

7.04 IBRUTINIB, Capsule 140 mg, Imbruvica[®], Janssen-Cilag Pty Ltd.

1 Purpose of Application

- 1.1 The resubmission requested an Authority Required listing for ibrutinib for first-line treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) patients with deletion 17p (del17p), to be identified by fluorescence in situ hybridisation (FISH). There is a concurrent minor submission to MSAC to consider the FISH test for use in first-line CLL/SLL. A listing for ibrutinib first-line treatment (in the overall CLL/SLL population) was considered by the PBAC in November 2017 with a minor submission considered in March 2018.
- 1.2 Listing was requested on the basis of a cost utility analysis versus obinutuzumab + chlorambucil (obi+chl). The key components of the clinical issue addressed by the resubmission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Patients with untreated CLL or SLL who have one or more 17p chromosomal deletions demonstrated by FISH.
Intervention	Ibrutinib administered orally 420mg/day (3x140mg capsules) until disease progression or ibrutinib is no longer tolerated.
Comparator	Chemoimmunotherapy: obinutuzumab + chlorambucil. Obinutuzumab administered intravenously on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1, and 1000 mg on Day 1 of each cycle up to 6 cycles; Chlorambucil ^a given orally at a dose of 0.5 mg/kg body weight up to a total of 6 cycles on Days 1 and 15 of each cycle. Maximum treatment is 6 cycles.
Outcomes	PFS, OS, ORR, TTNT, AEs.
Clinical claim	Ibrutinib is superior compared with obi+chl as assessed by a statistically and clinically significant improvement in PFS. Ibrutinib has a numerically similar incidence but different profile of adverse events (AEs) compared to obi+chl, over the first 9 months ^b of treatment. For treatment beyond 9 months ibrutinib has an inferior safety profile.

^a The resubmission had 'chlorambucil 10mg/m²/day for 7 days of each 28 day cycle' in Table 1.1 with the dose subsequently stated as 0.5 mg/kg body weight on days 1 and 15 of each cycle. Hence, the dose for chlorambucil is amended in the table above.

^b The resubmission had '6 months' in its Table 1.1 with this claim, however Section 2.17.2 of the resubmission used 9 months, and the presentation of AEs in the ILLUMINATE trial were based on 9 months and the overall trial. So the time period has been altered to 9 months in the table above.

AEs=adverse events; CLL=chronic lymphocytic leukaemia; FISH= fluorescence in situ hybridisation; PFS=progression-free survival; ORR=overall response rate; OS=overall survival; TTNT=time to next treatment; SLL=small lymphocytic lymphoma

Source: Table 1.1, p6 of Section 1.1.1, Table 3.9, p81 of Section 3.6.1 of the resubmission.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

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	Effective: \$ [REDACTED] Published: \$8,784.33	Imbruvica® Janssen-Cilag Pty Ltd

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 /S small lymphocytic lymphoma (SLL)
Treatment phase:	Initial treatment
Restriction Level:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
Clinical criteria:	The patient must require treatment for chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) AND The condition must be previously untreated, AND Patient must have a WHO performance status of 0, 1 or 2, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND The Patient must show evidence of one or more 17p chromosomal deletions demonstrated by fluorescence in situ hybridisation (FISH). The presence of 17p deletion without any signs of active disease is not an indication for treatment.

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Prescriber Instructions:	<p>PBS-subsidised ibrutinib for the treatment of CLL/SLL can only be used once in a patient's lifetime. If a patient has received PBS-subsidised ibrutinib for their first line of treatment, they will not be eligible to access PBS-subsidised ibrutinib for subsequent lines of therapy.</p> <p>A patient may only qualify for PBS subsidised initiation treatment once in a lifetime under:</p> <ol style="list-style-type: none"> i. the previously untreated CLL/SLL initial treatment restriction; ii. the relapsed or refractory CLL/SLL initial treatment restriction. <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
Administrative Advice:	<p>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</p>

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IBRUTINIB Capsule 140 mg, 90	1	5	Effective: \$ [REDACTED] Published: \$8,784.33	Imbruvica® Janssen-Cilag Pty Ltd

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:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition, been issued with an authority prescription for this drug for this condition</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition.</p>

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Prescriber Instructions:	<p>PBS-subsidised ibrutinib for the treatment of CLL/SLL can only be used once in a patient's lifetime. If a patient has previously received PBS-subsidised ibrutinib for their first line of treatment, they will not be eligible to access PBS-subsidised ibrutinib for subsequent lines of therapy.</p> <p><i>Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i></p>
Administrative Advice:	<p><i>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.</i></p>

- 2.2 The requested effective DPMQ for ibrutinib will increase to \$ [REDACTED] with the July 2019 increases in administration, handling and infrastructure (AHI) fees and dispensing fees. The price has not been updated in the economic model or financial estimates.
- 2.3 The ESC noted that the proposed published and effective prices [REDACTED].
- 2.4 The resubmission requested a General Schedule Authority Required (Written) listing for ibrutinib for initial treatment, and an Authority Required (Telephone) listing for continuing treatment. Separate listings is appropriate given demonstration of del17p is only required for initiation. The resubmission stated that an Authority Required (Written) initial listing was requested to ensure that treatment is limited to the subgroup of patients with del17p. The PBAC considered that an Authority Required (Telephone) listing was appropriate for both initial and continuing treatment.
- 2.5 The requested restriction limits ibrutinib for the treatment of CLL/SLL to once in a patient's lifetime, and thus ibrutinib treatment for CLL/SLL patients with del17p is moved to earlier in the treatment algorithm. The ESC noted that del17p and TP53 variants are the only validated predictive markers in CLL.¹ The ESC noted that while TP53 variants often coincide with del17p (80-90%), sole TP53 variants can also occur in the absence of del17p.¹ Aberrations in TP53 are detected by gene sequencing with the ESC noting that FISH may miss more than 30% of all TP53 variants.¹ The ESC considered that there was a clinical need for effective treatments in patients with aberrations in TP53 who are del17p negative. The ESC noted that a submission to extend genome-wide microarray testing (MBS item 73292), which can be used to identify both del17p and TP53 variants, to allow use in CLL and multiple myeloma would be considered by MSAC in November 2019.

¹ Kuss BJ & Tam CS. Management of high risk chronic lymphocytic leukaemia (CLL) patients in Australia. Internal Medicine Journal, 2017; 47:5-10

- 2.6 The ESC considered that, depending on the outcome of the MSAC recommendation regarding MBS item 73292, some patients may have del17p detected via genome-wide microarray testing rather than FISH. As such, the ESC advised it may be appropriate to remove specification of the del17p testing method from the restriction.
- 2.7 In March 2018 the PBAC considered that a definition of progressive disease during or after therapy characterised by at least one International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) criteria, as per the RESONATE-2 trial protocol, was appropriate (paragraphs 7.5 and 12.16, March 2018 Public Summary Document (PSD)). The requested restriction does not include a definition of progressive disease.
- 2.8 The resubmission noted the proposed continuing restriction includes the criterion that the ‘patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition’. The resubmission stated that the wording of the criterion was consistent with the ibrutinib R/R CLL/SLL and R/R mantle cell lymphoma (MCL) restrictions where treatment must be ceased upon disease progression and where a detailed definition of progressive disease is not provided.
- 2.9 The Pre-Sub-Committee Response (PSCR) stated that the sponsor has recently received several requests for access to ibrutinib for previously untreated del17p patients. The PSCR indicated that the sponsor may initiate an access program for these patients who will then be grandfathered across to the PBS listing.

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

3 Background

Registration status

- 3.1 Ibrutinib was approved by the TGA on 20 April 2015 and the registration was extended and modified in November 2016. The current TGA indications are for: patients with MCL who have received at least one prior therapy; adult patients with CLL/SLL who have received at least one prior therapy, or adult patients with previously untreated CLL/SLL; patients with CLL/SLL with del17p; adult patients with Waldenstrom’s macroglobulinemia (WM) who have received at least one prior therapy, or in first-line treatment for patients unsuitable for combination chemo-immunotherapy.

Previous PBAC consideration

3.2 Following is a summary of the key concerns identified in the November 2017 and March 2018 submissions and the response taken by the resubmission.

Table 2: Summary of outstanding matters of concern

Component	Matter of concern	How the resubmission addresses it
	<p>March 2018 Paragraph 12.16: The PBAC considered that the proposed restriction should include a definition of progressive disease per the RESONATE-2 trial; restrict ibrutinib use to once in a patient's lifetime and include separate restrictions for initial and continuing treatment</p>	<p>The requested restriction does not include a definition of progressive disease. The requested restriction specifies that if a patient has previously used ibrutinib for first-line treatment they will not be able to access PBS-subsidised ibrutinib for subsequent lines of therapy. Separate restrictions for initial and continuing therapy are requested.</p>
Clinical evidence	<p>Nov 2017: Paragraph 7.4: The PBAC did not accept the blended comparator of ritux+chl, obi+chl and ofa+chl. Either non-inferiority to obi+chl and/or superiority of ibrutinib versus ritux+chl would be the most relevant comparisons. Nov 2017: Paragraph 7.8: The PBAC considered the claim of non-inferior safety was supported by the indirect comparisons, but reiterated its concerns that ibrutinib is associated with an increased risk of clinically significant atrial fibrillation. The PBAC also noted the increased risk of bleeding with ibrutinib and was concerned the incidence of bleeding in the proposed PBS population would be higher than in RESONATE-2, where patients at high risk of bleeding had been excluded.</p>	<p>The resubmission claimed superiority of ibrutinib compared to obi+chl, which it identified as the most commonly used chemoimmunotherapy. Incidence and cost of atrial fibrillation were included in the economic model. The resubmission claimed the risk of bleeding observed in the ILLUMINATE trial was consistent with the known safety profile of ibrutinib. The ILLUMINATE trial excluded patients with known bleeding disorders.</p>
Economic evaluation	<p>Nov 2017: Paragraph 7.9: The PBAC considered the economic model unreliable and the resulting ICER to be high and optimistic, given the extrapolation of immature clinical trial data to a 20-year time horizon for patients >70 years of age who will likely have comorbidities, and the assumed high magnitude of clinical benefit over obi+chl.....the option of CUA over ritux+chl with a 10-year time horizon could be used to establish a cost-effective price, as was accepted for obi+chl in March 2015.</p>	<p>A 10 year time horizon was used in the March 2018 model and in the current model. The March 2018 model used ritux+chl as a comparator, however the comparator was changed to obi+chl in the current model.</p>
Financial estimates	<p>March 2018 Paragraph 12.21: The PBAC considered the financial estimates were substantially overestimated because the patient numbers, uptake rate and compliance rate were overestimated and/or uncertain.</p>	<p>Patient numbers decreased considerably given the requested restriction to patients with del17p. However the proportion of del17p patients assumed (■%) may not be accurate.</p>

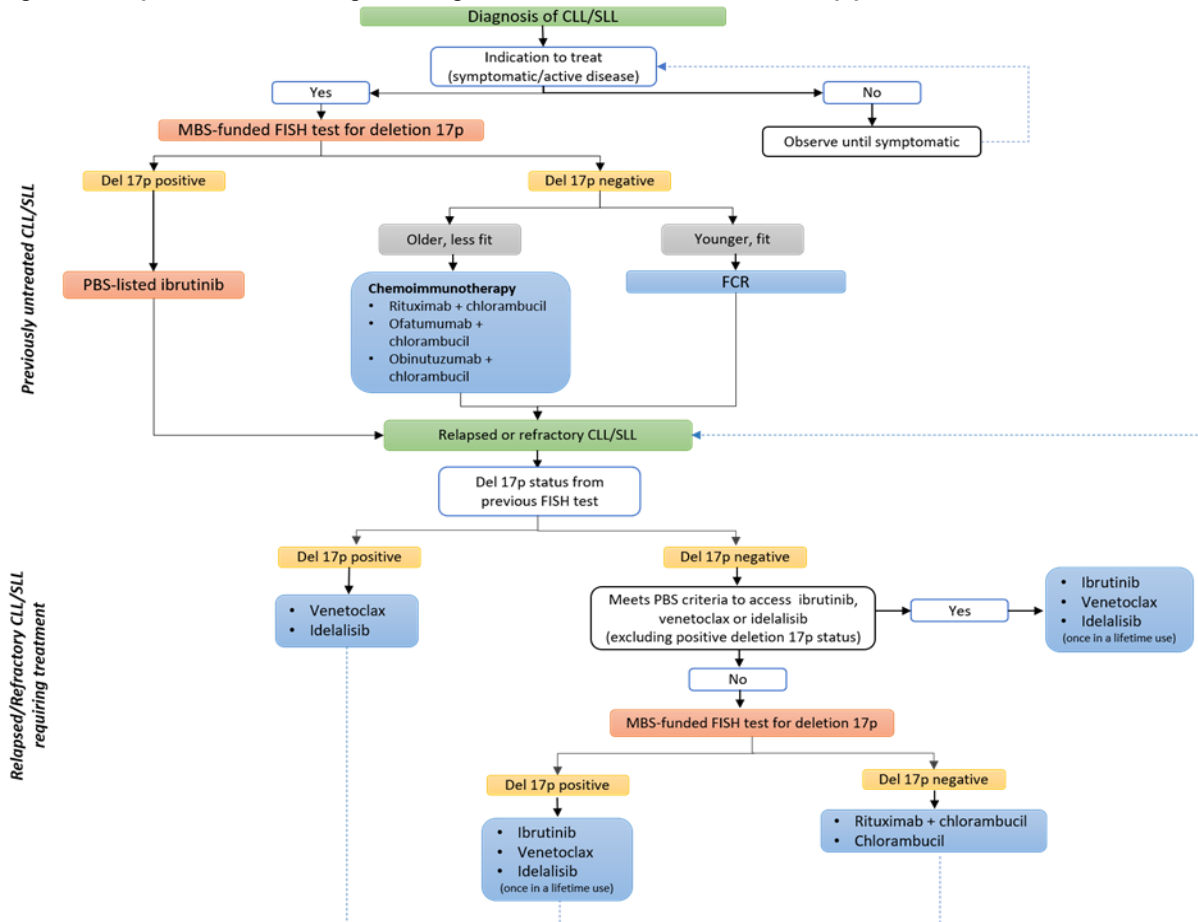
chl=chlorambucil; CLL=chronic lymphocytic leukaemia; ibr=ibrutinib; obi=obinutuzumab; ofa=ofatumumab; ritux=rituximab; R/R=relapsed/refractory; RSA=risk share arrangement; SLL=small lymphocytic lymphoma
Source: November 2017 PSD; March 2018 PSD.

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

4 Population and disease

- 4.1 CLL/SLL is an incurable disease with the current conventional therapies, and the natural history of the disease involves repeated periods of relapse and remission. CLL/SLL is most commonly a disease of the elderly and many patients with CLL/SLL will have major and/or multiple comorbidities.
- 4.2 Treatment is only initiated in CLL/SLL patients when they show evidence of progressive or symptomatic/active disease as defined by iwCLL guidelines. The clinical sequelae of CLL/SLL can have substantial negative impacts on patient quality of life (QoL) as a result of disease-related symptoms, treatment-related adverse events (AEs) and the psychological, socioeconomic and functional effects of living with the disease.
- 4.3 Currently, chemoimmunotherapy is the only available reimbursed first-line option for CLL/SLL in Australia. For young and fit patients with CLL/SLL, the standard first-line treatment is fludarabine, cyclophosphamide, and rituximab (FCR). Patients with comorbidities, those at an older age or del17p positive are considered unsuitable for FCR and the standard options for these patients include chlorambucil plus an anti-CD20 antibody such as obinutuzumab, ofatumumab, or rituximab (obi+chl, ofa+chl, and ritux+chl). Ofatumumab was de-listed from the PBS in September 2019.
- 4.4 At its November 2017 and March 2018 meetings, the PBAC considered there was no urgent clinical need for first-line ibrutinib for most patients, noting the current availability of other effective first-line therapies (paragraph 7.2, November 2017 PSD, paragraph 12.15, March 2018 PSD). In response, the resubmission proposed first-line use in a subgroup of patients for whom the currently available therapies are known to be ineffective, specifically patients with del17p.
- 4.5 The proposed clinical management algorithm with the availability of ibrutinib as a first-line treatment for del17p patients is presented in Figure 1.

Figure 1: Proposed clinical management algorithm with first-line ibrutinib for 17p patients



Note: PBS-subsidised treatment with ibrutinib in the relapsed/refractory setting is not allowed if the patient has previously received treatment with ibrutinib.

Source: Figure 1.6, p33 of Section 1.2.1.2 of the resubmission.

4.6 CLL/SLL patients with del17p have substantially inferior prognosis with shorter survival and marked resistance to the PBS-listed first-line regimens (FCR, obi+chl, ofa+chl, and ritux+chl). The table below provides a comparison of outcomes observed for del17p patients and ITT patients in trials identified by the resubmission, together with the outcomes for obi+chl from the ILLUMINATE trial.

Table 3: Outcomes for del17p patients compared to ITT population patients

	del17p	ITT population
Hallek (2010) – FCR arm		
Complete response (CR)	1/22 (5%)	180/408 (44%) ^a
Median PFS	11.3 months	51.8 months
Fischer (2012) – benda+ritux		
Complete response (CR)	0/8 (0%)	27/117 (23%)
Median PFS	7.9 months	33.8 months
Stilgenbauer (2014) – FCR arm		
Median PFS	15.4 months	59 months
ILLUMINATE – obi+chl arm		
Median PFS	█ months ^b	19.0 months

^a This total includes del17p patients, as reported by the publication. If del17p patients are removed, the proportion becomes 46%.

^b The resubmission reported median PFS in the obi+chl arm as ‘approximately █ months’.

benda=bendamustine; chl=chlorambucil; FC=fludarabine and cyclophosphamide; FCR=fludarabine, cyclophosphamide, and rituximab; obi=obinutuzumab; PFS=progression-free survival; ritux=rituximab;

Source: Section 1.1, p2-4 of the resubmission; Stilgenbauer (2014); Table 2.18, p87 of Section 2.5.1.1; Section 2.6.1, p123-124 of the resubmission.

- 4.7 Based on the above, the resubmission concluded there is a significant unmet clinical need for effective first-line treatments in del17p patients given they have a poor prognosis and poor response to the chemoimmunotherapy agents currently used to treat CLL/SLL. The ESC agreed with the resubmission that there was an unmet clinical need for effective first-line treatments in del17p patients. The ESC also considered there to be an unmet clinical need for effective first-line treatments for patients with aberrations in TP53 who are del17p negative. The pre-PBAC response agreed with the ESC that there is an unmet need for more effective treatments for patients with TP53 mutation.
- 4.8 Current international guidelines from the iwCLL (2018), National Comprehensive Cancer Network (NCCN 2018), and the European Society for Medical Oncology (ESMO 2015) recommend testing for del17p before treatment is commenced, to determine the most appropriate management strategy. The ESC noted that these guidelines also recommended testing for TP53 mutation before treatment is commenced and that ibrutinib was recommended for first-line use in patients with del17p or TP53 mutation.

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

5 Comparator

- 5.1 The resubmission nominated chemoimmunotherapy, of which it identified obi+chl as the most commonly used treatment in Australia, as the main comparator. This was changed from the March 2018 resubmission, which used ritux+chl as the main comparator, and the November 2017 submission which used a blended comparator (obi+chl; ofa+chl; ritux+chl). The ESC considered the nominated comparator was appropriate.

- 5.2 The resubmission noted that FCR is not a relevant comparator as del17p patients respond poorly and progress rapidly on this regimen, and hence patients with del17p are considered unsuitable for FCR. The ESC agreed with the resubmission that FCR was not a relevant comparator.

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.

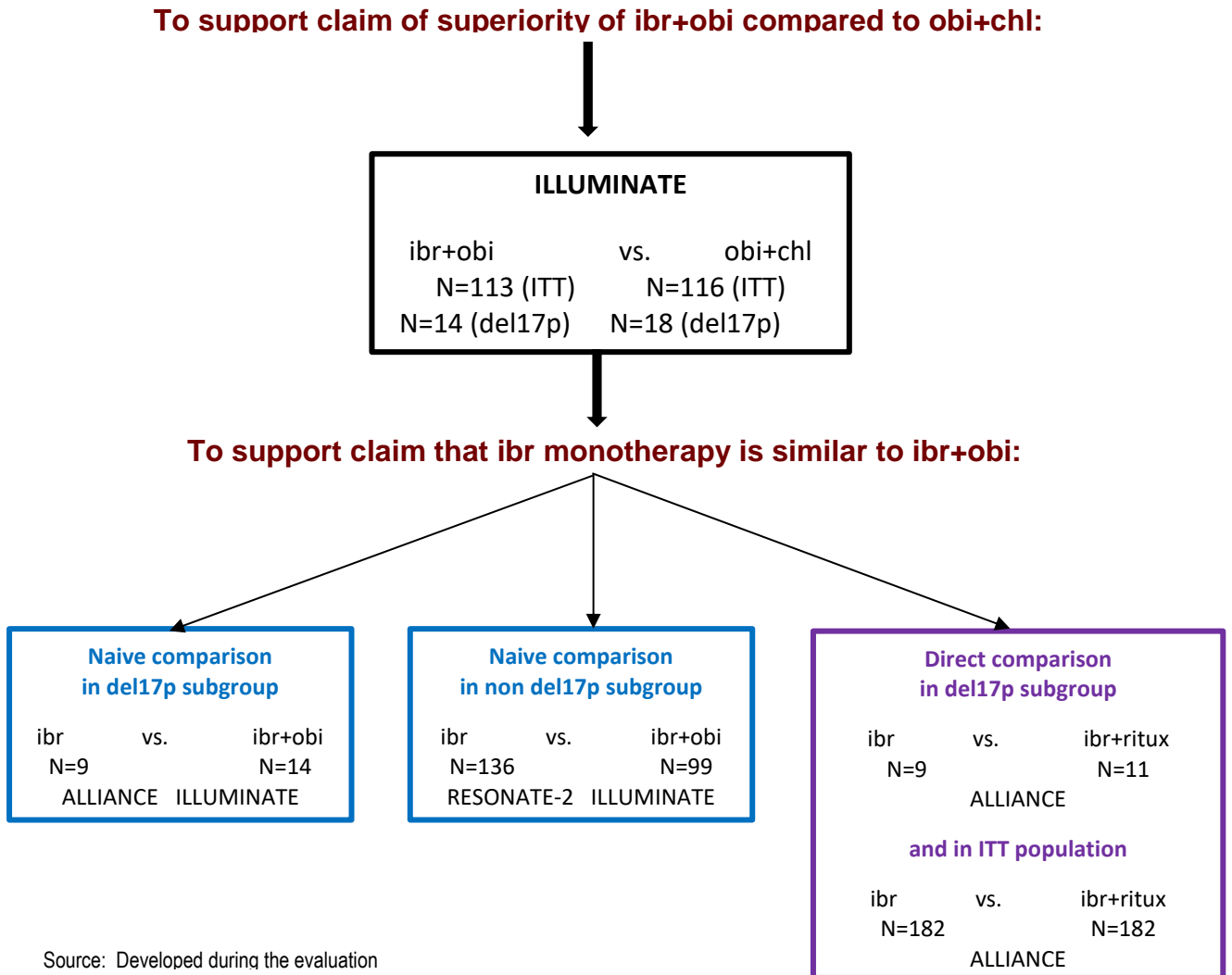
Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (8), health care professionals (3) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described concerns regarding the limited effectiveness and significant toxicity associated with currently available first-line treatment options for del17p (or mutation of TP53) CLL/SLL patients. The comments also described a range of benefits of treatment with ibrutinib including improved quality of life with side effects reported to be manageable.

Clinical trials

- 6.3 The resubmission was based on one head-to-head trial comparing ibr+obi and obi+chl (ILLUMINATE), to demonstrate superiority of an ibrutinib-containing regimen over obi+chl, along with two additional trials, one comparing ibrutinib to ibr+ritux and benda+ritux (ALLIANCE) and the second comparing ibrutinib to chlorambucil (RESONATE-2), to support the claim that ibrutinib monotherapy is similar to ibr+obi. The RESONATE-2 trial, which excluded del17p patients, was presented in the previous PBAC submissions requesting listing of ibrutinib for first-line treatment of CLL/SLL.
- 6.4 A diagrammatic representation of the clinical evidence included in the resubmission is presented in the figure below.

Figure 2: Evidence base presented in the resubmission



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6.5 Citation details of the trials presented in the resubmission are provided in Table 4.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ILLUMINATE	A multi-center study of ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in patients with treatment naïve CLL or SLL. Moreno C, Greil R, Demirkan F, Tedeschi A et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (ILLUMINATE): a multicentre, randomised, open-label phase 3 trial.	July 2018 <i>Lancet Oncol</i> 2019; 20(1): 43-56
ALLIANCE	Woyach JA, Ruppert AS et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL.	<i>NEJM</i> 2018; 379: 2517-2528.
RESONATE-2	A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 versus Chlorambucil in Patients 65 Years or Older with Treatment-naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma Burger JA, Tedeschi A, Barr PM et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. Barr P, Robak T et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2.	August 2015 <i>NEJM</i> 2015; 373:2425-2437 <i>Haematologica</i> 2018; 103(9):1502-1510.

Source: Table 2.4, p52 and Table 2.53, p1 of Section 2.11.3 of the resubmission.

6.6 Table 5 provides a summary of the included trials. For the ALLIANCE and RESONATE-2 trials the resubmission only provided information for the trial arms used in the resubmission's comparisons. Hence, information for the benda+ritux arm from ALLIANCE and the chlorambucil arm from RESONATE-2 are not included in the following tables.

Table 5: Key features of the included evidence

Trial	Design/follow-up	N	Patient population	Outcomes	Use in modelled evaluation
ILLUMINATE	R, OL, MC comparison of ibr+obi vs. obi+chl Median follow-up: 31.3 months	ibr+obi: N=113 obi+chl N=116 ibr+obi del17p: N=14 obi+chl del17p N=18	Previously untreated CLL/SLL; ≥65 years or if <65 years must have one of (CIRS >6 or creatinine clearance <70ml/min or del17p or TP53 mutation)	Primary: PFS Secondary: OS, ORR, MRD, CR, PROs, safety	PFS, OS, safety
ALLIANCE	R, OL, MC comparison of ibr vs. ibr+ritux vs. benda+ritux Median follow-up: 38 months	ibr; N=182 ibr+ritux: N=182 ibr del17p; N=9	Previously untreated CLL/SLL for which treatment is indicated as defined by iwCLL criteria; ≥65 years	Primary: PFS Secondary: OR, CR, OS, PROs, safety	Not used
RESONATE-2	R, OL, MC comparison of ibr vs. chl Median follow-up: 48 months efficacy; 29 months safety	ibr: N=136	Previously untreated CLL/SLL with comorbidities excluding use of fludarabine; ≥65 years	Primary: PFS Secondary: OS, MRD, safety	Not used

benda=bendamustine; chl=chlorambucil; CLL=chronic lymphocytic leukaemia; CR=complete response; ibr=ibrutinib; iwCLL=International Workshop on chronic lymphocytic leukaemia; obi=obinutuzumab; MC=multicentre; MRD=minimal residual disease; OL=open-label; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PROs=patient-reported outcomes; R=randomised; ritux=rituximab; SLL=small lymphocytic lymphoma

Source: Table 2.54, p6 of Section 2.12.1; Table 2.57, p16 of Section 2.13.1.2; Table 2.65, p30 of Section 2.14.1.1 of the resubmission.

6.7 All three trials were randomised and open-label in design. The resubmission considered the risk of bias within the trials was low given that outcome assessors were blinded, key outcomes including progression-free survival (PFS) and overall survival (OS) were objective and the primary efficacy evaluations were performed by an independent review committee (IRC).

6.8 The PBAC agreed with the ESC that while the individual trials had a low risk of bias, the naïve single arm comparisons of ibrutinib monotherapy and ibr+chl was associated with a high risk of bias.

Comparative effectiveness

Comparisons to support the claim of superiority of ibr+obi compared to obi+chl

6.7 Table 6 provides the results of the ILLUMINATE trial, comparing ibr+obi to obi+chl.

Table 6: Results of comparisons to support the claim of superiority of ibr+obi

Trial	Outcome	Ibr+obi n/N (%)	Obi+chl n/N (%)	HR (95% CI)
Comparisons to support the claim of superiority of ibr+obi compared to obi+chl				
ITT population of ILLUMINATE – PFS (IRC-assessed)				
ILLUMINATE (31.3 months median follow-up)	Events	24/113 (21.1%)	74/116 (63.8%)	
	Median months PFS	NE (33.6, NE)	19.0 (15.1, 22.1)	0.23 (0.15, 0.37)
ITT population of ILLUMINATE – OS				
ILLUMINATE (31.3 months median follow-up)	Dead	17/113 (15.0%)	19/116 (16.4%)	
	Median months OS	NE	NE	0.92 (0.48, 1.77)
del17p subgroup of ILLUMINATE – PFS (IRC-assessed)				
ILLUMINATE (31.3 months median follow-up)	Events	3/14 (21.4%)	14/18 (77.8%)	
	Median months PFS	NE	■ ^a	0.14 (0.04, 0.51)
del17p subgroup of ILLUMINATE – OS				
ILLUMINATE (31.3 months median follow-up)	Dead	■/14 (■%)	■/18 (■%)	
	Median months OS	NE	NE	■ (■, ■)

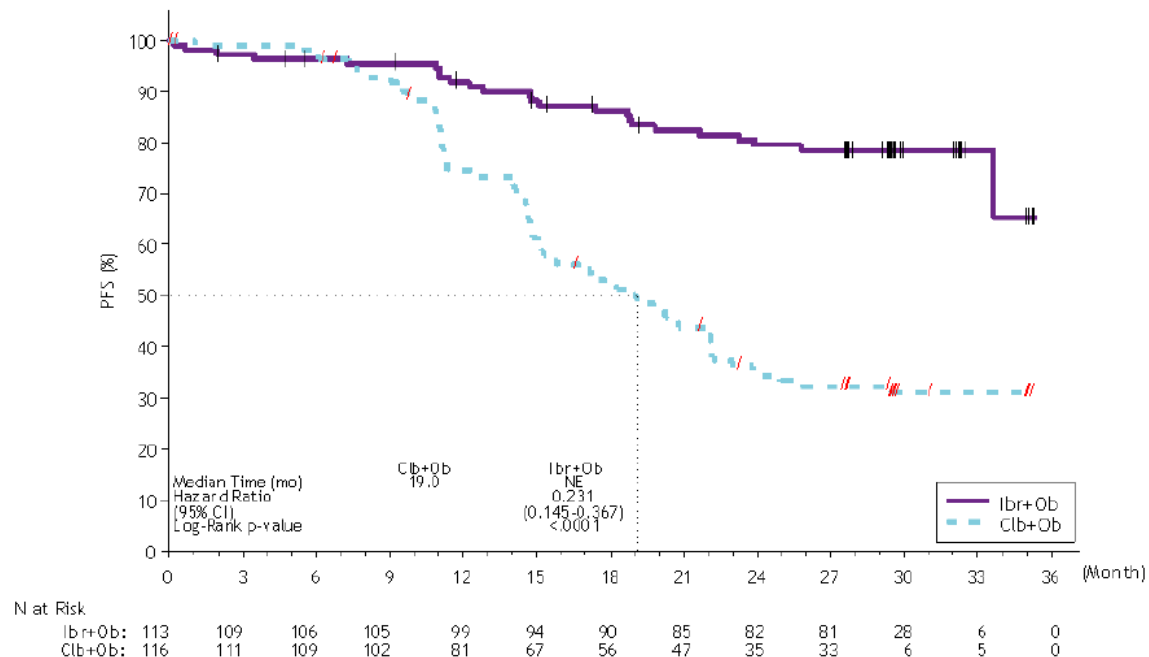
^a The resubmission reported median PFS in the obi+chl arm as ‘approximately ■ months’.

chl=chlorambucil; ibr=ibrutinib; IRC=independent review committee; NE=not estimable; obi=obinutuzumab; OS=overall survival; PFS=progression-free survival; **bold**=statistically significant.

Source: Table 2.18, p87 of Section 2.5.1.1; Table 2.20, p90-91 of Section 2.5.1.2 of the resubmission.

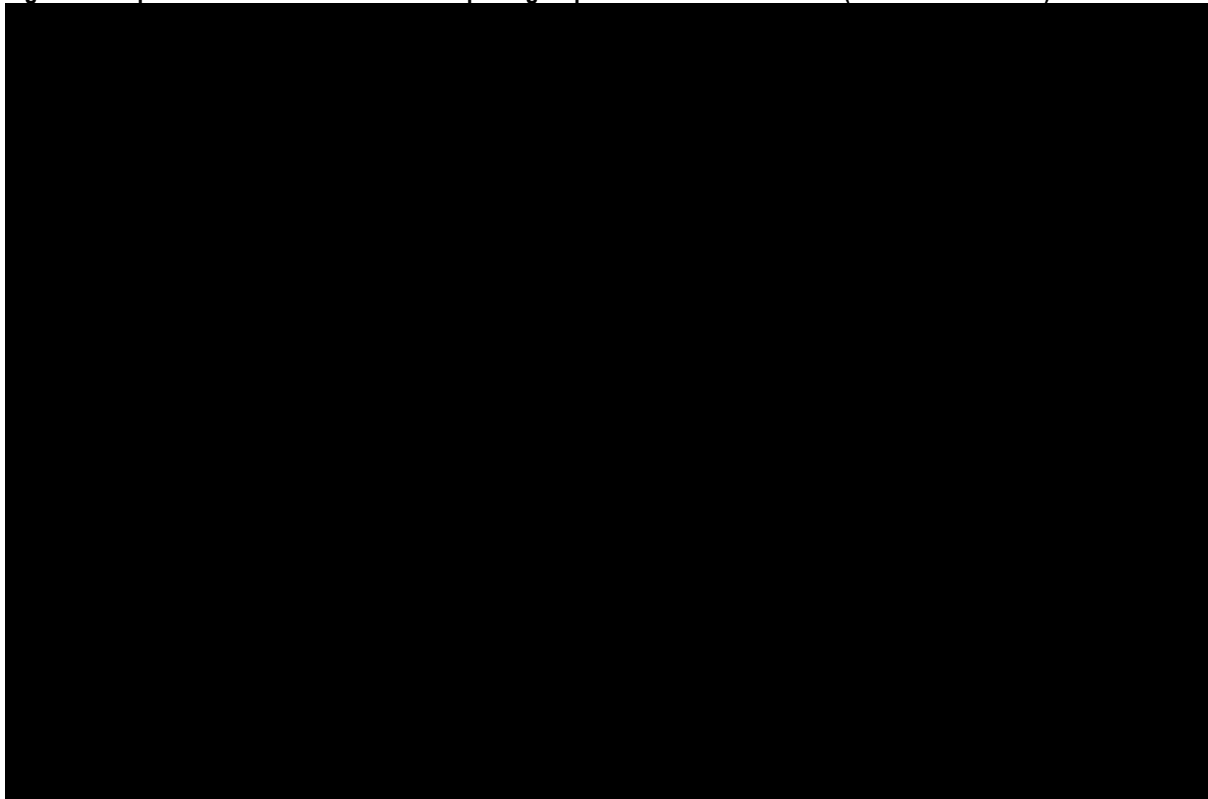
6.8 In the ILLUMINATE trial, the risk of progression or death (PFS) was significantly reduced with ibr+obi compared with obi+chl in the ITT population (HR=0.23; 95% CI: 0.15, 0.37) and the del17p population (HR=0.14; 95% CI: 0.04, 0.51). The Kaplan Meier PFS curves are provided below.

Figure 3: Kaplan-Meier curve of PFS – ITT population of the ILLUMINATE trial (ibr+obi vs. obi+chl)



Source: Figure 2.3, p87 of Section 2.5.1.1 of the resubmission.

Figure 4: Kaplan-Meier curve of PFS – del17p subgroup of the ILLUMINATE trial (ibr+obi vs. obi+chl)



Source: Figure 2.6, p124 of Section 2.6.1.1 of the resubmission.

- 6.9 The resubmission tested for treatment effect modification (i.e. interaction) between the treatment (ibr+obi versus obi+chl) and del17p status (yes or no) for PFS. The analysis showed there was no statistically significant interaction observed for PFS for del17p status, although the analysis was likely underpowered due to the small number of del17p patients.
- 6.10 The PBAC agreed with the ESC that, while the number of patients with del17p was small, the results of the ILLUMINATE trial support the claim that ibr+obi is associated with a statistically and clinically significant improvement in PFS for patients with del17p compared to obi+chl.
- 6.11 For the outcome of OS, there was no statistically significant difference between ibr+obi and obi+chl for both the ITT population (HR=0.92; 95% CI: 0.48, 1.77) and the del17p subgroup (HR=■■■■; 95% CI: ■■■■, ■■■■).
- 6.12 While EQ-5D data from the ILLUMINATE trial was applied for first-line treatment in the economic model, both the resubmission and the ILLUMINATE CSR only provided a comparison of the proportion of patients with clinically meaningful improvement from baseline (defined as a utility score increase ≥ 0.08 points over baseline at or prior to initiation of subsequent antineoplastic therapy). The ESC noted that there was no statistically significant difference between ibr+obi-treated patients and obi+chl-

treated patients in the proportion who recorded a clinically meaningful improvement in EQ-5D. The ESC noted that, due to the lack of a statistically significant difference, the resubmission used the pooled utility value from both arms () as the first-line PFS health state utility value in the economic model.

Comparisons to support the claim of similarity of Ibr vs. ibr+obi

6.13 To support the claim that ibrutinib monotherapy was similar to ibr+obi, the resubmission presented a series of analyses as outlined in Figure 2 above. Results for these comparisons are provided in Table 7.

Table 7: Results of comparisons to support the claim similarity of ibrutinib monotherapy and ibr+obi

del17p subgroup from ALLIANCE vs. del17p subgroup from ILLUMINATE - PFS				
Trial (median follow-up)	Outcome	Ibr n/N (%)	Ibr+obi n/N (%)	HR (95% CI)
ALLIANCE: ibr (38 months median follow-up)	Events	2/9 (22.2%)	-	
	Median months PFS	NE	-	
ILLUMINATE: ibr+obi (31.3 months median follow-up)	Events	-	/14 (%)	
	Median months PFS	-	NE	
Naïve single arm comparison ibr vs. ibr+obi				()
ITT population from RESONATE-2 vs. non-del17 subgroup from ILLUMINATE - PFS				
RESONATE-2: ibr (48.1 months median follow-up)	Events	31/136 (22.8%)	-	
	Median months PFS	NE	-	
ILLUMINATE: ibr+obi (31.3 months median follow-up)	Events	-	/99 (%)	
	Median months PFS	-	NE	
Naïve single arm comparison ibr vs. ibr+obi				()
ITT population from RESONATE-2 vs. non-del17 subgroup from ILLUMINATE - OS				
RESONATE-2: ibr (48.1 months median follow-up)	Dead	20/136 (14.7%)	-	
	Median months OS	NE	-	
ILLUMINATE: ibr+obi (31.3 months median follow-up)	Dead	-	/99 (%)	
	Median months OS	-	NE	
Naïve single arm comparison ibr vs. ibr+obi				()
del17p subgroup from ALLIANCE (direct comparison ibr vs. ibr+ritux) - PFS				
ALLIANCE: (38 months median follow-up)	Events	2/9 (22.2%)	3/11 (27.3%)	not reported
	Median months PFS	NE	NE	
ITT population from ALLIANCE (direct comparison ibr vs. ibr+ritux) - PFS				
ALLIANCE: (38 months median follow-up)	Events	34/178 (19.1%)	32/170 (18.8%)	1.00 (0.62, 1.62)
	Median months PFS	NE	NE	
ITT population from ALLIANCE (direct comparison ibr vs. ibr+ritux) - OS				
ALLIANCE: (38 months median follow-up)	Dead	24/182 (13.2%)	22/182 (12.1%)	not reported ^a
	Median months OS	NE	NE	

^a The resubmission stated there was no significant difference in OS between ibrutinib monotherapy and ibr+ritux and cited a p value of >0.65. However this p value was based on a comparison between the three groups in the ALLIANCE trial: ibr; ibr+ritux; and benda+ritux. chl=chlorambucil; ibr=ibrutinib; IRC=independent review committee; NE=not estimable; obi=obinutuzumab; OS=overall survival; PFS=progression-free survival.

Source: Section 2.6.1, p123-124; Section 2.6.2, p127-128; Table 2.6.5, p31 of Section 2.14.1.1; Section 2.14.1.1, p31; Table 2.66, p34 of Section 2.14.1.1; Table 2.67, p35 of Section 2.14.1.1; Table 2.68, p38 of Section 2.14.1.2 of the resubmission.

- 6.14 Based on the comparisons presented above, the resubmission concluded that the addition of obinutuzumab or rituximab to ibrutinib did not provide incremental PFS or OS benefit compared to ibrutinib monotherapy, for both patients with and without del17p.
- 6.15 The comparisons presented by the resubmission showed no statistically significant difference between ibrutinib monotherapy and combination therapy (see Table 7 above). However, for ibrutinib monotherapy and ibr+obi, naïve comparisons were used which were limited by heterogeneity across the single arms from different trials. In addition, the comparisons were limited by the small sample size of the del17p subgroup.
- 6.16 The PSCR stated that in the absence of direct head to head evidence comparing ibrutinib monotherapy with obi+chl or evidence enabling an indirect treatment comparison using a common comparator, the sponsor presented all available evidence using the most appropriate methodology, consistent with the PBAC guidelines. The PSCR stated that the studies used to conduct the single arm comparisons were assessed for confounding and risk of bias and the assessment showed that all studies were conducted in very similar patient populations, with no significant treatment modifying differences. In addition, the PSCR highlighted the high unmet need for effective treatment options in the del17p population and argued that further evidence generation in this population for the comparison presented is unlikely.

Comparative harms

- 6.17 The resubmission presented the harms in the ILLUMINATE trial, comparing ibr+obi and obi+chl, for the ITT population. The results were presented for the first 9 months of treatment (to account for active treatment in both arms given obi+chl were only delivered for 6 cycles) and for the entire trial period. Table 8 provides a summary of these results.

Table 8: Summary of safety outcomes for the ILLUMINATE trial

Comparison	Summary of AE results
Comparison of ibr+obi compared to obi+chl	
First 9 months of treatment (ILLUMINATE)	Significantly ^a fewer obi-related Grade ≥3 AEs in patients treated with ibr+obi (█%) compared to obi+chl-treated patients (█%) (RD=█; 95% CI: █, █) and any obi-related AEs (RD=█; 95% CI: █, █). Also significantly fewer AE leading to obi infusion interruption in patients treated with ibr+obi (█%) compared to obi+chl-treated patients (█%) (RD=█; 95% CI: █, █). No statistically significant differences between groups for other AEs.
Entire trial period (ILLUMINATE)	Significantly ^a greater incidence of SAEs in the ibr+obi arm compared to the obi+chl arm (RD=█; 95% CI: █, █); Grade ≥3 SAEs (RD=█; 95% CI: █, █) and any ibr/chl-related AE (RD=█; 95% CI: █, █). Also significantly fewer AE leading to obi infusion interruption in patients treated with ibr+obi (█%) compared to obi+chl-treated patients (█%) (RD=█; 95% CI: █, █) and obi-related AE (RD=█; 95% CI: █, █). No statistically significant differences between groups for other AEs. Grade 3 atrial fibrillation reported in 6 ibr+obi patients (5.3%) with no reports in obi+chl patients.

^a The CSR provided only descriptive statistics for safety outcomes in the ILLUMINATE trial. All statistical comparisons were conducted post-hoc by the resubmission.

AE=adverse event; chl=chlorambucil; ibr=ibrutinib; obi=obinutuzumab; RD=risk difference; SAE=serious adverse event

Source: Table 2.24, p98-99 of Section 2.5.2.1 of the resubmission.

- 6.18 The resubmission concluded that the ILLUMINATE trial demonstrated that ibr+obi was non-inferior to obi+chl for safety over the first 9 months of the trial. There were statistically significantly fewer obi-related AEs for ibr+obi-treated patients compared with obi+chl-treated patients (Table 8), and no other statistically significant differences for other AE outcomes. As all statistical comparisons were post-hoc, a more appropriate claim may be for similarity in AEs over the first 9 months of the trial.
- 6.19 Over the entire trial period there were statistically significantly more ibr+obi-treated patients with SAEs, and significantly more obi+chl patients with obi-related AEs (Table 8). The resubmission claimed inferior safety for ibr+obi beyond 9 months on the basis that obi+chl treatment ceased after 6 cycles (approximately 6 months) while ibrutinib was used until disease progression. While the trial evidence was for the overall trial period, there was a greater occurrence of SAEs with ibr+obi outside of the first 9 month period, which provided support for the resubmission’s claim of inferior safety for ibr+obi. However, the resubmission (and the ILLUMINATE CSR) only provided a time breakdown of AEs (first 9 months, overall trial period) for grouped AEs (e.g. any AE, SAEs) while AEs for other ibrutinib-relevant events such as atrial fibrillation were not broken down by time period. The ESC considered haemorrhagic events and atrial fibrillation to be important critical harms for ibrutinib.
- 6.20 The resubmission also presented AE data specific to del17p patients in the ILLUMINATE trial (Table 9).

Table 9: Adverse events observed in the ILLUMINATE trial for del17p and non-del17p patients

	Entire trial period			
	Del17p patients		Non-del17p patients	
	ibr+obi (N=14)	Obi+chl (N=18)	ibr+obi (N=99)	Obi+chl (N=98)
Any TEAE	() (%)	() (%)	() (%)	() (%)
Grade ≥3	() (%)	() (%)	() (%)	() (%)
Any SAE	() (%)	() (%)	() (%)	() (%)
Grade ≥3	() (%)	() (%)	() (%)	() (%)
Ibr/chl-related SAE	() (%)	() (%)	() (%)	() (%)
Obi-related SAE	() (%)	() (%)	() (%)	() (%)
Fatal AE	() (%)	() (%)	() (%)	() (%)
Major haemorrhage	() (%)	() (%)	() (%)	() (%)
Grade ≥3	() (%)	() (%)	() (%)	() (%)
SAE	() (%)	() (%)	() (%)	() (%)

AE=adverse event; chl=chlorambucil; ibr=ibrutinib; obi=obinutuzumab; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Source: Table 2.25, p100 of Section 2.5.2.1 of the resubmission.

- 6.21 The resubmission claimed that the safety profile of patients with del17p is similar to the safety profile of the complement subgroup and the ITT population in ILLUMINATE. The resubmission also stated there were no significant differences observed in the incidence of AEs that are associated specifically with del17p patients, either over the first 9 months or the overall duration of the trial. However, no statistical comparisons were presented.
- 6.22 There was a greater occurrence of SAEs in del17p patients treated with ibr+obi () (%) compared to non-del17p patients () (%) over the entire trial period. The resubmission did not report the occurrence of atrial fibrillation for the del17p subgroup. The proportion of patients with major haemorrhage was greater for del17p patients ()% compared to)% for non-del17p patients) with no incidents of major haemorrhage reported for obi+chl-treated patients. The ESC noted the higher incidence of major haemorrhage but considered that the small number of patients with del17p made it difficult to determine if the risk of this AE was significantly different from those without del17p.
- 6.23 To support the claim that the safety of ibrutinib monotherapy and ibr+obi are similar, the resubmission provided a naïve single arm comparison of ibrutinib monotherapy harm data from RESONATE-2 and ibr+obi data from ILLUMINATE, using the ITT populations. In addition, a direct comparison of ibrutinib monotherapy data and ibr+ritux data from the ALLIANCE trial was provided. Table 10 provides a summary of these results.

Table 10: Summary of safety outcomes across ILLUMINATE, RESONATE-2 and ALLIANCE

Comparison	Summary of AE results
Comparisons of lbr vs. lbr+obi and lbr vs lbr+ritux	
Naïve single arm comparison (RESONATE-2 vs. ILLUMINATE)	Ibrutinib monotherapy data from RESONATE-2 (N=135) compared to lbr+obi data in the ILLUMINATE trial (N=113), using the ITT population. No statistical comparisons were provided. Incidence of Grade 3 or 4 AEs, SAEs and Grade 3 or 4 SAEs was greater with lbr+obi compared to ibrutinib monotherapy.
Direct comparisons (ALLIANCE)	Comparison of ibrutinib monotherapy (N=180) to lbr+ritux (N=181) in ALLIANCE, using statistical comparisons. There were no statistically significant differences in Grade 3+ AEs between ibrutinib monotherapy and lbr+ritux.

AE=adverse event; lbr=ibrutinib; obi=obinutuzumab; RD=risk difference; ritux=rituximab; SAE=serious adverse event
Source: Table 2.69, p41; Table 2.70, p42; Table 2.71, p45; Table 2.72, p47 of Section 2.14.2 of the resubmission.

6.24 The resubmission concluded non-inferior safety with ibrutinib monotherapy compared to lbr+obi (p49, Section 2.17.1). The ESC considered that the use of naïve comparisons introduces uncertainty, however the Committee advised it was reasonable to assume non-inferior safety of ibrutinib monotherapy compared to lbr+obi.

6.25 The resubmission applied AE rates from the lbr+obi arm of ILLUMINATE (over the entire trial period) in the economic model (Table 11). The ESC noted that the resubmission also included costs of monitoring for atrial fibrillation in the economic model.

Table 11: Adverse events applied in the economic model (sourced from ILLUMINATE)

Adverse event	lbr+obi (N=113) n (%)	Obi+chl (N=115) n (%)
Neutropenia and neutrophil count reduced	45 (39.8%)	53 (46.1%)
Thrombocytopenia	21 (18.6%)	12 (10.4%)
Pneumonia	8 (7.1%)	5 (4.3%)
Atrial fibrillation	6 (5.3%)	0 (0.0%)
Febrile neutropenia	5 (4.4%)	7 (6.1%)
Anaemia	4 (3.5%)	9 (7.8%)
Infusion-related reaction	2 (1.8%)	9 (7.8%)

chl=chlorambucil; lbr=ibrutinib; obi=obinutuzumab
Source: Table 3.18, p90 of Section 3.6.1 of the resubmission.

Benefits/harms

6.26 Evidence from the ILLUMINATE trial showed that for every 100 del17p patients treated with lbr+obi in comparison to obi+chl over a median duration of follow-up of 31.3 months:

- Approximately 56 more patients would remain progression free. This estimate is not precise as it is based on small numbers of patients (3/14 patients progressed in the lbr+obi arm; 14/18 patients progressed in the obi+chl arm; Table 6 above).
- There were few deaths (5 in total), and no evidence of a reduced death rate with lbr+obi.

- 6.27 No results were available for the safety of ibrutinib monotherapy in the del17p population. The PBAC agreed with the ESC that there was no clinical reason to assume that ibrutinib-related harms would be different between the del17p and ITT populations.
- 6.28 Limited data prevented quantification of the benefits and harms of ibrutinib monotherapy relative to obi+chl in the del17p subgroup.

Clinical claim

- 6.29 The resubmission claimed that (i) ibr+obi is superior in effectiveness compared to obi+chl, and (ii) the effectiveness of ibrutinib monotherapy is similar to ibr+obi, and therefore that ibrutinib monotherapy is superior to obi+chl. The resubmission claimed the safety of ibrutinib monotherapy is non-inferior to obi+chl during the first 9 months of treatment and inferior thereafter.
- 6.30 The ESC considered that the claim of superior effectiveness of ibr+obi compared to obi+chl was adequately supported by the evidence sourced from the ILLUMINATE trial for the ITT population. In addition, the ESC considered that while the del17p population comprised only a small proportion of the ILLUMINATE trial (12.4%), the results supported the claim that ibr+obi is associated with a statistically and clinically significant improvement in PFS for patients with del17p compared to obi+chl.
- 6.31 The ESC considered the resubmission's claim that the safety of ibr+obi was non-inferior to obi+chl during the first 9 months of treatment and inferior beyond 9 months was reasonable.
- 6.32 The evidence presented by the resubmission does not strongly support the claim of similar effectiveness between ibrutinib monotherapy and ibr+obi as the key evidence was based on naïve single arm comparisons. The PSCR acknowledged the limitations of naïve single arm comparisons and highlighted the high unmet need for effective treatment options in the del17p population and that further evidence generation in this population for the comparison presented is unlikely. The ESC agreed with the evaluation that the use of naïve single arm comparisons made the evidence provided difficult to interpret as a high risk of bias was introduced due to the loss of the benefits of randomisation with this methodology². However, the ESC also agreed with the PSCR regarding the high unmet clinical need for CLL/SLL patients with del17p and considered that while the strength of the supporting evidence is limited by the naïve comparisons, the assumption of similar effectiveness between ibrutinib monotherapy and ibr+obi in this population was plausible.

² Available at: https://handbook-5-1.cochrane.org/chapter_16/16_6_2_indirect_comparisons.htm

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- 6.33 The ESC noted the use of naïve comparisons to support the claim that the safety of ibrutinib monotherapy and ibr+obi are similar. The ESC advised that the use of naïve comparisons introduces uncertainty, however the Committee considered it was reasonable to assume non-inferior safety of ibrutinib monotherapy compared to ibr+obi.
- 6.34 The PBAC considered that, while the strength of the supporting evidence is limited by the use of naïve indirect comparisons, the claim that ibrutinib monotherapy is superior to obi+chl was uncertain but not unreasonable.
- 6.35 The PBAC considered that, despite the use of naïve indirect comparisons, the claim of non-inferior safety of ibrutinib monotherapy compared to obi+chl during the first 9 months of treatment and inferior safety thereafter was reasonable.

Economic analysis

- 6.36 Table 12 provides a summary of the key components of the economic evaluation, along with corresponding information for the November 2017/March 2018 model.

Table 12: Summary of model structure

Component	November 2017/ March 2018 model	Current model
Type of analysis	Cost-utility analysis	Cost-utility analysis
Outcomes	QALYs; LYG	QALYs; LYG
Time horizon	20 years (Nov 17), 10 years (Mar 18)	10 years
Methods used to generate results	Markov cohort model	Hybrid model where partitioned survival analysis techniques were used to construct a Markov cohort
Health states	Three health states: - Unprogressed - Progressed - Death (absorbing) Plus patients can start a new treatment (second or third-line therapy) where they move to unprogressed for the new treatment.	Six health states: - First-line PFS (1L PFS) - First-line progressive disease (1L PD) - Second-line PFS (2L PFS) - Second-line progressive disease (2L PD) - Third and subsequent treatment line (3L+) - Death (absorbing)
Comparison	ibr → ritux+chl → 3 rd line versus blended comparator: ritux+chl → ibr → 3 rd line (61.3%) obi+chl → ibr → 3 rd line (29.4%) ofa+chl → ibr → 3 rd line (9.3%)	ibr → ven+ritux → idel+ritux versus obi+chl → ibr → ven+ritux
Cycle length	30 days, with no half cycle correction	28 days, with half cycle correction
Transition probabilities	PFS transition probabilities were based on RESONATE-2 data as well as CLL11 and COMPLEMENT-1 for the comparators. Time to progression for further lines of therapy were adjusted by multipliers based on the CLL8 and REACH trials used in first and second-line treatment of CLL with rituximab-fludarabine-cyclophosphamide.	First-line transitions were based on ILLUMINATE data. The resubmission assumed that the comparative efficacy of ibrutinib and ofatumumab in RESONATE was applicable to second-line therapy. The PSCR stated the model used the RESONATE PFS data as a proxy for the ven+ritux PFS, on the basis that the PBAC recommended ven+ritux for PBS listing in R/R CLL on a cost-minimisation basis with ibrutinib, having considered them non-inferior in efficacy. Thus, the base case applied a PFS HR=1 to model the progression free survival outcomes of ven+ritux. The third-line health state did not distinguish between progression-free or progressed disease, and the treatment duration was sourced from median PFS obtained from the idelalisib PI.
Utility values	Trial-based EQ-5D values from RESONATE-2 for first-line treatment; literature based for second and third-line treatment.	Trial-based EQ-5D values from ILLUMINATE for first-line treatment; literature based for second and third-line treatment.
Software package	Excel 2016	Excel 2016

chl=chlorambucil; CLL=chronic lymphocytic leukaemia; ibr=ibrutinib; idel=idelalisib; PD=progressive disease; PFS=progression-free survival; PI=Product Information; obi=obinutuzumab; ofa=ofatumumab; ritux=rituximab; ven=venetoclax

Source: Table 3.1, p51 of Section 3.1.1 of the resubmission.

6.37 Regarding the model structure, the ESC noted no difference in OS for the two treatment arms was assumed, and thus the increase in PFS with first-line ibrutinib compared with obi+chl resulted in patients starting treatment with ibrutinib receiving fewer lines of treatment on average (■■■■ [■ + ■■■■ + ■■■■] versus ■■■■ [■ + ■■■■ + ■■■■], Table 15). The ESC also noted the PFS for ibrutinib monotherapy was assumed to be the same as for ibr+obi, and the treatment algorithm modelled was a

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simplification of clinical practice. The impact of these assumptions were unable to be tested in sensitivity analyses.

6.38 The PBAC considered the modelled 10 year time horizon to optimistic but reasonable for the del17p CLL/SLL patient population.

6.39 A summary of the key drivers of the current economic model is provided in Table 13.

Table 13: Key drivers of the model

Description	Method/Value	Impact
Estimated difference in PFS for first line treatment	The economic model used clinical data for ibr+obi as being representative of ibrutinib monotherapy. This was based upon naïve indirect comparisons and hence is uncertain. The ESC noted the impact of this was unable to be tested in sensitivity analyses.	Unknown, favours ibrutinib
Extrapolation of PFS	First line PFS was extrapolated using a Weibull function. This was selected on the basis of AIC and BIC criteria. Second line PFS was extrapolated using an exponential function. This was selected on the basis of being the best fit to the latest RESONATE study update. The ESC noted based on AIC and BIC criteria the Weibull function would be selected. The ESC further noted use of the exponential function resulted in approximately █% of patients being progression free at 10 years which was higher than for first line (approximately █%). The ESC considered the Weibull function more appropriate for the extrapolation of second line PFS than the selected exponential function.	High, favours ibrutinib
Utility values	The resubmission applied utility values sourced from the ILLUMINATE trial (█) to both the ibrutinib and obi+chl arms for first-line PFS. Disutilities for second and third line treatments, sourced from Kosmas (2015), were applied to the first line utility value. The disutilities applied for second-line PFS was 0.16 resulting in a utility value of █. The disutility applied for third-line PFS was 0.29 resulting in a utility value of █.	High
Duration of first-line ibrutinib	The cycle specific probability of remaining on first line ibrutinib was estimated from ILLUMINATE assuming a constant (exponential) rate. This resulted in the average treatment duration (█ 28 day cycles or █ months) being less than the average PFS (█ cycles).	High, favours ibrutinib
Cost of subsequent therapies	The base case model used the effective price for ibrutinib and published prices for other treatments. The ESC noted the expected impact of the RSA on the ibrutinib and venetoclax prices was not considered. Incorporating the RSA impact on the prices increased the ICER from \$█ to \$█.	High, favours ibrutinib
Third-line treatment duration	The third-line health state did not distinguish between progression-free or progressed disease and the treatment duration was sourced from the median PFS obtained from the idelalisib PI. The resubmission did not justify the applicability of this treatment duration.	High

chl=chlorambucil; ibr=ibrutinib; obi=obinutuzumab; ritux=rituximab; PFS=progression-free survival; PI=product information; QoL=Quality of Life

Source: Section 3.1-Section 3.2, p50-65 of the resubmission.

6.40 The results of the stepped economic evaluation are provided in Table 14.

Table 14: Results of the stepped economic evaluation

Step and component	Ibrutinib	Obi+chl	Increment
Step 1: trial-based (36 months) time horizon			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
PF LY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra PF LY gained			\$ [REDACTED]
Step 2: trial-based including costs for AEs and atrial fibrillation monitoring			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
PF LY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra PF LY gained			\$ [REDACTED]
Step 3: trial-based with utilities; first-line therapy only			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 4: Modelled evaluation: 10 year time horizon; utilities; extrapolation of PFS and OS; subsequent therapies			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained (base case)			\$ [REDACTED]

chl=chlorambucil; ibr=ibrutinib; LY=life years; obi=obinutuzumab; PF=progression-free; ritux=rituximab

Source: Table 3.24, p100 of Section 3.8.2 of the resubmission; 6.05.COM.65, Table D.5.3; 7.10-MINOR OVR-16, Table 7.

- 6.41 The incremental QALY gain ([REDACTED]) has reduced considerably from the November 2017 and March 2018 models ([REDACTED] and [REDACTED], respectively) with incremental costs also decreasing. This is consistent with the treatment algorithm being revised to include venetoclax and the assumption of no difference in OS along with the use of different utility values in the November 2017/March 2018 model and the current model.
- 6.42 The benefit modelled was PFS. The increase in PFS with ibrutinib resulted in fewer patients transitioning to subsequent lines of therapy which were associated with reduced quality of life. The PFS benefit attributed to ibrutinib was sourced from the ILLUMINATE trial in which ibrutinib was used in combination with obinutuzumab. As per paragraph 6.32, while acknowledging the strength of the supporting evidence is limited, the ESC considered that the assumption of similar effectiveness between ibrutinib monotherapy and ibr+obi in the del17p population was plausible. However, the ESC agreed with the evaluation that the PFS benefit attributed to ibrutinib is a key driver of the economic model and, given the limited evidence base, a primary source of uncertainty.
- 6.43 Table 15 provides a summary of the disaggregated costs and health outcomes observed in the model. This table also includes the proportion of patients transitioning to second and third line treatments.

Table 15: Breakdown of outcomes and costs in the economic evaluation (discounted)

Cost breakdown	Ibrutinib	Obi+chl	Increment	% of total increment ^a
Health outcomes				
Total QALYs				-
First-line, % of patients	100%	100%		
PFS				%
PD				%
Total first-line				%
Second-line, % of patients	%	%		
PFS				%
PD				%
Total second-line				%
Third-line, % of patients	%	%		
Total third-line				%
Costs				
First-line, % of patients	100%	100%		
FISH test	\$196	-	\$196	%
Administration, monitoring and AE cost	\$	\$	\$	%
First-line drug	\$	\$	\$	%
Total first-line	\$	\$	\$	%
Second-line, % of patients	%	%		
Administration	\$	-	\$	%
Second-line drug	\$	\$	-\$	%
Total second-line	\$	\$	-\$	%
Third-line, % of patients	%	%		
Administration	\$	\$	-\$	%
Third-line drug	\$	\$	-\$	%
Total third-line	\$	\$	-\$	%
Total	\$	\$	\$	

^a Percentages may not add exactly to 100 due to rounding.

chl=chlorambucil; obi=obinutuzumab

Source: Excel workbook 'Attachment 3.2.1_cost utility model ibrutinib del17p_Final', worksheet 'IBR engine_del17p'; worksheet 'OBI_CLB engine_del17p'; worksheet 'Key Inputs & Results' provided with the resubmission.

6.44 The increase in QALYs with the first line treatment is substantial (█). This is offset by a reduction in QALYs in the second (█) and third (█) treatment lines reflecting that with first line ibrutinib fewer patients are subsequently treated with second and third line treatments.

6.45 The ESC noted that the cost of first-line ibrutinib treatment (\$█) is offset to a considerable degree by the cost of second-line ibrutinib (\$█) and third-line venetoclax (\$█). The ESC considered that for these cost-offsets to be realised the caps for the current RSA for ibrutinib and venetoclax for the treatment of R/R CLL would need to be reduced, and advised that a combined RSA across the first-line and R/R settings may be appropriate. The PBAC considered the cost-offsets modelled were generally appropriate as, in clinical practice, del17p CLL/SLL patients move quickly from current PBS-listed first-line regimens to use of ibrutinib or venetoclax in the R/R

setting. The PBAC agreed with the ESC that a combined RSA across first-line and R/R settings would be required to enable the cost-offsets to be realised.

- 6.46 In addition, the ESC noted the RSA arrangements in place for the use of ibrutinib and venetoclax in the R/R CLL/SLL setting and the expected impact of these arrangements on the average price of ibrutinib and venetoclax for this indication (see Risk Sharing Arrangements section below). The ESC advised that incorporating the expected average price of ibrutinib and venetoclax for R/R CLL/SLL in the economic model increased the ICER from \$75,000-\$105,000/QALY to \$105,000-\$200,000/QALY. The pre-PBAC response noted the expected average price referred to by the ESC is derived from the [REDACTED], accepted by PBAC in January 2017. The pre-PBAC response argued that as the model assesses cost effectiveness of ibrutinib in first-line CLL/SLL in only high risk del17p patients it is not appropriate to apply this [REDACTED]. The PBAC agreed with the pre-PBAC response and considered that use of the cost-effective price of ibrutinib and venetoclax for R/R CLL/SLL for the high risk population only (DPMQ \$ [REDACTED], see paragraph 6.74) may be more appropriate for the economic model.
- 6.47 The sensitivity analyses provided below demonstrate the key drivers of the model.

Table 16: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change ICER
Base case	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	-
OS source (base case: ILLUMINATE trial using exponential extrapolation)				
Baliakas (2018) using Weibull function	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	- [REDACTED] %
PFS extrapolation (base case: Weibull first-line; exponential second-line)				
Gamma first-line and exponential second-line	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	- [REDACTED] %
Weibull first-line and log-logistic second-line	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED] %
Gamma first line; Weibull second-line ^a	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED] %
Weibull first-line, Weibull second-line ^b	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED] %
OS (base case: ILLUMINATE trial using exponential extrapolation) and PFS extrapolation (base case: Weibull first-line; exponential second-line) ^a				
OS Weibull and PFS log-logistic second-line ^a	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED] %
Time horizon (base case: 10 years)				
15 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	- [REDACTED] %
18.4 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	- [REDACTED] %
Utility values (base case: ILLUMINATE-based for first-line PFS (0.791) and re-scaled Kosmas 2015 values for later lines)				
Use Kosmas (2015) values as published	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED] %
Kosmas (2015) first-line PFS (0.71) ^a	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED] %
Third-line cycles of ven and idel (base case: 17)				
12 cycles (29% reduction)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED] %
22 cycles (29% increase)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	- [REDACTED] %
Duration of first-line ibrutinib treatment (base case: hazard rate of [REDACTED])				
Based on PFS	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED] %
Cost of ibrutinib and venetoclax in R/R setting (base case: tier 1 effective price for ibrutinib, published price for venetoclax)				
RSA average price for ibrutinib and venetoclax (AEMP \$ [REDACTED], DPMQ \$ [REDACTED]) ^d	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED] %
Cost of ibrutinib first-line setting (base case: tier 1 effective price for ibrutinib) and ibrutinib and venetoclax in R/R setting (base case: tier 1 effective price for ibrutinib, published price for venetoclax) and PFS extrapolation (base case: Weibull first-line; exponential second-line)				
RSA tier 1 effective price for ibrutinib and venetoclax (AEMP \$ [REDACTED], DPMQ \$ [REDACTED] and PFS extrapolation Weibull first-line, Weibull second-line ^e	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED] %

Idel=idelalisib; OS=overall survival; PFS=progression-free survival; ritux=rituximab; ven=venetoclax

^aCompiled during the evaluation

^b Section 3_del17p cost utility model.xlsm, Key Inputs & Results worksheet cell D37 changed to Weibull

^c Section 3_del17p cost utility model.xlsm, IBR engine_del17p worksheet formula in column BA changed to =AJXX where XX = row numbers

^d Section 3_del17p cost utility model.xlsm, Key Inputs & Results worksheet cells D11 and D15 changed to \$ [REDACTED], IBR engine_del17p worksheet cells BM2, BM3, BN2 and BN3 changed to \$0, OBI_CLB engine_del17p worksheet cells BX2, BX3, BY2, BY3 changed to \$0.

^e Section 3_del17p cost utility model.xlsm, Key Inputs & Results worksheet cells D10, D11 and D15 changed to \$ [REDACTED] and cell D37 changed to Weibull. Note: cell D14 – venetoclax DPMQ (11630D) – first cycle (combo) price not changed. IBR engine_del17p worksheet cells BM2, BM3, BN2 and BN3 changed to \$0, OBI_CLB engine_del17p worksheet cells BX2, BX3, BY2, BY3 changed to \$0.

Source: Table 3.29, p106 of the resubmission.

6.48 If the trial-based utility value for first-line PFS was lowered to 0.71 (sourced from Kosmas 2015), and hence the disutility for second line treatment was reduced from 0.16 to [REDACTED] and the disutility for third line treatment was reduced from 0.29 to [REDACTED] the ICER/QALY increased from \$ \$75,000 - \$105,000 to \$ 105,000 -\$200,000. The PSCR noted that in the analysis conducted by the evaluation the utility value of the anchor

state was reduced to the published first-line PFS utility estimate from Kosmas whilst leaving the other utilities re-scaled to the ILLUMINATE anchor state. The PSCR argued that using this approach, the evaluation has ignored the data reported for the subsequent health states in Kosmas. The ESC considered that the use of the pooled utility value from both arms (██████) of the ILLUMINATE trial as the first-line PFS health state utility value and the subsequent use of disutility increments from Kosmas (2015), as per the resubmission was appropriate.

- 6.49 The resubmission noted that the model was most sensitive to changes in PFS extrapolations. There was minimal change in the ICER when the first-line extrapolation was changed to Gamma (ICER decreased from \$75,000/QALY - \$105,000/QALY to \$45,000/QALY - \$75,000/QALY). Second line PFS was extrapolated using an exponential function. The resubmission stated that it was selected on the basis of being the best fit to the latest RESONATE study update. The ESC noted that based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) criteria, the Weibull function would be selected. The ESC further noted use of the exponential function resulted in approximately █████% of patients being progression free at 10 years which was higher than for first line (approximately █████%). The ESC considered the Weibull function more appropriate for the extrapolation of second line PFS than the selected exponential function. The ESC noted that when both the first and second-line extrapolation functions used Weibull functions the ICER increased from \$75,000/QALY - \$105,000/QALY to \$75,000/QALY - \$105,000/QALY.
- 6.50 The pre-PBAC response stated ‘the selection of the exponential extrapolation for second line PFS can now be further validated against more mature data (median follow up 65.3 months) from RESONATE (Munir 2019³)’ and that the exponential function predicted the observed PFS results (from Munir 2019) more closely than the Weibull function, based on observations at two time points (the median and 60 months). The PBAC noted this was based on two single points in time and the pre-PBAC response had not directly fitted parametric functions to the updated data from Munir 2019. The PBAC considered that, based on the information available, the Weibull function was more appropriate for extrapolation of second-line PFS as it: had the lowest AIC/BIC for the RESONATE trial data-cut that was used in the economic model; and resulted in a more conservative extrapolation. The PBAC considered that a conservative approach was required given the uncertainty associated with the use of clinical data for ibr+obi as being representative of ibrutinib monotherapy. Further, the PBAC noted use of the exponential function resulted in approximately █████% of patients being progression free at 10 years which was higher than for first line

³ Munir.T, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol. 2019; 1–11. <https://doi.org/10.1002/ajh.25638>

(approximately █%). While the pre-PBAC response indicated that ‘the ICER is insensitive to differences in PFS beyond the 5-year time point because █% of progression events have already occurred’, the PBAC considered the 10 year PFS estimates indicated that the exponential function overestimated survival and resulted in survival estimates that were not clinically plausible.

- 6.51 The model was sensitive to the treatment duration for first-line ibrutinib. The cycle specific probability of remaining on first line ibrutinib was estimated from ILLUMINATE assuming a constant (exponential) rate. The ESC noted this resulted in the average treatment duration (█ 28 day cycles or █ months) being less than the average PFS (█ cycles), despite treatment being recommended until disease progression, although ESC also acknowledged that some patients may discontinue ibrutinib treatment due to not tolerating it. Assuming treatment until progression in all patients increased the ICER from \$75,000/QALY - \$105,000/QALY to \$75,000/QALY - \$105,000/QALY.
- 6.52 The model demonstrated sensitivity to the number of third-line treatment cycles. Decreasing the number of cycles by 5 from the base case of 17 cycles increased the ICER/QALY to \$75,000 - \$105,000 while increasing cycle numbers by 5 decreased the ICER to \$45,000/QALY - \$75,000/QALY. The ESC agreed with the evaluation that the number of third-line treatment cycles was a key driver of the model. While third-line treatment did not distinguish between progression-free and progressed disease, the sensitivity of the model to the third-line treatment duration indicated the impact of this line of treatment. The PSCR stated that the resubmission did not include further treatments and further progression after the third-line health state, as there is a lack of information to inform such transitions (particularly in the del17p population). The PSCR argued that the omission was conservative as the impact of including further progression effects would likely reduce the ICER in favour of ibrutinib.
- 6.53 The PBAC noted the ICER to be highly dependent on the expected average price of ibrutinib and venetoclax for R/R CLL/SLL and the second line PFS extrapolation function used in the model. The PBAC noted that when a DPMQ of \$█ (see paragraph 6.74) was used for ibrutinib and venetoclax in the R/R setting the ICER increased from \$75,000/QALY - \$105,000/QALY to approximately \$75,000/QALY - \$105,000/QALY⁴, and when in addition both the first and second-line PFS extrapolation functions used Weibull functions the ICER increased to approximately

⁴ Section 3_del17p cost utility model.xlsm, Key Inputs & Results worksheet cells D11 and D15 changed to \$█. Note: cell D14 – venetoclax DPMQ (11630D) – first cycle (combo) price not changed. IBR engine_del17p worksheet cells BM2, BM3, BN2 and BN3 changed to \$0, OBI_CLB engine_del17p worksheet cells BX2, BX3, BY2, BY3 changed to \$0.

\$105,000/QALY - \$200,000/QALY⁵.

Drug cost/patient/course

6.54 The drug cost/patient/course was based on time on treatment estimated by the economic model. The table below provides the cost per patient per month based on the price requested in the resubmission, with results from the November 2017 model provided for reference.

Table 17: Estimated drug cost/patient

	Resubmission	November 2017 model
Time on treatment in the economic model	■ months	■ months
Cost of treatment based on model-estimated treatment duration	\$ ■ ^a	\$ ■
Cost per month	\$ ■ ^a	\$ ■

^aBased on the price requested in the resubmission (DPMQ \$ ■)

Source: Excel workbook 'Attachment 3.2.1_cost utility model ibrutinib del17p_Final', worksheet 'IBR engine_del17p' provided with the resubmission.

6.55 The cost per patient per month relies on time on treatment estimated by the economic model. The average time on treatment in the model is less than the average PFS.

Estimated PBS usage & financial implications

6.56 The resubmission was not considered by DUSC. The November 2017 submission was considered by DUSC.

6.57 The November 2017 submission and March 2018 resubmission applied an epidemiological approach to estimate the number of first-line patients treated with ibrutinib and a similar approach was applied to estimate the number of first-line del17p patients in the resubmission. The resubmission’s approach included estimation of incident patients; estimation of prevalent patients; and the determination of the proportion of incident and prevalent CLL/SLL patients with del17p.

6.58 The resubmission conducted a literature review to identify the proportion of del17p patients in studies with CLL patients. The literature review identified 58 studies, which included genetic studies (n=11; 19%), non-randomised trials (n=10; 17%), randomised trials (n=7; 12%) and retrospective reviews (n=30; 52%). These studies had considerable variation, as follows:

⁵ Section 3_del17p cost utility model.xlsm, Key Inputs & Results worksheet cells D11 and D15 changed to \$ ■ and cell D37 changed to Weibull. Note: cell D14 – venetoclax DPMQ (11630D) – first cycle (combo) price not changed. IBR engine_del17p worksheet cells BM2, BM3, BN2 and BN3 changed to \$0, OBI_CLB engine_del17p worksheet cells BX2, BX3, BY2, BY3 changed to \$0.

- Age of included patients ranged from 55 to 83.2 years, although age was not reported for nine (15.5%) of the studies. Only seven of the studies (12.1%) included patients aged ≥ 70 years, which corresponded to the mean age of ILLUMINATE patients (71 years) used at the start of the economic model.
- The number of patients in each study with del17p data ranged from 23 to 1,557, with del17p proportions ranging from 1.47% (=2/136) to 29.92% (=117/391).
- Some studies included patients with disease progression, and no information was provided as to whether these patients were included in the counts of patients with del17p. Another study had more than half of its patients on second-line treatment (58/105), indication that its patient population did not match with untreated or first-line patients.

6.59 While the resubmission acknowledged the wide range of study types it did not provide a consideration of the type of data available (e.g. patients on second-line treatment; some treated, some not treated; varying age and other potentially confounding variables). Table 18 provides a brief summary of the studies used to determine the proportion of patients with del17p. The PSCR stated that when analysing the proportion estimates, stratified by the four sets of study types, the mid-point estimates are very close to the base case estimate of █% used in the submission: for the genetic analysis studies it was █%, for the retrospective studies it was █%, for the non-randomised studies it was █% and the for the randomised trials it was █%. As such, the PSCR maintained that █% was an appropriate assumption for estimating del17p prevalence due to the variability in the published estimates.

Table 18: Summary of studies^a used to determine proportion of patients with del17p

	Genetic analysis (N=11; 19%)	Retrospective reviews (N=30; 52%)	Non-randomised trial (N=10; 17%)	Randomised trial (N=7; 12%)
Age range	58 to >70 yrs; age not reported in 5/11 (45%) of studies.	57 to 83.2 years; age not reported in 4/30 (13%) of studies.	55 to 71 years; age reported for all trials.	56 to 70 years; age reported for all trials.
Proportion treated	Patients not treated in 6/11 studies (55%). In one study 41% had disease progression; in another 55% were on second-line treatment.	Patients treated in 20/30 studies (67%). Resubmission provided no information on treatment duration.	Patients treated in 8/10 studies (80%). Resubmission provided no information on treatment duration.	Patients treated in 5/7 studies (71%). Resubmission provided no information on treatment duration.
N assessed for del17p	N assessed ranged from 23 to 317.	N assessed ranged from 27 to 1,557.	N assessed ranged from 31 to 626.	N assessed ranged from 64 to 930.
Proportion with del17p	1.47% to 17.39%	3.06% to 29.92%	3.0% to 12.12%	3.8% to 13.11%

^a Study types were re-categorised during the evaluation as inconsistencies between study type and the descriptions provided in Table 1.3 of the document 'Literature search – proportion of patients with del 17p' in Appendix 4 of the resubmission were noted.

Source: Table 1.3 of the document 'Literature search – proportion of patients with del 17p' in Appendix 4 of the resubmission.

6.60 The resubmission stated that to determine the mean proportion of patients with del17p an inverse variance weighted meta-analysis was conducted. As the test of heterogeneity was significant ($p < 0.0001$) the resubmission used results from the

random effects model. The mean proportion returned by the meta-analysis was █% (95% CI: █%, █%). The resubmission indicated that given the variability in the published estimates, the 95% CI upper limit, █%, was used in the financial estimates. This proportion was applied to both prevalent and incident patient populations. The PBAC considered that the mean proportion returned by the meta-analysis (█%), rather than the 95% CI upper limit (█%), should be used in the financial estimates.

- 6.61 The ESC considered that estimates based on a proportion of █% and including a small number of prevalent patients in the first year of listing ibrutinib for this indication may be appropriate if patients with TP53 mutations were included in the proposed PBS population. The pre-PBAC response stated the prevalence of TP53 aberrations (i.e. del17p and TP53 mutations) in treatment naïve CLL/SLL patients is █-█%.⁶ In addition, the pre-PBAC response noted TP53 mutations occur in the absence of del17p in about 5% of untreated patients.⁷ The pre-PBAC response argued that, assuming del17p prevalence is between █% and █%, an additional █% for TP53 mutations results in an overall prevalence of TP53 mutations and del17p of █-█%. The pre-PBAC response proposed that should the PBAC recommend ibrutinib for PBS listing for both TP53 mutations and del17p, the prevalence be adjusted to █%.
- 6.62 The resubmission included both incident and prevalent patients in its estimates, with prevalent patients accounting for approximately 15% of the treated population. While the PBAC has previously considered that a prevalent population was necessary (paragraph 7.11, November 2017 PSD), this was in the context of a much broader population of untreated CLL/SLL patients. The PBS population proposed in the current resubmission comprised CLL/SLL patients with del17p only. Patients with del17p are known for having a poor prognosis and rapid disease progression. It would be anticipated that such patients would have already received first-line treatment and most likely moved on to second-line treatment. Consequently, inclusion of prevalent patients may essentially double-count patients. The ESC agreed with the evaluation that as patients with del17p have rapid disease progression it was likely that the majority of prevalent patients would have already received first-line treatment. However, the ESC considered that it would be appropriate for inclusion of a small number of prevalent patients in the first year of listing ibrutinib for this indication. The pre-PBAC response argued that a prevalent pool of patients should remain in the estimates of eligible patients for each of the first six years of listing as a high proportion of CLL/SLL (including del17p) patients are asymptomatic at diagnosis. The PBAC advised that prevalent del17p CLL/SLL patients should be excluded from the

⁶ Kuss BJ & Tam CS. Management of high risk chronic lymphocytic leukaemia (CLL) patients in Australia. *Internal Medicine Journal*, 2017; 47:5-10

⁷ Malcikova J, et al. ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukaemia—update on methodological approaches and results interpretation *Leukaemia* 2018; 32: 1070-1080.

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financial estimates as the Committee considered that rapid disease progression in this population means patients would already have commenced first-line therapy.

6.63 Table 19 provides a summary of the estimated usage and financial implications of the proposed PBS listing of ibrutinib for first-line treatment.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of incident patients	████████	████████	████████	████████	████████	████████
Proportion requiring treatment	████████	████████	████████	████████	████████	████████
Proportion with del17p	████████	████████	████████	████████	████████	████████
Uptake	████████	████████	████████	████████	████████	████████
Number of incident patients commencing treatment	████	████	████	████	████	████
Number of prevalent patients	████████	████████	████████	████████	████████	████████
Proportion eligible for treatment	████████	████████	████████	████████	████████	████████
Proportion require treatment	████████	████████	████████	████████	████████	████████
Proportion with del17p	████████	████████	████████	████████	████████	████████
Uptake	████████	████████	████████	████████	████████	████████
Number of prevalent patients commencing treatment	████	████	████	████	████	████
Total number commencing treatment	████	████	████	████	████	████
Number of scripts dispensed ^a	████████	████████	████████	████████	████████	████████
Estimated financial implications of ibrutinib						
Cost to PBS/RPBS less co-payments	████████	████████	████████	████████	████████	████████
Cost offsets for change in use of other medicines	████████	████████	████████	████████	████████	████████
Net financial implications						
Net cost to PBS/RPBS	████████	████████	████████	████████	████████	████████
Net cost to MBS	████████	████████	████████	████████	████████	████████
Overall net cost to Government	████████	████████	████████	████████	████████	████████

^a Based on the following mean script numbers: Year 1: █████; Year 2: █████; Year 3: █████; Year 4: █████; Year 5: █████; Year 6: █████.
 Source: Table 4.2, p117 of Section 4.2.1.1; Table 4.3, p118 of Section 4.2.1.2; Table 4.4, p119 of Section 4.2.1.3; Table 4.6, p120-121 of Section 4.2.1.4; Table 4.9, p123 of Section 4.2.4; Table 4.12, p127; Table 4.13, p128 of Section 4.3.3; Table 4.14, p130 of Section 4.4.2; Table 4.17, p132 of Section 4.5.2; Table 4.18, p133 of Section 4.5.3 of the resubmission; Excel workbook 'Section 4_del17p financial estimates', worksheet '4b. Displaced – PUB'; 6.05.COM.20, Table 13; 7.10-MINOR OVR-22, Table 10.

6.64 In Year 6 the estimated net cost to the PBS would be less than \$10 million. The PBAC noted these costs were based on the published prices of obinutuzumab, venetoclax and idelalisib.

6.65 The resubmission calculated that script numbers for second-line ibrutinib would decrease by less than 10,000 scripts in Year 1 and by less than 10,000 scripts in Year 6. Script numbers for second-line venetoclax were expected to decrease by less than 10,000 scripts (less than 10,000 initial and less than 10,000 continuing) in Year 1 and to increase by less than 10,000 scripts (less than 10,000 initial and less than 10,000 continuing) in Year 6.

continuing) in Year 6, with an overall decrease of less than 10,000 scripts (less than 10,000 initial and less than 10,000 continuing) over Years 1-6. While the treatment sequences applied in the resubmissions economic model were likely to reflect clinical practice, the calculated treatment durations were not likely to reflect usage and cost in practice. The ESC considered that in current clinical practice del17p CLL/SLL patients were progressing quickly through a limited number of first-line treatment cycles onto second-line ibrutinib or venetoclax therapy. Thus the ESC expected the increase in the overall number of ibrutinib prescriptions with a first-line listing for del17p patients to be relatively small.

- 6.66 Given the uncertainty noted above with the resubmission’s estimate of the proportion of del17p patients (█% of the tested CLL/SLL population), along with the likelihood that inclusion of prevalent patients may result in double-counting, sensitivity analyses varying these two parameters were conducted. The results are provided in Table 20.

Table 20: Impact of proportion of del17patients on patient numbers and estimated costs

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	% change
Base case █% del17p and prevalent patients included							
N commencing treatment	█	█	█	█	█	█	
Overall net cost to Govt	█	█	█	█	█	█	
Prevalent patients removed							
N commencing treatment	█	█	█	█	█	█	
Estimated net cost	█	█	█	█	█	█	-22%
█% del17p							
N commencing treatment	█	█	█	█	█	█	
Estimated net cost	█	█	█	█	█	█	-25%
█% del17p							
N commencing treatment	█	█	█	█	█	█	
Estimated net cost	█	█	█	█	█	█	-43%
Prevalent patients removed and █% del17p							
N commencing treatment	█	█	█	█	█	█	
Estimated net cost	█	█	█	█	█	█	-53%
Prevalent patients removed and █% del17p							
N commencing treatment	█	█	█	█	█	█	
Estimated net cost	█	█	█	█	█	█	-75%

Govt=Government

Source: Compiled during the evaluation using Excel workbook ‘Section 4_del17p financial estimates’, worksheet ‘2a. Patients – epi’.

- 6.67 The analyses show that overestimation of the proportion of del17p patients will result in considerably greater cost to Government. Applying the point estimate (█%) from the resubmission’s meta-analysis to determine the proportion of del17p patients dropped patient numbers by just over 30 per year and decreased the estimated net cost to Government by 25%, to \$10 – \$20M over the first 6 years of listing.
- 6.68 Removal of prevalent patients from the estimates decreased estimated net cost to \$10 – \$20M over 6 years, a 22% decrease. Removal of prevalent patients and decreasing the proportion of del17p patients to █% decreased estimated net cost to

Government to \$ \$10 – \$20M over 6 years, a decrease of 53% compared to the resubmission’s base case estimate of \$20 - \$30M.

- 6.69 The PBAC advised that estimates based on the ■% proportion of del17p patients, with prevalent patients excluded, were appropriate for the proposed PBS population of del17p CLL/SLL patients.

Quality Use of Medicines

- 6.70 The resubmission provided a summary of quality use of medicines activities relative to the use of ibrutinib. The outlined strategies were similar to those presented in the November 2017 submission (methods the sponsor believes will ensure the quality use of ibrutinib; identification of groups who play a role in the appropriate use of ibrutinib in practice; and provision of appropriate education, resources and support from the sponsor), along with updated detail on the patient support program for ibrutinib and further detail on available educational materials.

Financial Management – Risk Sharing Arrangements

- 6.71 The resubmission indicated that a RSA was not proposed as the patient population is clearly defined by the FISH test for del17p. The PSCR argued that the proposed Authority Required (Written) restriction for initial treatment provides an additional mechanism to ensure that the use of ibrutinib will be limited to the PBS-eligible population.
- 6.72 The PSCR argued that the impact on second-line use of ibrutinib in CLL/SLL (i.e. a decrease in patients moving to second-line use of ibrutinib), is already estimated in the submission’s financial implications and accounted for. Therefore, no change is required to the existing RSA for second-line CLL patients. The ESC noted that the cost-effectiveness of ibrutinib in the first-line treatment of del17p patients relied on cost-offsets for ibrutinib and venetoclax as second and third line treatments, and for these cost-offsets to be realised the caps for the current RSA for ibrutinib and venetoclax for the treatment of R/R CLL/SLL would need to be reduced. The PBAC agreed with the ESC that a combined RSA across the first-line and R/R settings may be appropriate.
- 6.73 The resubmission stated the cost-effective price of ibrutinib for use in R/R CLL is managed through an RSA. It was noted that the cost-effective price below the first cap was \$ ■■■■■ ex-factory per month and was based on ■■■■■ which included ■■■■■. Therefore, the submission considered this price relevant to use as the ■■■■■ of ibrutinib in the ■■■■■ of the model. The ESC noted advice from the Department that the RSA for ibrutinib (and now venetoclax) for R/R CLL includes financials caps which were based on ■■■■■ with the aim being

to [REDACTED]
Specifically, the estimates were [REDACTED]
[REDACTED] should be considered when determining the average price for ibrutinib and venetoclax for the treatment of R/R CLL. The average price for ibrutinib is calculated in Table 21.

Table 21: Effective and average AEMPs for ibrutinib use in R/R CLL/SLL

	Proportion of cap	Effective AEMP
SC1: Subsidisation cap 1 (high need group)	[REDACTED] %	[REDACTED]
SC2: Subsidisation cap 2	[REDACTED] %	[REDACTED]
Average price		[REDACTED]
Average price including [REDACTED] % reduction in financial caps		[REDACTED]

AEMP=approved ex-manufacturer price

Source: Cap proposal for ibrutinib from sponsor in January 2017

- 6.74 The PBAC noted the ibrutinib average price including [REDACTED] % reduction in financial caps specified in Table 21 is derived [REDACTED]. As per paragraph 6.46, the PBAC considered that the average price for ibrutinib and venetoclax for R/R CLL/SLL should be based on a [REDACTED] % reduction applied to the [REDACTED], leading to an AEMP \$ [REDACTED] and DPMQ \$ [REDACTED].
- 6.75 The ESC noted the average price for ibrutinib and venetoclax for R/R CLL will only be achieved if [REDACTED], and requested that the Department provide the PBAC with a comparison of the ibrutinib and venetoclax expenditure with the agreed and expected financial caps. As the expected expenditure above the financial caps [REDACTED]
- 6.76 The pre-PBAC response acknowledged that Subsidisation cap 2 of the current RSA was [REDACTED]. However, the pre-PBAC response suggested that the cost-effectiveness of ibrutinib and venetoclax in [REDACTED] will be significantly more favourable than that which the RSA was based on. The pre-PBAC response suggested that this will occur as: subsidisation caps [REDACTED]; mature data the from RESONATE trial (Munir 2019⁸) indicates the treatment duration for patients receiving ibrutinib is significantly longer than what was assumed at the time of the RSA negotiations; and the addition of venetoclax to the RSA on 1 March 2019 allowed

⁸ Munir.T, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma. Am J Hematol. 2019; 1–11. <https://doi.org/10.1002/ajh.25638>

patients to be treated with two novel agents in R/R disease with [REDACTED].

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required listing of ibrutinib for first-line treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) patients with deletion 17p (del17p). The PBAC recognised the high clinical need for effective treatments in this population and is satisfied that ibrutinib provides, for some patients, a significant improvement in progression-free survival (PFS) over obinutuzumab + chlorambucil (obi+chl).
- 7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment, that ibrutinib was cost-effective in the proposed population if the price of ibrutinib was the same as for the relapsed/refractory (R/R) CLL/SLL PBS listing, and a risk sharing arrangement (RSA) is implemented which included both first-line and R/R use, while accounting for the cost-offsets for reduced use of ibrutinib and/or venetoclax in the R/R setting as per the updated financial estimates.
- 7.3 The PBAC welcomed the input from individuals, health care professionals and organisations which highlighted the limited effectiveness and significant toxicity associated with currently available first-line treatments.
- 7.4 The PBAC acknowledged that there is a high clinical need for additional therapies for del17p CLL/SLL patients given they have a poor prognosis and as current treatments are characterised by poor response rates and short durations of response.
- 7.5 The PBAC also acknowledged that patients with mutations of the TP53 gene have the same poor prognosis and poor response to current alternative treatments as del17p positive patients. The PBAC agreed with the ESC that there was a clinical need for effective treatments in patients with aberrations in TP53 who are del17p negative. However, the PBAC noted that aberrations in TP53 are detected by gene sequencing and that fluorescence in situ hybridisation (FISH) may miss more than 30% of all TP53 variants. The PBAC advised that, while it was of a mind to recommend extending the proposed PBS restriction to include TP53 mutations as an alternative to del17p, advice from the MSAC was required to inform this decision.
- 7.6 The PBAC noted that listing of ibrutinib for first-line treatment of del17p CLL/SLL patients would be consistent with International Workshop on Chronic Lymphocytic Leukaemia (iwCLL 2018), National Comprehensive Cancer Network (NCCN 2018), and the European Society for Medical Oncology (ESMO 2015) guideline recommendations. The PBAC considered that restriction of ibrutinib for treatment of CLL/SLL to once in a patient's lifetime appropriately moves ibrutinib treatment for CLL/SLL patients with

del17p to earlier in the treatment algorithm.

- 7.7 The PBAC considered that obi+chl as the nominated comparator was appropriate.
- 7.8 The PBAC agreed with the ESC that while the number of patients with del17p in the ILLUMINATE trial was small, the results supported the claim that an ibrutinib-containing regimen (ibr+obi) is associated with a statistically significant improvement in PFS for patients with del17p compared to obi+chl. The PBAC noted that no statistically significant differences in OS were reported in the ILLUMINATE trial.
- 7.9 The PBAC noted that the resubmission's claim of superior PFS for ibrutinib monotherapy compared with obi+chl relied on acceptance of ibrutinib monotherapy having similar efficacy to ibr+obi, and that this was based on naïve indirect comparisons. The PBAC noted the high unmet clinical need for CLL/SLL patients with del17p and agreed with the ESC that, while the strength of the supporting evidence is limited by the use of naïve indirect comparisons, the assumption of similar effectiveness between ibrutinib monotherapy and ibr+obi in this population was plausible. As such, the PBAC considered the claim of superior PFS for ibrutinib monotherapy compared to obi+chl was uncertain but not unreasonable.
- 7.10 The PBAC accepted the resubmissions claim that the safety of ibr+obi was non-inferior to obi+chl during the first 9 months of treatment and inferior beyond 9 months based on data from the ILLUMINATE trial. In addition, the PBAC considered that despite the use of naïve indirect comparisons it was reasonable to assume non-inferior safety of ibrutinib monotherapy compared to obi+chl during the first 9 months of treatment and inferior safety thereafter.
- 7.11 The PBAC noted the economic model used clinical data for ibr+obi as being representative of ibrutinib monotherapy with the impact of this unable to be tested in a sensitivity analysis. The PBAC agreed with the ESC that the PFS benefit attributed to ibrutinib is a key driver of the economic model and, given the accepted but limited evidence base, a primary source of uncertainty.
- 7.12 The PBAC considered the ICER to be highly dependent on the expected average price of ibrutinib and venetoclax for R/R CLL/SLL and the second line PFS extrapolation function used in the model.
- 7.13 The PBAC noted the RSA in place in the R/R CLL/SLL setting determines [REDACTED].
[REDACTED].
As the economic model assessed ibrutinib in first-line CLL/SLL in high risk patients the PBAC considered the use of the cost-effective price of ibrutinib and venetoclax for R/R CLL/SLL for the [REDACTED] (\$ [REDACTED]) appropriate. The PBAC noted reducing the price of ibrutinib and venetoclax when used in the R/R setting from \$ [REDACTED] to \$ [REDACTED] increased the ICER to approximately \$75,000 - \$105,000 per QALY gained.
- 7.14 The PBAC considered that, given the uncertainty associated with the modelled PFS, the use of conservative PFS extrapolation functions in the first-line and second line

settings was appropriate. As such, the PBAC considered that the Weibull function was more appropriate for the extrapolation of second line PFS than the selected exponential function. Using a DPMQ of \$ [REDACTED] for ibrutinib and venetoclax in the R/R setting, and Weibull functions for both first and second-line PFS extrapolation, the ICER was between \$105,000 and \$200,000 per QALY gained.

- 7.15 The PBAC considered that ibrutinib was not cost-effective at the price proposed in the submission (DPMQ \$ [REDACTED]). However, the PBAC noted that if the first-line average price was the same as for use in the R/R setting (\$ [REDACTED]), the ICERs decreased to approximately \$15,000-\$45,000⁹ (with exponential extrapolation of second-line PFS) or to approximately \$75,000-\$105,000 (with Weibull extrapolation of PFS) and accepted that under this scenario ibrutinib for the first-line treatment of CLL/SLL patients with del17p was cost-effective.
- 7.16 The PBAC considered that the mean proportion returned by the meta-analysis ([REDACTED]%), rather than the 95% CI upper limit ([REDACTED]%), should be used in the financial estimates to determine the proportion of CLL/SLL patients with del17p. In addition, the PBAC advised that prevalent patients should be excluded from the financial estimates as rapid disease progression in this population means that prevalent del17p patients would have already commenced first-line therapy. Hence, the PBAC advised that estimates based on [REDACTED]% of CLL/SLL with del17p and with prevalent patients excluded were appropriate to determine the proposed PBS population of del17p CLL/SLL patients.
- 7.17 The PBAC noted that the cost-effectiveness of ibrutinib in the first-line treatment of del17p patients relied on cost-offsets for ibrutinib and venetoclax as second and third line treatments. The PBAC advised that for these cost-offsets to be realised a combined RSA across the first-line and R/R settings was required. The PBAC noted that the expected financial caps for ibrutinib and venetoclax for R/R CLL/SLL were [REDACTED] and hence the average price for ibrutinib and venetoclax for R/R CLL is [REDACTED]. The PBAC noted that the resubmission is for del17p CLL/SLL patients and that this patient subgroup was [REDACTED] for R/R CLL/SLL. Hence, the PBAC advised that Subsidisation cap 1 should be recalculated to include first-line del17p CLL/SLL patients treated with ibrutinib as per the revised estimates in paragraph 7.16, after accounting for the reduction of del17p R/R CLL/SLL patients treated with ibrutinib or venetoclax consistent with the cost-offsets for these patients. The PBAC noted that current expenditure is [REDACTED].

⁹ Section 3_del17p cost utility model.xlsm, Key Inputs & Results worksheet cells D10, D11 and D15 changed to \$3293.23. Note: cell D14 – venetoclax DPMQ (11630D) – first cycle (combo) price not changed. IBR engine_del17p worksheet cells BM2, BM3, BN2 and BN3 changed to \$0, OBI_CLB engine_del17p worksheet cells BX2, BX3, BY2, BY3 changed to \$0.

[REDACTED] The PBAC was therefore of the view that it would not be appropriate to amend [REDACTED].

- 7.18 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for ibrutinib:
- a. The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, as the PBAC considered current treatments are characterised by poor response rates and short durations of response (see paragraph 7.4).
 - b. The treatment is not expected to address a high and urgent unmet clinical need as patients currently progress quickly to accessing ibrutinib or venetoclax in the R/R setting.
 - c. It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.19 The PBAC advised that ibrutinib is not suitable for prescribing by nurse practitioners.
- 7.20 The PBAC recommended that the Early Supply Rule should apply.
- 7.21 The PBAC noted the flow-on restriction changes would be required to the initial treatment restriction for R/R CLL/SLL (item number: 11213E) to specify that patients who have received ibrutinib as first-line therapy are not eligible for PBS-subsidised ibrutinib in the R/R setting, thereby restricting ibrutinib use to once in a patient's lifetime.
- 7.22 The PBAC noted that this resubmission was not eligible for an Independent Review as it was a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Add new indication:

Ibrutinib: Restriction Summary [new] / Treatment of Concept: [new]

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Name, Restriction, Manner of administration and form	Max. Qty (Packs)	Max. Qty (units)	No. of Rpts	PBS item code	Proprietary Name and Manufacturer	
IBRUTINIB Capsule 140 mg, 90	1	90	5	11213E	Imbruvica®	Janssen-Cilag Pty Ltd

Concept ID	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
	Restriction Level: <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
	Episodicity: Untreated
	Severity:
	Condition: chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
new	Indication: Untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: Initial treatment
8594	Clinical criteria:
8593	The condition must be previously untreated
	AND
9628	Clinical criteria:
9627	Patient must have a WHO performance status of 2 or less
	AND
7890	Clinical criteria:
7889	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
21097	Clinical criteria:
21096	Patient must have evidence of one or more 17p chromosomal deletions as demonstrated by fluorescence <i>in situ</i> hybridisation.
	AND
21045	Clinical criteria:
21044	The treatment must be once in a lifetime with this drug for this condition.
edit 25135 draft	Prescribing Instructions: A patient may only <i>qualify</i> for PBS-subsidised initiation/ treatment once in a lifetime under: 1- (i) the previously untreated CLL/SLL initial treatment restriction; or 2- (ii) the relapsed or refractory CLL/SLL initial treatment restriction.
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.

Amend existing restrictions as follows:

Ibrutinib: Restriction Summary 7866 / ToC: 7871: Authority Required

insert	Episodicity: <i>Relapsed or refractory</i>
	Severity: [nil]
	Condition: chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
edit 18476	Indication: <i>Relapsed or refractory</i> chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: Initial treatment
7890	Clinical criteria:

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7889	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
17702	Clinical criteria:
21191	The condition must have relapsed or be refractory to at least one prior therapy
	AND
10859	Clinical criteria:
10858	Patient must have a WHO performance status of 0 or 1
	AND
14393	Clinical criteria:
14392	Patient must not have previously received PBS-subsidised treatment with this drug for this condition
	AND
20320	Clinical criteria:
20319	Patient must be considered unsuitable for treatment or retreatment with a purine analogue
	AND
insert 21045	Clinical criteria:
21044	<i>The treatment must be once in a lifetime with this drug for this condition.</i>
insert 25135 draft	Prescribing Instructions: A patient may only qualify for PBS-subsidised initial treatment once in a lifetime under: <i>(i) the untreated CLL/SLL initial treatment restriction; or (ii) the relapsed or refractory CLL/SLL initial treatment restriction</i>
19736	Prescribing Instructions: A patient is 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; b) Age is 70 years or older; c) Age is 65 years or older and the presence of comorbidities (Cumulative Illness Rating Scale of 6 or greater, or creatinine clearance of less than 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) Evidence of one or more 17p chromosomal deletions demonstrated by fluorescence in situ hybridisation (FISH).
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.

Ibrutinib: Restriction Summary 7841 / ToC: 7858: Authority Required

17770	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
edit	Treatment Phase: Continuing treatment of <i>previously untreated CLL/SLL, or, relapsed or refractory CLL/SLL</i>
7890	Clinical criteria:
7889	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
11365	Clinical criteria:
11364	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
21104	Clinical criteria:
21103	Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.