5.13 IBRUTINIB, Tablet 140 mg, 280 mg, 420 mg and 560 mg, Imbruvica®, Janssen-Cilag Pty Ltd

1 Purpose of Application

1.1 The minor submission requested the listing of ibrutinib (Imbruvica®) 140 mg, 280 mg, 420 mg and 560 mg tablets under the same conditions as the currently listed ibrutinib 140 mg capsules.

2 Background and current situation

Registration status

2.1 Ibrutinib 140 mg capsules were approved by the TGA on 20 April 2015. Ibrutinib 140 mg, 280 mg, 420 mg and 560 mg tablets were approved by the TGA on 4 August 2020. The TGA accepted ibrutinib tablets as bioequivalent to the currently available capsules.

2.2 The current TGA indications of ibrutinib (tablets and capsules) are for:

- patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
- adult patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma (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 who have received at least one prior therapy, or in first-line treatment for patients unsuitable for combination chemo-immunotherapy.

Previous PBAC consideration

2.3 Ibrutinib 140 mg capsules were listed on the PBS on 1 December 2017 for relapsing remitting (RR) CLL/SLL and on 1 August 2018 for RR MCL.

2.4 At its November 2019 meeting, the PBAC recommended listing ibrutinib capsules for first line treatment of CLL/SLL and MCL. The PBAC noted that this recommendation has not yet been implemented.

2.5 Ibrutinib in tablet form has not been considered by the PBAC.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Requested listing

3.1 The submission requested the same restriction for ibrutinib 140 mg, 280 mg, 420 mg tablets as the existing listings for ibrutinib capsules for CLL/SLL and MCL (PBS item codes 11419B and 11213E). The submission only requested listing the 560 mg tablets for the MCL indication.

3.2 The requested additional listings are shown below in italics. No changes were proposed to the restrictions of the treatment of the initial or continuing treatment of RR CLL/SLL or RR MCL.

CLL/SLL indication:

medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	DPMQ[a]	Proprietary name, Manufacturer
ibrutinib 140 mg tablet, 30	*NEW*	*3*	*90*	*5*	*$8,794.45*	*Imbruvica* *Janssen-Cilag Pty Ltd*
ibrutinib 280 mg tablet, 30	*NEW*	*1*	*30*	*5*	*$5,916.69*	
ibrutinib 420 mg tablet, 30	*NEW*	*1*	*30*	*5*	*$8,794.45*	

[a] The proposed DPMQs are based on mark-ups and fees as of 1 January 2021 as a result of implementation of the 7th Community Pharmacy Agreement.

MCL indication:

medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	DPMQ[a]	Proprietary name, Manufacturer
ibrutinib 140 mg tablets, 30	*NEW*	*4*	*120*	*5*	*$11,672.21*	*Imbruvica* *Janssen-Cilag Pty Ltd*
ibrutinib 280 mg tablets, 30	*NEW*	*1*	*30*	*5*	*$5,916.69*	
ibrutinib 420 mg tablets, 30	*NEW*	*1*	*30*	*5*	*$8,794.45*	
ibrutinib 560 mg tablets, 30	*NEW*	*1*	*30*	*5*	*$11,672.21*	

[a] The proposed DPMQs are based on mark-ups and fees as of 1 January 2021 as a result of implementation of the 7th Community Pharmacy Agreement.

3.3 The PBAC considered the proposed maximum quantities and number of repeats for the lower than recommended doses (i.e. tablet strengths lower than 420 mg for RR CLL/SLL and tablet strengths lower than 560 mg for RR MCL) to be appropriate. The PBAC noted that the pre-PBAC Response maintained that the proposed maximum quantities and repeats for the lower than standard doses were appropriate, based on feedback from clinicians and market research with 25 haematologists, advising that a proportion of patients who require a dose reduction may remain on the reduced dose until progression.

3.4 Advice received from the Secretariat was that under the proposed listing, there would be no technical basis for Services Australia to decline prescriber requests for multiple prescriptions of different strengths from being requested and claimed concurrently (e.g. one 420 mg prescription with 5 repeats, in addition to one 140 mg prescription with 5 repeats in CLL/SLL). The PBAC considered that the was that this risk of dosing beyond that recommended in the Product Information is low given the toxicity associated with ibrutinib treatment. [from para 6.4]

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

4.1 The submission nominated ibrutinib 140 mg capsules as the comparator. The sponsor expected that ibrutinib tablets would replace the currently PBS listed capsules, given they are the same active medicine, daily dose, manner of administration and PBS-subsidised population.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item.

Consumer comments

5.2 The PBAC noted and welcomed the input from the Leukaemia Foundation. The Leukaemia Foundation provided comments from patients with CLL/SLL who have been treated with ibrutinib which described benefits of treatment including tolerable side effects and improving quality of life. The Leukaemia Foundation strongly supported the listing of 140 mg, 280 mg, 420 mg and 560 mg ibrutinib tablets on the basis that it would provide a more convenient dosing regimen and reduce the pill burden for patients.

Clinical studies

5.3 The minor submission presented four Phase I, open-label, randomised studies. There were two pivotal bioequivalence studies and two supportive relative bioavailability studies. The TGA's acceptance of the bioequivalence between ibrutinib capsules and tablets was based on these studies.

5.4 Details of the studies presented in the submission are provided in Table 1 below.

Table 1: Studies presented in the submission

	Study CLL1018	Study CLL1019	Study CLL1021	Study CLL1022
Study type	Relative bioavailability (BA) study	Relative bioavailability (BA) study	Pivotal bioequivalence (BE) study	Pivotal bioequivalence (BE) study
Study design and population	Single-dose, open-label, randomised, 4-way crossover study in healthy adult subjects (fasting)	Open-label, randomised, 2-way crossover study in healthy adult subjects	Single-dose, open-label, randomised, replicate crossover study in healthy adult subjects (fasting)	Single-dose, open-label, randomised, replicate crossover study in healthy adult subjects (fasting)
N	N=32	N=24	N=102	N=102
Study aim	To assess the relative BA of 4 ibrutinib tablet formulations (560 mg only) compared to the capsule (4x140 mg)	To determine the effect of food on the pharmacokinetics (PK) of ibrutinib administered as a 560 mg tablet	To assess the BE of ibrutinib 560 mg tablet compared to 4x140 mg capsules	To assess the BE of ibrutinib 140 mg tablet compared to the 140 mg capsule
Main results	Formulation D was selected as the to-be-marketed tablet formulation for further evaluation in the pivotal BE studies as it was most similar to 140 mg capsule	The effect of food on the PK of ibrutinib 560 mg tablets was similar to that previously observed for ibrutinib capsules	The 560 mg tablet met the BE criteria for AUC compared with 4×140 mg capsules. Did not meet BE criteria for C_{max} however this was not considerable clinically meaningful.	140 mg ibrutinib tablet met the BE criteria for all PK parameters of interest (C_{max}, AUC) compared with the 140 mg capsule.
Safety results	Acceptable safety and tolerability profile after single dose administration of 140 mg and 560 mg tablets and capsules in healthy subjects. No new or unanticipated safety signals were identified.			
TGA conclusion	TGA considered that the ibrutinib tablets are bioequivalent to the capsule (see TGA BE statement).			

Source: Table 7, p15 of the submission.

Economic analysis

5.5 The proposed approved ex-manufacturer prices (AEMPs) for ibrutinib tablets were based on the same price per mg as the currently listed capsules. The proposed published and effective prices for ibrutinib tablets are shown below.

Table 2: Studies presented in the submission

PBS item code	Name, strength, pack size	Published AEMP for CLL and MCL	Effective AEMP	
			CLL	MCL
11213E	Ibrutinib, 140 mg, 90-capsule pack	$8,633.29	$[redacted]	*Not applicable*
11419B	Ibrutinib, 140 mg, 120-capsule pack	$11,511.05	*Not applicable*	$[redacted]
TBC	Ibrutinib, 140 mg, 30-tablet pack	$2,877.76	$[redacted]	$[redacted]
TBC	Ibrutinib, 280 mg, 30-tablet pack	$5,755.53	$[redacted]	$[redacted]
TBC	Ibrutinib, 420 mg, 30-tablet pack	$8,633.29	$[redacted]	$[redacted]
TBC	Ibrutinib, 560 mg, 30-tablet pack	$11,511.05	*Not applicable*	$[redacted]

Source: Table 4, p12 of the submission

Estimated PBS usage & financial implications

5.6 The submission considered the listing of ibrutinib tablets would be cost neutral to the PBS as ibrutinib tablets are expected to substitute for ibrutinib capsules.

5.7 Any increase in daily divided dosing (e.g. instead of 420 mg once daily, 280 mg in the morning and 140 mg at night) should not be a concern from a financial perspective given that the pricing of the various strengths appears to be proportional.

5.8 As a minor submission, the financial estimates have not been independently evaluated.

Risk Sharing Arrangements

5.9 Risk sharing arrangements (RSAs) are currently in place for ibrutinib for RR CLL/SLL and RR MCL. The submission proposed that ibrutinib tablets be included in the existing RSAs without any change to the existing caps.

5.10 A Special Pricing Arrangement (SPA) is currently in place for the ibrutinib 140 mg capsules for both the RR CLL/SLL and RR MCL indications with rebates of [redacted]% and [redacted]% of Commonwealth expenditure respectively. The submission proposed an SPA for ibrutinib tablets with [redacted]% and [redacted]% rebates of Commonwealth expenditure for RR CLL/SLL and RR MCL respectively. The submission stated the rebate percentages are calculated based on the highest recommended strength of the tablets for each indication using the proposed mark-ups and fees as of 1 January 2021 resulting from the implementation of the 7th Community Pharmacy Agreement. The proposed SPA rebates therefore represent the highest SPA rebate possible across all tablet strengths for the RR CLL/SLL and RR MCL indications.

Quality use of medicines

5.11 The submission noted that the introduction of ibrutinib tablets could represent a significant change for patients treated with ibrutinib who currently need to take multiple capsules a day to reach the prescribed daily dose.

5.12 To ensure patients safely transition to ibrutinib tablets, the sponsor proposed colour coding of different tablet strengths in addition to implementing a quality use of medicines program one month prior to PBS listing to inform prescribers of the changes.

5.13 The pre-PBAC Response considered that listing various strengths of ibrutinib tablets was unlikely to result in higher than recommended doses being prescribed given that clinicians and patients are already familiar with ibrutinib dosing, the existing information in current clinical management guidelines and the sponsor's quality use of medicines initiatives for ibrutinib tablets.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC recommended listing ibrutinib 140 mg, 280 mg, 420 mg and 560 mg tablets for the treatment of patients with RR CLL/SLL and MCL, under the same conditions as the currently listed ibrutinib 140 mg capsules.

6.2 The PBAC considered the proposed price of ibrutinib tablets, which was based on the same cost per milligram as the 140 mg capsules, was appropriate. The PBAC considered that the equi-effective doses were ibrutinib 140 mg capsule and ibrutinib 140 mg tablet.

6.3 The PBAC recalled that it has previously recommended that for RR CLL/SLL both acalabrutinib and venetoclax in combination with rituximab are also relevant pricing comparators.

6.4 The PBAC considered that, due to the different pack sizes compared with 140 mg capsules, the proposed maximum quantity and the number of repeats were appropriate. The PBAC acknowledged that in clinical practice, a proportion of patients who receive a dose reduction would remain on the reduced dose until disease progression, to manage side effects of treatment or due to tolerability. As such, the PBAC considered that the maximum quantity and the number of repeats proposed for the lower strength tablets (i.e. tablet strengths lower than 420 mg for RR CLL/SLL and tablet strengths lower than 560 mg for RR MCL) which provide up to 6 months treatment for patients on lower than recommended dosages was appropriate.

6.5 The PBAC considered the risk that the listing of various strengths of ibrutinib tablets would result in higher than recommended doses being prescribed in clinical practice was low given the toxicity associated with ibrutinib treatment.

6.6 The PBAC advised that ibrutinib tablets should be included in the existing RSAs in place for ibrutinib without any increase to the financial caps.

6.7 The PBAC noted the 420 mg and 560 mg tablets would reduce the pill burden to one tablet daily from three capsules daily for patients with CLL/SLL and four capsules daily for patients with MCL on the maximum recommended dose.

6.8 The PBAC recalled that it had recommended ibrutinib for first-line treatment in CLL/SLL at its November 2019 meeting, but that this recommendation had yet to proceed. Should the November 2019 recommendation proceed, the PBAC considered it reasonable to add the 3 new relevant strengths/form (140 mg, 280 mg and 420 mg tablets) to the November 2019 recommendation for first-line use in CLL/SLL.

6.9 The PBAC advised that, because ibrutinib tablets are not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over currently listed form of ibrutinib, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

6.10 The PBAC advised, under Section 101 (4AACD) of the Act, that ibrutinib tablet and ibrutinib capsule should not be considered equivalent for the purposes of substitution. This is because the different pack sizes between ibrutinib capsules and ibrutinib tablets could lead to serious adverse events due to potential confusion as a result of substitution.

6.11 The PBAC noted that this submission would not meet the criteria for an Independent Review because it received a positive recommendation.

Outcome:
Recommended

7 Recommended listing

7.1 Add three new medicinal product packs (140 mg, 30, 280 mg, 30, and 420 mg, 30 tablets) to the existing 140 mg capsule medicinal product pack that has the 'Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)' indication as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
IBRUTINIB					
ibrutinib 140 mg capsule, 90	11213E	1	90	5	Imbruvica
ibrutinib 140 mg tablet, 30	*NEW*	*3*	*90*	*5*	*Imbruvica*
ibrutinib 280 mg tablet, 30	*NEW*	*1*	*30*	*5*	*Imbruvica*
ibrutinib 420 mg tablet, 30	*NEW*	*1*	*30*	*5*	*Imbruvica*
Restriction Summary 10654 / ToC: 10647					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction Type: ☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.				
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)				
	Treatment Phase: Initial treatment				
	Clinical criteria:				
	The treatment must be the sole PBS-subsidised therapy for this condition				
	AND				
	Clinical criteria:				
	The condition must have relapsed or be refractory to at least one prior therapy				
	AND				

	Clinical criteria:
	Patient must have a WHO performance status of 0 or 1
	AND
	Clinical criteria:
	Patient must not have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not have received treatment with another Bruton's tyrosine kinase (BTK) inhibitor for any line of treatment of CLL/SLL (untreated or relapsed/refractory disease); or
	Patient must have developed intolerance to another Bruton's tyrosine kinase (BTK) inhibitor of a severity necessitating permanent treatment withdrawal when being treated for relapsed or refractory CLL/SLL
	AND
	Clinical criteria:
	Patient must be considered unsuitable for treatment or retreatment with a purine analogue
	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).
Restriction Summary 10659 / ToC: 7858	
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: Continuing treatment
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition

7.2 Add four new medicinal product packs (140 mg, 30, 280 mg, 30, 420 mg, 30 & 560 mg tablets, 30) to the existing Mantle cell lymphoma indication that is attached to the existing 140 mg capsule, 120 medicinal product pack as follows:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
IBRUTINIB					
ibrutinib 140 mg capsule, 120	11419B	1	120	5	Imbruvica
ibrutinib 140 mg tablets, 30	*NEW*	*4*	*120*	*5*	*Imbruvica*
ibrutinib 280 mg tablets, 30	*NEW*	*1*	*30*	*5*	*Imbruvica*
ibrutinib 420 mg tablets, 30	*NEW*	*1*	*30*	*5*	*Imbruvica*
ibrutinib 560 mg tablets, 30	*NEW*	*1*	*30*	*5*	*Imbruvica*

Restriction Summary 10834 / ToC: 7818 – NO CHANGE	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction Type: ☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Indication: Mantle cell lymphoma
	Treatment Phase: Initial treatment
	Clinical criteria:
	The condition must have relapsed or be refractory to at least one prior therapy
	AND
	Clinical criteria:
	Patient must have a WHO performance status of 0 or 1
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	Patient must not have previously received PBS-subsidised treatment with this drug for this condition
Restriction Summary 10898 / ToC: 7865 – NO CHANGE	
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Indication: Mantle cell lymphoma
	Treatment Phase: Continuing treatment

	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition

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

8 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.

9 Sponsor's Comment

The sponsor had no comment.