥ 6 or creatinine clearance <70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen d. History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia e. del17p

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IBRUTINIB Capsule 140 mg, 90	1	5	Published \$ [REDACTED] Effective \$ [REDACTED]	Imbruvica Janssen

Authority required (TELEPHONE)

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:	Relapsed or refractory small lymphocytic lymphoma
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

<p>Clinical criteria: <i>(To be finalised)</i></p>	<p>The patient must have received at least one prior therapy for this indication</p> <p>AND</p> <p>The patient must be considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following:</p> <ul style="list-style-type: none"> a. Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles <p>OR</p> <ul style="list-style-type: none"> b. Age \geq 70 years <p>OR</p> <ul style="list-style-type: none"> c. Age \geq 65 and the presence of comorbidities (Cumulative Illness Rating Scale \geq 6 or creatinine clearance $<$70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen. <p>OR</p> <ul style="list-style-type: none"> d. History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia <p>OR</p> <ul style="list-style-type: none"> e. del17p <p>AND</p> <p>Patient must have a WHO performance status score of less than 2.</p>
<p>Prescriber Instructions <i>(To be finalised)</i></p>	<p>Treatment must be discontinued in patients who experience disease progression while on treatment</p>
<p>Administrative Advice <i>(To be finalised)</i></p>	<p>A patient is considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following:</p> <ul style="list-style-type: none"> a. Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles b. Age \geq 70 years c. Age \geq 65 years and the presence of comorbidities (Cumulative Illness Rating Scale \geq 6 or creatinine clearance $<$70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen d. History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia e. del17p

2.2 The proposed PBS restriction suggests that ibrutinib would be used as a second-line therapy in patients with CLL/SLL deemed unfit for further treatment with a purine analogue (i.e. fludarabine).

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 chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma (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 July 2015 PBAC did not recommend the previous submission for ibrutinib. The minor resubmission sought to address the following concerns raised by the PBAC for the July 2015 submission: (1) inadequate definition of the patient population and clinical place in therapy for ibrutinib; (2) the size of the comparative clinical benefit over the nominated comparator (i.e. rituximab + chlorambucil) could not be quantified; and (3) an unacceptably high ICER of \$45,000/QALY – \$75,000/QALY and an underestimation of the financial cost. The minor resubmission sought to respecify the base case ICER by: (1) reducing the ex-manufacturer price by ■% from \$■■■■■ to \$■■■■■; and (2) adjusting the overall survival gain for the effect of cross-over using the rank preserving structural failure time (RPSFT) methodology. Table 1 provides a summary of the key differences between the July 2015 submission and the minor resubmission, including PBAC comments on the July 2015 submission.

Table 1: Key differences between the July 2015 submission and the November 2015 minor resubmission

	July 2015 major submission	November 2015 minor resubmission
Requested PBS listing for:	<p>Relapsed or refractory CLL and SLL, where the patient must have received at least one prior therapy, and be considered unsuitable for treatment or retreatment with a purine analogue.</p> <p>PBAC comment (5.07 PBAC Minutes July 2015, ibrutinib, paragraph 7.1): “...the PBAC considered that the patient population and clinical place of ibrutinib were not adequately defined...”.</p> <p>PBAC comment (5.07 PBAC Minutes July 2015, ibrutinib, paragraph 7.1): “The PBAC noted the main TGA approval is for second-line treatment of relapsed or refractory CLL and SLL, while the proposed restriction was further limited to patients for whom fludarabine is considered inappropriate. Usage of ibrutinib beyond restriction was a distinct possibility”.</p> <p>PBAC comment (5.07 PBAC Minutes July 2015, ibrutinib, paragraph 7.3): “The PBAC noted that the TGA approved indication for ibrutinib included first line treatment of patients with CLL with 17p deletion; and patients with mantle cell lymphoma who have received at least one prior therapy. The PBAC noted the clinical need for an effective treatment for these patient populations”.</p>	<p>As per the July 2015 submission. Additional criteria have been 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.</p>
Requested restriction	Authority required (STREAMLINED)	<p>Authority required (TELEPHONE)</p> <p>The Pre-Sub-Committee Response for the July 2015 submission (page 1) considered that a Telephone Authority would reduce the risk of ibrutinib being used in patients who were suitable for treatment with fludarabine.</p>
Clinical evidence	<p>RESONATE (main evidence)</p> <p><u>Interim analysis (median follow-up 9.4 months)</u> Median PFS Ibrutinib (N=195): not reached Ofatumumab (N=196): 8.1 months Hazard ratio: 0.22 [95% CI 0.15, 0.32]; p<0.001 Median OS Ibrutinib (N=195): not reached Ofatumumab (N=196): not reached Hazard ratio: 0.43 [95% CI: 0.24, 0.79]; p = 0.0049 ORR Ibrutinib (N=195): 62.6% Ofatumumab (N=196): 4.1% P<0.001</p> <p><u>Longer-term follow-up (median follow-up 16 months)</u> Median PFS</p>	<p>No change.</p> <p>A comparison of ibrutinib to idelalisib + ofatumumab using ofatumumab as the common comparator was provided in Attachment 3 of the minor resubmission. This information was not pivotal to the minor resubmission.</p> <p>The survival outcome adjusted using the RPSFT method for the median follow-up of 16 months was HR [REDACTED]</p>

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	July 2015 major submission	November 2015 minor resubmission
	<p>Ibrutinib (N=195): not reached Ofatumumab (N=196): 8.1 months Hazard ratio: 0.11 [(95% CI 0.07, 0.15); p<0.001] Median OS Ibrutinib (N=195): [REDACTED]</p>	
Main comparator	<p>Chlorambucil + rituximab</p> <p>PBAC comment (5.07 PBAC Minutes July 2015, ibrutinib, paragraph 7.5): “The PBAC considered that rituximab plus chlorambucil (Rit+Chl) was the appropriate comparator, for the proposed restriction. However, the choice of comparator in any future submission should be reassessed in regards to the clinical place where ibrutinib would be used. For example, if listing aligned with the TGA indication, fludarabine plus cyclophosphamide plus rituximab (FCR) may be the more appropriate comparator”.</p>	No change
Clinical claim	<p>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.</p> <p>PBAC comment (5.07 PBAC Minutes July 2015, ibrutinib, paragraph 7.7): “... the PBAC considered the claim of ibrutinib as superior in terms of comparative effectiveness compared to rituximab plus chlorambucil for patients with relapsed or refractory CLL/SLL was not supported in the submission. The PBAC considered that the comparative safety of ibrutinib and rituximab plus chlorambucil could not be determined from evidence provided in the submission...”.</p> <p>PBAC comment (5.07 PBAC Minutes July 2015, ibrutinib, paragraph 7.7): “The PBAC agreed with its ESC that there was insufficient evidence to support applying the treatment effect of ofatumumab monotherapy, in the pivotal RESONATE trial, as a proxy for the nominated comparator, Rit+Chl. In addition, the PBAC noted that the treatment benefit for ofatumumab in the RESONATE trial was lower than observed in other trials”.</p>	<p>No change</p> <p>The minor resubmission did not identify any new evidence to determine the magnitude of benefit of ibrutinib over rituximab given in combination with chlorambucil.</p>
Adjustment for cross-	Adjustment for cross-over, presenting RPSFT method provided in pre-PBAC response.	The minor resubmission examined four methodologies to adjust for cross-over.

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	July 2015 major submission	November 2015 minor resubmission
over	<p>PBAC comment (5.07 PBAC Minutes July 2015, ibrutinib, paragraph 7.14): “The Pre-PBAC considered that there was insufficient detail to verify the re-specified ICER of \$ [REDACTED] per QALY presented in the Pre-PBAC response which was based on an overall survival estimate which had been adjusted for patient cross over using RPSFTM”.</p>	<p>At the request for the PBAC Secretariat, additional information was provided by the sponsor on 24 September 2015 on its selected RPSFT methodology that was used to adjust overall survival to re-specify the base-case ICER.</p>
Special pricing arrangement	<p>A special pricing arrangement (SPA) was sought for the supply of ibrutinib for both CLL and SLL. The proposed published and effective prices (DPMQ) were \$ [REDACTED] and \$ [REDACTED], respectively.</p> <p>The effective ex-manufacturer price was \$ [REDACTED].</p>	<p>The minor resubmission offered a [REDACTED]% price reduction with a new effective ex-manufacturer price of \$ [REDACTED]. The proposed published and effective DPMQ prices were \$ [REDACTED] and \$ [REDACTED], respectively.</p> <p>All results of the incremental economic and financial analyses used the new price.</p>
Economic model	<p>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.</p> <p>PBAC comment (5.07 PBAC Minutes July 2015, ibrutinib, paragraph 7.12): “...the PBAC considered that there was an overestimation of the clinical benefit and the modelled time horizon. The PBAC noted the sponsor’s argument in its Pre-PBAC response that a time horizon of between 10 and 15 years, which has been previously accepted for the treatment of CLL, may not apply to ibrutinib as it has improved survival compared to existing therapy. The PBAC considered that the time horizon would depend on the prognosis of the eligible patient group(s). The PBAC noted the sponsor’s argument that a three-state economic model structure, excluding states for progressed disease, reflected the use of ibrutinib in a salvage setting. The PBAC considered that the simplified model structure was inconsistent with the sponsor’s proposed 20 year time horizon and the exclusion of further states for disease progression with and without treatment would not capture the additional benefits and costs which would occur over this time period. The PBAC considered that the economic model in any future submission should address the concerns of the ESC and that the model’s structure and time horizon should reflect</p>	<p>The structure of the economic model was unchanged.</p> <p>The following model inputs were revised:</p> <ul style="list-style-type: none"> • Discounted price for ibrutinib. • Time horizon truncated to 15 years (from 20 years). • [REDACTED]% 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. • Revised prices for the comparators (chlorambucil and rituximab). The private price for rituximab 100 mg has changed since last revised by the resubmission (\$ [REDACTED] August 2015 vs. \$ [REDACTED] October 2015). Correcting this had a negligible impact on the calculated ICER. • Revised mark-up, administration of IV infusion cost and dispensing fees. Assumptions for the public (35%) vs. private (65%) use of rituximab were unchanged. These assumptions were consistent with more recent figures for August 2014 to August 2015 with a proportional use of the public listing for rituximab (item 4615X) of 34.4%. Updating the National

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	July 2015 major submission	November 2015 minor resubmission
	the place in therapy, such as an earlier place in the treatment algorithm may be modelled with additional health states and a longer time horizon than in a salvage setting...".	efficient price for the average cost of public hospital activity ¹ (\$█████ vs. \$█████) and cost weights for non-admitted medical oncology treatment (0.0514 vs. 0.0614) reduced the weighted administration cost of IV infusion from \$170.62 (sourced from the Commentary on the July 2015 submission, Table D.4.1 page 58) to \$152.61.
Base case ICER	<p>Main submission: base case \$█████ per QALY, with overall survival based on the unadjusted ITT analysis</p> <p>Pre-PBAC response: respecified base case \$█████ per QALY, with overall survival adjusted for patients in the ofatumumab arm crossing-over to treatment with ibrutinib.</p> <p>PBAC comment (5.07 PBAC Minutes July 2015, ibrutinib, paragraph 7.13): "The PBAC considered that the base case ICER of \$█████ per QALY at the price proposed was unacceptably high. The PBAC noted that the incremental cost could be underestimated through using a trial-based assumption for the treatment time with ibrutinib (█████ months) which could be longer in practice".</p> <p>PBAC comment (5.07 PBAC Minutes July 2015, ibrutinib, paragraph 7.14): "The Pre-[sic] PBAC considered that there was insufficient detail to verify the re-specified ICER of \$█████ per QALY presented in the Pre-PBAC response which was based on an overall survival estimate which had been adjusted for patient cross over using RPSFTM".</p>	<p>\$█████ per QALY</p> <p>The respecified ICER was based on the following key assumptions and revisions:</p> <ul style="list-style-type: none"> • convergence applied at the end of follow-up (24 months) and run to 25 years adjusted for cross-over • the overall survival benefit was adjusted for cross-over using RPSFT methodology • a 15-year time horizon • the efficacy of ofatumumab was increased by █% to address the unknown efficacy of the appropriate comparator, rituximab + chlorambucil in the requested patient population • a █% price reduction for ibrutinib.
Financial estimates	<p>Incidence based approach.</p> <p>PBAC comment (5.07 PBAC Minutes July 2015, ibrutinib, paragraph 7.15): "...the PBAC agreed with its DUSC that the number of patients was underestimated in the submission and there was the potential for use outside the proposed restriction in patients suitable for purine analogues and as a first-line therapy. The PBAC considered that the financial estimates would need to be amended in line with a revised restriction...".</p>	The financial estimates prepared by the DUSC for the July 2015 submission were accepted.
Risk sharing arrangement		The DUSC estimates were used to calculate caps for the proposed risk

¹ The derivation of the efficient price excludes: (1) Section 100 funding for Highly Specialised Drugs, Efficient Funding of Chemotherapy and trastuzumab for early stage breast cancer; (2) PBS Access Program funding from the Pharmaceutical Reform Agreements; and (3) Commonwealth funding to the National Blood Authority. Source: Independent Hospital Pricing Authority National Efficient Price Determination 2015-16, page 8.

	July 2015 major submission	November 2015 minor resubmission
		<p>sharing arrangement for the minor resubmission. The proposed caps were based upon the assumption that all eligible patients as proposed by the DUSC's estimates would access ibrutinib.</p> <p>The sponsor acknowledged the potential for leakage to other populations (purine suitable, first-line CLL with 17p deletion and mantle cell lymphoma) but argues that a punitive rebate above the cap is inappropriate as ibrutinib would have value for these populations. An additional rebate of █% for all Commonwealth payments exceeding the subsidisation caps is proposed.</p>

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

4 Clinical place for the proposed therapy

- 4.1 The July 2015 submission proposed that ibrutinib was a second-line therapy in patients with CLL/SLL deemed unfit for further treatment with a purine analogue (i.e. fludarabine). This was based on the eligible population from the RESONATE trial.
- 4.2 The clinical place for ibrutinib proposed in the July 2015 submission was unchanged in this minor resubmission. However, the TGA-approved indication for ibrutinib does not restrict use to patients unsuitable for re-treatment with a purine analogue. The TGA indication also recommends use in first-line patients with CLL with 17p deletion and mantle cell lymphoma.
- 4.3 The minor resubmission noted that studies are in progress for ibrutinib in other populations. A summary of the clinical development program for ibrutinib was provided in Attachment 1 of the minor resubmission.

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 minor resubmission. 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 resubmission.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (12) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ibrutinib including fewer side effects and improvements in quality of life associated with less frequent hospital visits for treatments when compared to patients treated with chemotherapy.

Clinical trials

6.3 No new clinical trials were presented in the minor resubmission.

Comparative effectiveness

6.4 The trial results remain unchanged from the previous major submission considered in July 2015. A supplementary comparison of ibrutinib to idelalisib plus ofatumumab using ofatumumab as the common comparator was provided in Attachment 3 of the minor resubmission.

Comparative harms

6.5 As above for comparative effectiveness.

Clinical claim

6.6 The minor resubmission claimed superior comparative effectiveness and a different but acceptable safety and tolerability profile compared with ofatumumab monotherapy (and by extension chlorambucil plus rituximab). See Table 1 for PBAC comments on the July 2015 submission.

Economic analysis

6.7 The July 2015 submission presented a cost-effectiveness analysis of ibrutinib against ofatumumab monotherapy (considered by the sponsor to be equivalent to the nominated comparator, chlorambucil plus rituximab).

6.8 The PBAC did not accept that ofatumumab monotherapy was equivalent to the nominated comparator (5.07 PBAC Minutes July 2015 paragraph 7.5). The minor resubmission noted that there is an absence of head to head trial data or trials with a common comparator to inform an indirect comparison to determine the incremental benefit of ibrutinib over chlorambucil plus rituximab. In acknowledgement of the uncertainty around the size of the comparative clinical benefit of ibrutinib versus the comparator (chlorambucil plus rituximab), the sponsor incorporated a ■% reduction in the benefit of ofatumumab in the economic evaluation. This adjustment was

undertaken to recognise that the treatment effect of ofatumumab monotherapy is likely to be less than rituximab and chlorambucil (or ofatumumab and chlorambucil).

- 6.9 The minor resubmission did not alter the economic model structure from July 2015, but respecified the base case ICER to \$45,000/QALY – \$75,000/QALY by: (1) reducing the ex-manufacturer price by █% from \$█ to \$█; (2) adjusting the overall survival gain to account for 61% of patients randomised to ofatumumab crossing over to treatment with ibrutinib using the rank preserving structural failure time (RPSFT) methodology; (3) reducing the time horizon to 15 years; and (4) a █% reduction in the hazard arm (progression and death) to address the uncertainty in the magnitude of the treatment effect of ofatumumab versus rituximab plus chlorambucil. The calculation of the respecified base case ICER was independently verified. The following table compares the impact of adjusting the overall survival estimates for cross-over on the economic analysis.

Table 2: Summary of modelled economic analysis over a 15-year time horizon comparing overall survival adjusted and unadjusted for patient cross-over

Parameter	Based on ITT analysis	Based on RPSFT-adjusted analysis
LYG	█	█
QALY	█	█
Incremental cost ^b	█	█
ICER per QALY	\$ █	\$ █

Statistical adjustment of trial results

- 6.10 The minor resubmission explored four potential methods to adjust overall survival for cross-over, including: (1) RPSFT; (2) inverse probability of censoring weights (IPCW); (3) the iterative parameter estimation (IPE) algorithm; and (4) the “two-stage” method. The RPSFT method was selected by the sponsor as the most reliable based on the following main arguments: IPE is conceptually similar to RPSFT, but involves more uncertainty through having an additional assumption about the parametric form of the function to describe time-to-event data; there was inadequate data on progression of patients in the ofatumumab arm who do not cross over to inform the two-stage method; predictions from the IPCW method were considered as unstable as this method is limited by the requirement to measure all time-dependent and time-independent variables than can predict switching which cannot be fully verified. The cross-over adjusted result for IPCW calculated by the minor resubmission (█) was more favourable to ibrutinib than that derived using the RPSFT method (█, █). The calculation of the RPSFT-adjusted overall survival estimate derived by the minor resubmission was independently verified.
- 6.11 A range of other factors have been identified by the PBAC as influential in its review of statistical adjustment methods in the context of cross-over, including:
- the degree of cross-over; in this instance 61% of patients from the ofatumumab arm of the trial crossed over to ibrutinib;
 - whether there is a sufficient number of patients to inform the adjustment methods. Of the 196 patients randomised to ofatumumab, 120 patients (61.2%) crossed over to receive ibrutinib (noting that the proportion of these who crossed

over following a progression event against the proportion who crossed over following a protocol change affecting all trial participants at a single point in time was not clear);

- the extent to which cross-over was triggered by progression events, and if so, how these were assessed using evaluation of symptomatic or asymptomatic events;
- the duration of post-progression survival relative to other cancers and to progression-free survival;
- the ITT results did show a statistically significant improvement in OS [HR █████ (95%CI: █████); p=████] however the magnitude of this benefit was smaller than for the RPSFT-adjusted results [HR █████ (95% CI: █████), p=████]; and
- whether there is any corroborating evidence provided to support the use of progression-free survival as a surrogate measure for overall survival in this specific condition.

6.12 At the request of the PBAC Secretariat, further information was provided by the sponsor to verify assumptions and the approach that was used for its RPSFT analysis presented in the minor resubmission. Main areas addressed in this response included: (1) a description of the stratified Cox model that was used to derive the adjusted overall survival estimate; (2) whether the assumption of a common treatment effect, which underpins the RPSFT method, was met; (3) quantification of the treatment multiplier effect for ibrutinib derived by the RPSFT model and whether this was clinically plausible; and (4) an assessment of whether there was potential bias in cross-over events from investigator rather than independent review of progression events.

6.13 The RPSFT derives a treatment effect multiplier, also referred to as an acceleration factor, of the additional overall survival benefit that is gained from an active treatment over a comparator. Using a Cox proportional hazards model including the treatment (ibrutinib or ofatumumab) and adjusting for baseline prognostic and risk factors as per the subgroup analyses presented in the main Byrd et al. (2014) publication of the RESONATE trial, the minor resubmission calculated a treatment effect multiplier for ibrutinib of █████, i.e. the counterfactual survival time for patients had they not crossed-over to receive ibrutinib was calculated as: counterfactual survival time = time on ofatumumab + (time on ibrutinib x █████). The sponsor considered that the modelled acceleration factor was plausible based on two assessments: (1) comparing Kaplan-Meier estimates of the probability of survival at 12 and 18 months between ibrutinib and ofatumumab, the same probability of survival for patients in the ofatumumab arm was shorter by █% and █%, respectively, when compared to ibrutinib; and (2) censoring all patients who were alive at the date of protocol amendment to allow cross-over gave a similar survival estimate as the RPSFT-adjusted estimate (HR █████ vs. HR █████, respectively). However, the assumption that all patients who crossed over to ibrutinib would have had only █% of the survival time while on ibrutinib had they remained on ofatumumab cannot be tested.

6.14 A stratified Cox proportional hazards model was applied to the counterfactual survival times resulting from the RPSFT model for the ofatumumab patients who crossed-over to receive ibrutinib. As per the stratification used for randomisation to the RESONATE trial, the model was stratified by two factors: refractory to purine

analogue and anti-CD20 and 17p deletion status. The same stratified Cox model was used for the ITT analysis.

- 6.15 The “common treatment effect” assumption of the RPSFT model requires that patients who cross-over receive the same treatment benefit from ibrutinib (measured from the time from which ibrutinib is commenced) as those patients who were initially randomised to ibrutinib. The minor resubmission used a non-inferential approach to test the validity of this assumption. The minor resubmission presented Kaplan-Meier estimates of patients randomised to ibrutinib compared to those who crossed over to ibrutinib. The overall survival outcomes appeared similar for both groups, however the analysis was limited by the relatively short follow-up period and heavy censoring of the time to death for the cross-over patient group. Similar cumulative hazards of death between patients randomised to ibrutinib vs. ofatumumab patients who crossed-over to ibrutinib were presented in Nelson-Aalen plots. The sponsor considered that the Kaplan-Meier and Nelson-Aalen plots demonstrated that the overall survival outcomes in the randomised and cross-over groups were similar, and as such, an assumption of a common treatment effect was reasonable. The sponsor further stated that there was also no evidence that treatment resistance to ibrutinib could develop from prior use of ofatumumab and that these agents have different modes of action.
- 6.16 The PBAC did not accept the survival results adjusted using the RPSFT method. The PBAC considered that the common treatment assumption was not met because patients who crossed over to ibrutinib had a different survival outcome compared to patients who were originally randomised to ibrutinib. The PBAC also considered that, because ofatumumab is an active treatment, there are difficulties interpreting these results in this resubmission because this method relies on estimating effects during “on treatment” and “off treatment” time periods. Since the control patients were receiving an active treatment then supportive care on treatment failure – the “off treatment” is more than one type of treatment.

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

- 6.17 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 6 months, using the listed prices for chlorambucil and rituximab as at October 2015. The comparator cost was not adjusted by the dose intensity of [REDACTED]% for ibrutinib, as was done for the July 2015 submission. The evaluation of the July 2015 submission considered that this adjustment for oral therapy may not apply to rituximab which is given intravenously.
- 6.18 In the July 2015 PBAC minutes, the drug cost per patient per course was \$ [REDACTED].

Estimated PBS usage & financial implications

- 6.19 The minor resubmission presented updated financial estimates based on the methodology used by DUSC to revise the estimates for the July 2015 submission. The calculation of the revised financial estimates was independently verified. The minor resubmission estimated a net cost to the PBS of \$ [REDACTED] 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. This is summarised in the table below as well as the expected patient and pack numbers. Costs were based on the revised effective DPMQ of \$[REDACTED].

Table 3: Estimated utilisation of ibrutinib

Year	2016	2017	2018	2019	2020
Number of patients	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of packs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost (packs x effective DPMQ)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Patient copayments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS (at the effective DPMQ)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Minor resubmission, Table 1.9 page 27 and the revised Section E financial estimates model, sheet 'Prevalence'.

Financial Management – Risk Sharing Arrangements

6.20 The resubmission stated that main areas of uncertainty that needed to be addressed in a risk sharing arrangement for ibrutinib for the treatment of relapsed or refractory CLL and SLL were:

- uncertainty in the size of cost-effective population
- uncertainty in the cost effectiveness outside the cost effective population.

6.21 The resubmission proposed:

- [REDACTED] ([REDACTED])
- a subsidisation caps based upon the assumption that all eligible patients as proposed by the DUSC's estimates would access ibrutinib (see table below)
- an additional rebate ([REDACTED]%) above the subsidisation caps to address uncertainty in the cost effectiveness outside the intended population (first line treatment of patients with CLL with 17p deletion; and patients with mantle cell lymphoma (TGA approved) and other B cell malignancies, such as DLBCL, non-Hodgkin's lymphoma and Waldenstrom's disease (currently being investigated)).

Table 4: Updated financial estimates based on DUSC methodology and subsidisation caps

Year	2016	2017	2018	2019	2020
Net cost to PBS/RPBS (at the effective DPMQ)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Subsidisation cap (assumption: all eligible patients access ibrutinib)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Minor resubmission, Table 1.9 page 27, the revised Section E financial estimates model, sheet 'Prevalence' and Section 8.2, page 28.

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation to list ibrutinib as an Authority Required (TELEPHONE) listing for the second-line treatment of chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL).
- 7.2 The PBAC noted that the requested PBS restriction, for CLL and SLL patients unfit for further treatment with a purine analogue, was narrower than the TGA-registered indication for ibrutinib. The PBAC recognised the attempt (through telephone authority) to confine the use of ibrutinib to a highly selected group of patients. However the PBAC considered that this measure would not mitigate the high risk of leakage outside the proposed restriction to the other registered indications, including as first-line treatment for patients with 17 p deletion, second-line CLL and SLL patients suitable for treatment with fludarabine and patients with mantle cell lymphoma.
- 7.3 The PBAC considered that ibrutinib is an effective treatment and a meaningful clinical advance for the group of patients as represented in the RESONATE trial. However, the PBAC considered that the incremental treatment effect of ibrutinib observed in this trial was overestimated as the trial comparator, ofatumumab monotherapy, is inferior to agents used in clinical practice in Australia.
- 7.4 The PBAC did not accept the survival results adjusted for cross-over using the RPSFT method. The PBAC considered that, because ofatumumab is an active treatment, there are difficulties interpreting these results in this resubmission because this method relies on estimating effects during "on treatment" and "off treatment" time periods. The PBAC considered that patients crossing over to ibrutinib after treatment with ofatumumab would not have the same survival outcomes as those patients randomised to ibrutinib. The PBAC considered that the overall survival results for the ITT population were more appropriate as the basis for the economic evaluation, noting that this was still a likely overestimate as ofatumumab is inferior to alternative agents used in practice.
- 7.5 The PBAC did not consider that ibrutinib was cost-effective at the price proposed in the resubmission. The PBAC recommended that the base case of the economic evaluation should be revised to obtain an ICER of \$45,000/QALY – \$75,000/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 minor resubmission, 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. The PBAC considered that a major resubmission would be required should the sponsor not wish to accept the proposed re-specifications of the base case of the modelled economic evaluation.

- 7.6 The PBAC noted that there was a high risk that ibrutinib would be used in broad population including patients with a good prognosis. For this reason the duration of therapy was a source of uncertainty in the financial estimates. The PBAC recommended that a risk-sharing arrangement would be required consisting of a cap on expenditure with a ■% rebate for budget certainty. The PBAC recommended that the risk-sharing arrangement should be based on the DUSC estimates of the patient population representative of those included in the RESONATE trial

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

The sponsor had no comment.