4.1 RUXOLITINIB tablets 5mg, 15mg and 20mg; Jakavi®; Novartis Pharmaceuticals Australia Pty Limited.

1 Purpose of Application

1.1 Authority Required listing for ruxolitinib for first-line or second-line management of myelofibrosis in patients satisfying certain clinical criteria. The first submission was considered in July 2013, with a subsequent re-submission considered in July 2014.

2 Requested listing

Requested PBS listing:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts (initiation)	№.of Rpts (continuing)	Published dispensed price for Max. Qty	Effective Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
RUXOLITINIB						
Tablet 5 mg	56	2	5	$[redacted]	$[redacted]	Jakavi® NM
Tablet 5 mg	112	2	5	$[redacted]	$[redacted]	Jakavi® NM
Tablet 15 mg	56	2	5	$[redacted]	$[redacted]	Jakavi® NM
Tablet 20 mg	56	2	5	$[redacted]	$[redacted]	Jakavi® NM

	Intermediate-2 and High risk patients	Intermediate-1 patients	Intermediate-1 , Intermediate-2 and High risk patients
Treatment phase:	Initiation		Continuation
Episodicity	Chronic		
Condition	Myelofibrosis		
Restriction	Authority Required		
Clinical criteria	The condition must be primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis AND The condition must be intermediate risk level-2 or high risk AND The patient must be experiencing MF related symptoms	The condition must be primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis AND The condition must be intermediate risk level-1 AND The patient must have severe disease-related symptoms that are resistant, refractory or intolerant to available therapy	The condition must be primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis AND Patient must have previously been treated with PBS-subsidised ruxolitinib for this condition AND Patient must not be experiencing disease progression
Administrative advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) (or the Age Adjusted DIPSS)			Note: No increase in the maximum quantity may be authorised

The requested listing was based on a cost-effectiveness comparison with placebo in both intermediate-1 and intermediate-2 or high risk patients.

Changes to the eligibility criteria for initial and continuing treatment between the current and previous re-submission are summarised below. The current proposed restriction is in line with the stakeholder meeting consensus.

Eligibility criteria for initial and continuing treatment between the current and previous re-submission

Criteria	July 2014 re-submission	Current re-submission	Rationale
Initiation			
Splenomegaly	Must have splenomegaly, defined as a spleen palpable ≥ 5cm from the left costal margin	No requirement to have splenomegaly. Instead, must have MF related symptoms which may include splenomegaly.	Splenomegaly is just one of the symptoms of MF and is largely unrelated to constitutional symptom burden.
Intermediate-1 risk patients	Not eligible unless they would have met intermediate-2 criteria except they are aged <65 years	Requirement for intermediate-1 patients to have severe symptoms which are resistant, refractory or intolerant to available therapy	Possible for patients with severe symptoms (e.g. significant pruritus) to not be classified as intermediate-2 or high risk given the scoring focuses on night sweats, weight loss and fever. It was possible for intermediate-1 patients to be excluded due to age, which is not preferable from a clinical and ethical point of view.
Prognostic tool for risk grading	IPSS only	IPSS, DIPSS or aaDIPSS	IPSS is not designed to reassess risk categories over the course of the disease, whereas DIPSS is designed to assess prognosis at any time point after diagnosis.
Continuation			
Symptom improvement	Must demonstrate splenic response or symptom improvement on EORTC QLQ AND not experiencing disease progression	Eligible to continue treatment as long as not experiencing disease progression	Clinical opinion that there is no objective feature of MF that can be used consistently to determine when ruxolitinib should be discontinued. Criteria in current submission is based on continuation criteria for azacitidine for treatment of myelodysplastic syndrome.

Abbreviations: IPSS=International Prognostic Scoring System; DIPSS=Dynamic International Prognostic Scoring System, aaDIPSS=age adjusted Dynamic International Prognostic Scoring System
Source: pp40-46 of the re-submission

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

3 Background

3.1 TGA status: Ruxolitinib was TGA registered on 5 November 2013 for treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis

3.2 Ruxolitinib has previously been considered by the PBAC twice, in July 2013 and July 2014.

3.3 Key issues compared to the previous re-submission are summarised below.

Summary of the previous re-submission and current re-submission

<table>
<tr><th></th><th>Ruxolitinib July 2014</th><th>Current re-submission</th></tr>
<tr><td>Requested PBS listing</td><td>Second line treatment in intermediate-2 or high risk MF patients

PBAC Comment: In a stakeholder meeting (22 September 2014) it was noted that intermediate-1 patients with high symptom burden would likely benefit from ruxolitinib treatment.</td><td>First line in intermediate-2 or high risk MF patients, and second line in intermediate-1 MF patients with severe symptoms</td></tr>
<tr><td>Requested price</td><td>[redacted]% rebate on published DPMQ.
<table><tr><th></th><th>Published DPMQ</th><th>Effective price</th></tr><tr><td>5mg (56 tabs)</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>5 mg (112 tabs)</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>15mg (56 tabs)</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>20 mg (56 tabs)</td><td>$[redacted]</td><td>$[redacted]</td></tr></table></td><td>Increased to [redacted]% rebate on published DPMQ
<table><tr><th></th><th>Published DPMQ</th><th>Effective price</th></tr><tr><td>5mg (56 tabs)</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>5 mg (112 tabs)</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>15mg (56 tabs)</td><td>$[redacted]</td><td>$[redacted]</td></tr><tr><td>20 mg (56 tabs)</td><td>$[redacted]</td><td>$[redacted]</td></tr></table></td></tr>
<tr><td>Main comparator</td><td>Placebo or best supportive care

PBAC Comment: The comparator was accepted by ESC (7.8.ESC.ADV.5, July 2014)</td><td>Placebo or best supportive care</td></tr>
<tr><td>Clinical evidence</td><td>Based on COMFORT-I and COMFORT-II, which enrolled intermediate-2 or high risk patients, with data up to 144 weeks

PBAC Comment: Unchanged from July 2013 submission</td><td>Mainly based on COMFORT-I. Three single armed studies (ROBUST, Barosi 2012 and JUMP) provide supporting evidence for efficacy in intermediate-1 risk patients</td></tr>
<tr><td>Key effectiveness data</td><td>Ruxolitinib treatment is likely associated with improved survival but magnitude is confounded by high crossover. At 144 weeks, 73.5% and 61.6% of patients originally treated with placebo or BAT in the COMFORT I and II trials had crossed over to ruxolitinib respectively.

Overall survival at 144 weeks (HR (95%CI))
<table><tr><th></th><th>ITT</th><th>PP</th></tr><tr><td>COMFORT-I</td><td>0.69 (0.49, 1.03)</td><td>[redacted]</td></tr><tr><td>COMFORT-II</td><td>0.48 (0.28, 0.70)</td><td>[redacted]</td></tr></table>
PBAC Comment: The PBAC agreed with ESC that the point estimates generated by the Week 144 Kaplan Meier analyses for the ITT and PP populations should represent a lower and upper bound for the likely OS benefit base case. The PBAC noted the sponsor's argument that the PP population are likely to represent those with the greatest clinical need and thus represent the likely OS benefit base case, however the committee did not agree with this logic, stating that the economic analysis conducted did not reflect conventional economic analysis.</td><td>Same as previous re-submission. PP results from COMFORT-I used in economic modelling. Results from ROBUST and Barosi 2012 are not used in the economic model, and only median age from JUMP is used to inform relative baseline mortality of intermediate-1 patients compared to intermediate-2 or high risk patients. Mortality is adjusted based on Australian life tables and the median ages of patients in JUMP and COMFORT-1.</td></tr>
<tr><td>Key safety data</td><td>Statistically significantly more patients treated with ruxolitinib experienced anaemia and thrombocytopenia compared to those who were treated with placebo or best available therapy (BAT) for MF.

Number of adverse events
<table><tr><td>Anaemia</td><td>Rux</td><td>PBO/BAT#^</td><td>RR (95% CI)</td></tr><tr><td>COMFORT-I</td><td>64</td><td>21</td><td>2.97 (1.9, 4.6)</td></tr><tr><td>COMFORT-II</td><td>64</td><td>12</td><td>2.67 (1.5,4.6)</td></tr><tr><td colspan="4">Thrombocytopenia</td></tr></table></td><td>Same as previous submission</td></tr>
</table>

	Ruxolitinib July 2014			Current re-submission
	COMFORT-I 77 16 4.69 (2.9, 7.7) COMFORT-II 67 10 3.35 (1.8, 6.1) # COMFORT I at 24 weeks, versus PBO ^ COMFORT II, at 48 weeks, versus BAT			
Clinical claim	The submission describes ruxolitinib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo. PBAC Comment: ESC considered that although all evidence supports a conclusion of superior survival, estimating the magnitude of the actual benefit remains difficult. (7.8.ESC.ADV.8, July 2014)			Same as previous submission for both intermediate-1 and intermediate-2 or high risk patients
Economic evaluation	Cost-utility model with cost/QALY of $[redacted]. PBAC Comment: The PBAC considered that there was a lack of clarity around the appropriate clinical place of ruxolitinib in Australian practice, concerns regarding the proposed restriction, and an unacceptably high price. Each of these matters precluded the committee from reaching a conclusion that ruxolitinib was cost-effective. (7.1, PBAC minutes, July 2014)			Cost-utility model with weighted cost/QALY of [redacted] (assuming [redacted]% intermediate-2 or high risk patients (ICER = [redacted]) and [redacted]% intermediate-1 patients. (ICER = [redacted]))
Number of patients	[redacted] in Year 1 increasing to [redacted] in Year 5. PBAC Comment: DUSC considered the method used by the re-submission produced implausibly high prevalence in later years and requested that the number of patients be estimated based on literature prevalence each year rather than carried forward from the previous year			[redacted] in Year 1 increasing to [redacted] in Year 5 using the same methodology as previous re-submission. This submission however has: • A revised prevalence figure of 3.82/100,000, reduced from 4.6/100,000; and • A revised incidence figure of 1.7/100,000, increased from 1.5/100 000.
Estimated cost to PBS	$[redacted] in Year 1 increasing to $[redacted] in Year 5 for a total of $[redacted] over the first 5 years of listing.			$[redacted] in Year 1 increasing to $[redacted] in Year 5 for a total of $[redacted] over the first 5 years of listing.
PBAC decision	The PBAC deferred the proposed Authority Required listing for ruxolitinib for second line management of myelofibrosis in patients satisfying certain clinical criteria due to a lack of clarity around the appropriate clinical place of ruxolitinib in Australian practice, concerns regarding the proposed restriction, and an unacceptably high price. Each of these matters precluded the committee from reaching a conclusion that ruxolitinib was cost-effective. (7.1, PBAC minutes, July 2014)			-

Source: Compiled during the evaluation

4 Clinical place for the proposed therapy

4.1 Myelofibrosis (MF) is a rare, debilitating neoplasm associated with substantial morbidity and mortality. The re-submission sought first-line treatment for patients with intermediate-2 risk or high-risk MF (in accordance with IPSS, DIPSS or aaDIPSS) who are experiencing MF related symptoms and for patients with intermediate-1 risk MF who are experiencing severe MF related symptoms which are resistant, refractory, intolerant or not a candidate for available therapy. In comparison, the previous re-submission requested second line treatment for patients with intermediate-2 risk or high-risk myelofibrosis (in accordance with IPSS) who are resistant refractory, or intolerant or not a candidate for available therapy.

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

5 Comparator

5.1 The nominated comparator was placebo or best supportive care. While the ESC acknowledged that best available therapy (BAT) may be a more appropriate comparator for the first-line therapy request, it was considered that the comparator choice was reasonable as the benefits of ruxolitinib over placebo as measured by survival in COMFORT-I were similar to the benefit of ruxolitinib over BAT in COMFORT-II.

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 that no consumer comments were received for this item.

Clinical trials

6.3 The re-submission was based mainly on the results of one head-to-head trial comparing ruxolitinib to placebo (COMFORT-I (n=309; randomised 1:1, double blind, 24 week follow up)), which was the same as in the previous re-submission. The re-submission also presented data from COMFORT-II, ROBUST, Barosi 2012 and JUMP; however these were not relied upon in the modelled economic evaluation.

6.4 Details of the trials and studies presented in the re-submission are provided in the table below.

Trials and associated reports presented in the re-submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
COMFORT-I	A randomised, double-blind placebo-controlled trial of the JAK inhibitor INCB018424 tablets administered orally to subjects with Primary Myelofibrosis (PMF), Post-Polycythemia Vera-Myelofibrosis (PPV-MF) or Post-Essential Thrombocythemia-Myelofibrosis (PET-MF).	24th July 2013
	Verstovsek et al. A double-blind, placebo controlled trial of ruxolitinib for myelofibrosis.	NEJM 2012; 366(9):799-
	Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety and survival with ruxolitinib in patients with myelofibrosis: Results of a median 2-year follow-up of COMFORT-I.	Haematologica 2013; 98(12): 1865–1871.
	Verstovsek S, Mesa RA, Gotlib J, et al. Long-term outcomes of ruxolitinib therapy in patients with myelofibrosis: 3-year update from COMFORT-I.	Blood 2013; 122(21)
COMFORT-II	I A randomised trial of the JAK inhibitor INC424 tablets compared to best available therapy in subjects with Primary Myelofibrosis (PMF), Post-Polycythemia Vera-Myelofibrosis (PPV MF) or Post-Essential Thrombocythemia-Myelofibrosis (PET MF).	19th June 2013
	Harrison et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis.	NEJM 2012; 366(9):787-798.
	Cervantes F. Three year efficacy, safety and survival findings from COMFORT-II, a phase 3 trial comparing ruxolitinib with best available therapy for myelofibrosis.	Blood 2013; 122 (25)
ROBUST	Harrison C, Clark R, Chacko J et al. Response To Ruxolitinib In Patients With Intermediate-1, Intermediate-2 and High-Risk Myelofibrosis: Interim Results Of The UK Robust Trial.	Blood 2013, 122 (21)
	Harrison C, Clark R, Chacko J et al. Response To Ruxolitinib In Patients With Intermediate-1, Intermediate-2 and High-Risk Myelofibrosis: Interim Results Of The UK Robust Trial – poster presented at ASH December 2013 http://www.incyte.com/sites/default/files/ASH%202013_Harrison_ROBUST.pdf	ASH December 2013
Barosi 2012	Barosi G, Agarwal M, Zweegman S et al. An Individual Patient Supply Program for Ruxolitinib for the Treatment of Patients with Primary Myelofibrosis (PMF), Post-Polycythemia Vera Myelofibrosis (PPV-MF), or Post-Essential Thrombocythemia Myelofibrosis (PET-MF)	ASH Annual Meeting Abstracts 2012; 120(21)
JUMP	Martino B, le Coutre P, Friesshammer M et al. Safety and Efficacy of Ruxolitinib in an Open-Label, Multicenter, Single-Arm, Expanded-Access Study in Patients with Myelofibrosis (MF): An 1144-Patient Update	ASH Annual meeting Abstracts 2014. Available from https://ash.confex.com/ash/2014/webprogram/Paper70819.html

Source: Table B.2-4, pp66-69 the re-submission.

6.5 The key features of the direct randomised trial are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Ruxolitinib vs Placebo						
COMFORT-I	309	R, DB 24 week plus extension study (144 weeks FU so far) Cross over allowed during DB period	Low during R DB phase	IPSS intermediate 2 or high risk, splenomegaly, refractory or intolerant to BAT	Patients with ≥35%reduction in spleen volume OS MF symptom	Yes primary source of evidence
Ruxolitinib versus BAT						
COMFORT-II	219	R, OL 48 weeks plus extension study (144 weeks FU so far) Cross over allowed at end of DB period, but those who discontinued*could continue to the crossover/extension phase	Low during R DB phase	IPSS intermediate 2 or high risk patients , splenomegaly	Patients with ≥35%reduction in spleen volume OS MF symptom	Not used
Ruxolitinib						
ROBUST	48	OL, SA 48 weeks[a]	High	19 Int-1, 12 Int-2, 17 High risk MF[b]	• Spleen Length • MF-SAF Total and Individual Symptom Scores • Haematology Parameters	Not used
JUMP	2,025	OL, SA 24 months	High	Patients MF[b] who are treatment naïve and are intolerant of or had progressed on other therapies	• Reduction in palpable spleen length • FACT-Lym TS	Not used
Barosi 2012	1,428	OL, SA Unknown duration	High	Patients with MF[b] (Int-1, Int-2 or High) and an enlarged spleen who were determined to require ruxolitinib treatment by their doctor were considered for the IPSP	• Spleen response • Constitutional symptoms response	Not used

* Patients having a ≥25% increase in spleen volume from the on study nadir OR splenectomy

DB=double blind; MC=multi-centre; OL=open label; SA=single arm; OS=overall survival; PFS=progression-free survival; R=randomised, FU=follow up; IPSS= myelofibrosis international prognostic scoring system; Int-1=intermediate-1, Int-2=intermediate-2, High=high risk, MF=myelofibrosis, IPSP=individual patient supply program.

6.6 Information on COMFORT-II, ROBUST, Barosi 2012 and JUMP have been presented but the results of these trials have not been applied in the modelled economic evaluation.

6.7 The re-submission acknowledged that no randomised controlled trials of ruxolitinib have included intermediate-1 patients. Clinicians at the PBAC stakeholder meeting for ruxolitinib advised that intermediate-1 patients with a high symptom burden should be included in the requested population and advised that, in the absence of comparative evidence, it would be reasonable to assume that the efficacy of ruxolitinib for intermediate-1 patients would be the same as for intermediate-2 for the purpose of determining cost effectiveness. The ESC accepted this approach.

Comparative effectiveness

6.8 Results for comparative effectiveness were unchanged from the previous re-submission and are summarised in the table below.

Summary of OS events at each reporting time point in the COMFORT-I

Study	Hazard ratio (Confidence interval)	p-value
COMFORT-I (ITT)		
24 weeks[a]	0.67 (0.3,1.5)	0.33
48 weeks[b]	0.50 (0.25, 0.98)	0.0395
112 weeks[b]	0.58 (0.36, 0.95)	0.028
144 weeks	0.69 (0.49, 1.03)	0.687
COMFORT-I (PP) 144 weeks	[redacted]	[redacted]
COMFORT-I (RPSFT corrected) 144 weeks	[redacted]	[redacted]

[a] denotes original trial duration, [b] denotes unplanned analysis

RPSFT: rank preserving structural failure time model

Source: Table B.6-2, pp94-95 and Table B.6-3, p95 of the re-submission

In terms of symptom (and quality of life) improvement, in COMFORT-I, at 24 weeks:

- MF-SAF total symptom score (TSS): 45.9% of patients treated with ruxolitinib had achieved a decrease of 50% or more in the MF-SAF total symptom score (TSS); compared to only 5.3% of patients in the placebo group (OR 15.28; 95% CI: 6.93, 33.66; p<0.0001); improvements in symptoms were also rapid with the majority of responses occurring within 4 weeks of ruxolitinib initiation. The median percent improvement from baseline in the ruxolitinib group was significantly higher (p<0.0001) than in the placebo group for all 7 of the individual symptoms measured. The biggest improvement in symptoms compared to placebo treatment was for itch (111% increase in placebo versus 43% decrease in ruxolitinib treatment arm).
- Patient Global Impression of Change (PGIC): From Week 4 through to 24, the median PGIC was 2.0 (Much improved) in the ruxolitinib group versus 4.0 (no change) in the placebo group in the COMFORT-I trial. Over time, the ruxolitinib group maintained a mean PGIC score associated with symptom improvement (P<0.0001 versus baseline), whereas the placebo group maintained a mean PGIC score associated with no change.

Comparative harms

6.9 Results for comparative harms were unchanged from the previous re-submission and are summarised in the table below.

Summary of comparative harms for ruxolitinib and placebo in COMFORT-I at 144 weeks

Preferred term Maximum grade	COMFORT-I		
	Ruxolitinib (N=155) n (%)	Placebo (N=151) n (%)	OR (95%CI)
Any preferred term	115 (74.2)	84 (55.6)	**2.3 (1.3, 3.7)**
Grade 3	31 (20)	25 (16.6)	1.3 (0.7, 2.3)
Grade 4	12 (7.7)	0	**26.4 (1.6, 449.9)**
Thrombocytopenia	47 (30.3)	8 (5.3)	**7.8 (3.5, 17.1)**
Grade 3	10 (6.5)	1 (0.7)	**10.3 (1.3, 81.8)**
Grade 4	1 (0.6)	0	2.9 (0.1, 72.8)
Anaemia	38 (24.5)	9 (6.0)	**5.1 (2.4, 11.0)**
Grade 3	10 (6.5)	5 (3.3)	2.0 (0.7, 6.0)
Grade 4	6 (3.9)	0	13.2 (0.7, 235.9)
Erythropenia	NR	NR	NA
Grade 3-4	NR	NR	NA
Platelet count decreased	14 (9.0)	2 (1.3)	**7.4 (1.7, 33.1)**
Grade 3	2 (1.3)	0	4.9 (0.2, 103.6)
Oedema peripheral	9 (5.8)	10 (6.6)	0.9 (0.3, 2.2)
Haemoglobin decreased	13 (8.4)	1 (1.3)	**13.7 (1.8, 106.3)**
Grade 3	8 (5.2)	2 (1.3)	**4.0 (0.9, 19.4)**
Grade 4	2 (1.3)	0	4.9 (0.2, 103.6)
Serious AE	NR	NR	NA
*AE requiring concomitant medication**	NR	NR	NA
Clinically notable AE^*	NR	NR	NA
Haemorrhagic events	51 (32.9)	28 (25.2)	**2.2 (1.3, 3.7)**
Bruising	36 (23.2)	22 (14.6)	1.8 (0.99, 3.2)
UTI	14 (9.0)	8 (5.3)	1.8 (0.7, 4.4)
Herpes Zoster infection	3 (1.9)	1 (0.7)	3.0 (0.3, 28.8)

NA= Not applicable NR = not reported

*These events are not limited to drug related events but all reported adverse events

Text in bold indicate statistically significant differences, text in italics indicate values calculated during evaluation

Source: Table B.6.2 of the July 2014 Ruxolitinib Commentary.

The submission stated that the safety profile of ruxolitinib in ROBUST was comparable to that observed in COMFORT-I and -II. Barosi 2012 states that 81 cases of adverse or serious adverse events were reported by the investigators. It is unknown whether these led to discontinuation of ruxolitinib. The interim results for JUMP reported that 32.3% of all patients (n=1,144) reported a serious adverse event at 48 weeks, which is substantially greater than that reported in patients treated with ruxolitinib in COMFORT-II (9.6%, n=146). The ESC noted that the PSCR (p4) stated that 30.1 % of patients reported a serious adverse event at week 48 in the COMFORT II study regardless of relationship to the study drug. The PSCR states that the figure of 9.6 % in COMFORT II is for serious adverse events determined by investigators to be related to treatment with ruxolitinib. The PSCR considered that the rate of 30.1 % from COMFORT II should be compared to the rate of 32.3 % in JUMP, as the relationship of the serious adverse events to ruxolitinib in JUMP was not reported.

Benefits/harms

6.10 A summary of the comparative benefits and harms for ruxolitinib versus placebo, based on the results reported in COMFORT-I (the basis of the modelled economic evaluation) is presented in the table below.

Summary of comparative benefits and harms for ruxolitinib and placebo in COMFORT-I at 144 weeks

Trial	RUX	PBO/BAT	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				RUX	Pbo/BAT	
BENEFITS						
Spleen response defined as (≥35% reduction in volume) (at end of weeks 24 and 48 respectively)						
COMFORT I#	65/155	1/154	63.59 (8.9, 452.6)	41.9	0.6	0.41 (0.33, 0.49)
OS: COMFORT I (week 144)						
ITT		RUX	PBO	Absolute Difference		HR (95% CI)
Dead*		42/155	54/154	8		0.69 (0.49, 1.03)
Median (mths)		Not reached	Not reached	Cannot estimate		-
PP (censoring at cross over)				Absolute Difference		HR (95% CI)
Dead*		[redacted]	[redacted]	[redacted]		[redacted]
Median (mths)		Not reached	Not reached	Cannot estimate		-
HARMS (WEEK 144)				Event rate/100 patients*		
Anaemia	RUX	PBO/BAT#^	RR (95% CI)	RUX	PBO/BAT#^	RD(95% CI)
COMFORT I	64	21	2.97 (1.9, 4.6)	41.3	13.9	0.27 (0.2,0.4)
Thrombocytopenia						
COMFORT I	77	16	4.69 (2.9, 7.7)	49.7	10.6	0.39 (0.3, 0.5)

Abbreviations: RUX=ruxolitinib; PBO = placebo; RD = risk difference; RR = risk ratio; ITT=intention to treat, PP=per protocol

Source: Table 2, July 2014 commentary

6.11 On the basis of direct evidence presented by the resubmission, for every 100 intermediate-2 and high risk patients treated with ruxolitinib in comparison to placebo;

- Approximately 8 fewer patients will have died over a median duration of follow-up of 144 weeks.
- Approximately 41 additional patients who are intolerant or irresponsive to BAT would have a spleen response over a maximum duration of follow-up of 24 weeks.
- Approximately 27 additional patients would have at least one anaemic episode over a median duration of follow-up of 144 weeks compared to placebo.
- Approximately 39 additional patients would have at least one thrombocytopenia episode over a median duration of follow-up of 144 weeks compared to placebo.

6.12 The PBAC recalled that based on the corresponding data from the COMFORT-II study presented in July 2014, for every 100 intermediate-2 and high risk patients treated with ruxolitinib in comparison with BAT;

- Approximately 10 additional patients will be alive at 144 weeks.

The PBAC also noted that for both the COMFORT-1 and COMFORT-II studies, the crossover of patients from placebo or BAT to ruxolitinib means that the degree of improvement in overall survival is uncertain, and may be greater than the observed estimates, which are based on the intention-to-treat analyses.

Clinical claim

6.13 The re-submission described ruxolitinib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo or BAT in intermediate-1, intermediate-2 and high risk MF patients. The ESC considered this reasonable, noting the lack of comparative data for the intermediate-1 population. The ESC also considered that the magnitude of benefit in overall survival and quality of life for intermediate-2 and high risk MF patients is highly uncertain given the high degree of cross over in COMFORT-I and COMFORT-II.

6.14 The PBAC noted that the pre-PBAC response highlighted that modelled survival estimates in the arm representing the current scenario (i.e. ruxolitinib not being available) were validated with observed historical cohort data as reported by Price et al, 2014.

6.15 The PBAC agreed with ESC that the claim of superior comparative effectiveness was reasonable; noting the lack of comparative data for the intermediate-1 population and the continuing difficulty of estimating the magnitude of the benefit due to crossover in the COMFORT trials.

6.16 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.17 The re-submission presented a modelled economic evaluation, which is identical in structure to the previous re-submission from July 2014. The main changes to the model were:

- Cost of ruxolitinib decreased from $[redacted] per cycle to $[redacted], reflecting an additional [redacted]% discount for a total of [redacted]% on the ex-manufacturer price; and
- Inclusion of intermediate-1 patients, representing [redacted]% of all patients treated with ruxolitinib. Mortality in intermediate-1 patients is lower (47% of intermediate-2 or high risk patients) but efficacy is assumed to be the same as in intermediate-2 or high risk patients.

The ESC noted that even though the proposed restrictions no longer contained discontinuation criteria, the economic model continued to assume that patients would stop treatment if they transition to spleen non-responder with uncontrolled symptoms. Given the absence of discontinuation criteria in the proposed restrictions, the ESC did not accept the assumption of discontinuation in the model. The Pre-PBAC response accepted the ESC concern and provided a revised ICER with the discontinuation in the model removed.

Summary of model structure and rationale

Component	Summary
Time horizon	20 years in the model base case versus 3 years in trial
Outcomes	LYG and QALYs
Methods used to generate results	Cohort expected value analysis
Health states	In the model, patients are cycled through the following health states over the modelled time horizon: •baseline state with controlled pain/fatigue • spleen response with controlled pain/fatigue • no spleen response but controlled pain/fatigue • dead
Cycle length	24 weeks/44 cycles
Transition probabilities	Derived from the COMFORT I trial using individual patient data (IPD) and following the per protocol principle.

Source: Table 3, July 2014 commentary

Key drivers of the model

Description	Method/Value	Impact
Cost of ruxolitinib	Changing cost of ruxolitinib rebate significantly changes cost effectiveness	High
Discontinuation	The re-submission assumes that patients with no spleen response and uncontrolled pain and fatigue will discontinue treatment. However, in these patients, COMFORT-I showed that there is a 24% chance for the patient to return to a state with controlled pain and fatigue (with or without splenic response) and, given the lack of alternatives and lack of discontinuation criteria in the proposed restriction, the ESC considered discontinuation to be unreasonable.	Moderate, favours ruxolitinib.
Proportion of patients crossing over to ruxolitinib with uncontrolled pain/fatigue	Base case assumes 80% of patients who crossed over from placebo to ruxolitinib in COMFORT-I had uncontrolled pain/fatigue. The model is not very sensitive to minor changes (such as decreasing to 50%).	Minor
Risk category according to IPSS	Intermediate-2 or high risk patients have a lower ICER compared to intermediate-1 patients in the model, as intermediate-1 patients have a lower baseline mortality rate. The re-submission assumes only [redacted]% of all patients using ruxolitinib are intermediate-1 patients, but as this proportion increases, the ICER will also increase	Moderate

Source: compiled during the evaluation

Results of the economic evaluation

Modelled evaluation (specify which parameters have changed)			
Intermediate-1 patients			
	Ruxolitinib	Placebo	Incremental
Costs	$	$10,356	$
Life years gained*	5.015	2.389	2.626
		Incremental cost/ life year gained	$
Cost	$	$10,356	$
QALY	3.163	0.936	2.227
		Incremental cost/QALY gained	$
Intermediate-2 or high risk patients			
Costs	$	$10,822	$
Life years gained*	5.015	2.389	2.626
		Incremental cost/ life year gained	$
Cost	$	$10,822	$
QALY	3.163	0.936	2.227
		Incremental cost/QALY gained	$
Intermediate-2 or high risk patients (July 2014 submission)			
Cost	$	$10,822.04	$
QALY	5.015	2.389	2.626
		Incremental cost/QALY gained	$
Weighted ICER in current re-submission			
	ICER	Proportion	
Intermediate-2 or high risk	$		
Intermediate-1	$		
		Total weighted ICER for base case in re-submission	$

*The submission assumes that the efficacy, defined by life years and QALY gain, is the same in intermediate-1 and intermediate-2 or high risk patients

Source: Tables D.5-1 and D.5-2, p122 of the re-submission; Tables D.5-3 p123 of the re-submission; Tables D.5-4 p123 of the re-submission and table 5, July 2014 commentary

6.18 The ICER was lower than the previous re-submission, reflecting an increase in the rebate from % of published DPMQ to %, but was partially offset by inclusion of intermediate-1 patients, who had a lower baseline risk of mortality and therefore incur more drug costs for the same (assumed) benefit. For intermediate-2/high risk patients, the ICER in the previous re-submission was $75,000/QALY - $105,000/QALY over 20 years compared with $45,000/QALY - $75,000/QALY in the current re-submission.

6.19 As in the previous re-submission, the results of the sensitivity analyses indicated that the model is by far the most sensitive to the price of ruxolitinib. The ICER was also sensitive to the assumption that patients will stop ruxolitinib if there is no splenic response even if symptoms are much improved; this assumption favoured ruxolitinib. As the ESC did not accept the assumption of discontinuation in the model, it considered that the ICER for the assumption of no discontinuation ($75,000/QALY - $105,000/QALY) [Table D.6.1, Comm. p42] would be more realistic in the context of the proposed restrictions.

6.20 The pre-PBAC response accepted the ESC advice that the ICER for the assumption of no discontinuation would be more realistic, and proposed to increase the rebate to the Government from % to %, thus revising the weighted ICER from $75,000/QALY - $105,000/QALY to $75,000/QALY - $105,000/QALY.

6.21 The PBAC noted the Pre-PBAC response's revision of the ICER to $75,000/QALY – $105,000/QALY, however considered that this ICER was still not acceptably cost-effective. The PBAC considered that ruxolitinib would be cost-effective at a reduced price that produced an ICER between $45,000/QALY – $75,000/QALY and $45,000/QALY – $75,000/QALY.

6.22 The PBAC did consider whether to limit the population eligible for PBS listing to intermediate-2 and high risk patients only, as the ICER would be more certain at $45,000/QALY – $75,000/QALY based on the revised price offer in the pre-PBAC response. However, the committee's preference was to make the PBS listing available for patients with an unmet need who will benefit clinically, and as identified at the stakeholder meeting this includes intermediate-1 patients with high symptom burden.

Drug cost/patient/year:

6.23 Assuming 13 packs of ruxolitinib per year, with each pack lasting for 28 days, the drug cost per patient per year (based on the effective price) was $[redacted] (at a dose of 5mg twice daily), $[redacted] (at a dose of 10mg, 15mg or 20mg twice daily) and $[redacted] (at a dose of 25mg twice daily). This compared with $[redacted], $[redacted] and $[redacted] in the previous re-submission, respectively.

Estimated PBS usage & financial implications

6.24 The re-submission was not considered by DUSC. An epidemiological approach was used to estimate the extent of use and financial impact for ruxolitinib. Changes compared to the previous re-submission include:

- New prevalence and incidence rate estimates;
- Lower price to reflect increase of rebate; and
- Inclusion of intermediate-1 patients to reflect changes to requested restriction.

6.25 The re-submission's estimates are provided in the table below.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Int-2 or high risk MF patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severely symptomatic Int-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake - Int-1	[redacted] %	[redacted] %	[redacted] %	[redacted] %	[redacted] %
Uptake – Int-2	[redacted] %	[redacted] %	[redacted] %	[redacted] %	[redacted] %
Estimated net cost to Government PBS/RPBS/MBS					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to Government (PBS/RPBS/MBS)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Patients assumed to use 13 packs, or 7 packs if they discontinue treatment.
Costs reported are effective prices, net of patient co-payments. Hospitalisation costs are not included.
Source: Technical document 8: JAKAVI myelofibrosis – Excel Section E – NOV 2014 FINAL.xslx,

6.26 The redacted table above shows the estimated net cost to the PBS/MBS to be $20 - $30 million per year in years 1-2 and $30 - $60 million in years 3 to 5.

6.27 The ESC noted that the sponsor acknowledged some errors in the financial estimates which were corrected in the recalculations undertaken during the evaluation (PSCR, p3). These include;

- An error in the half cycle correction for patients who discontinued treatment. For patients who discontinued treatment a mid-cycle correction of 0.46 was used in the submission. 7 packs was used for the correction;
- Patients who were newly diagnosed were considered untreated in the year of diagnosis in the submission. The recalculated estimates included a half cycle correction for the incident patients to account for the treatment of new patients.

6.28 The ESC noted that the sponsor stated it was unable to replicate the recalculations presented in the Commentary (PSCR, p3). The recalculated estimates undertaken during the evaluation followed the submission's methodology, with the exceptions of correcting the errors noted above and using the prevalence rate of 3.82/100,000 sourced from Mehta 2013 to calculate the number of prevalent patients each year. The parameters used by the evaluator for the recalculation of estimates are as follows:

- Prevalence used to determine existing patients each year;

- Existing patients (adjusting for uptake rate and eligibility) are assumed to be treated with 13 packs per year. The number of packs is further adjusted by an assumed compliance rate ([redacted]% for int-1 and [redacted]% for int-2 or high risk) and also dose distribution from COMFORT-I;
- Patients who died are assumed to die at the beginning of the cycle and received no treatment. However, deaths do not carry over and has no impact on number of patient estimates for following cycles;
- Patients who discontinued had half cycle adjustment of 7 packs per year;
- Incidence rate used to estimate patients who were diagnosed with MF. Number of patients treated is based on number of newly diagnosed patients, adjusted by uptake rate and eligibility criteria based on risk score. New patients who are treated with ruxolitinib are assumed to use 7 packs (same as those who discontinued);
- Mortality has no influence in these estimates.

6.29 The ESC noted that the PSCR (p.3) stated that using a point prevalence estimate to determine the number of patients with myelofibrosis over time does not account for a survival benefit being associated with ruxolitinib. The ESC agreed that inclusion of survival benefit associated with ruxolitinib is appropriate and that that this will increase the prevalent pool over time. It was noted however that inclusion of a survival advantage in the financial estimates does not have a large effect on the estimated total net cost to the PBS, as shown in the sensitivity analyses around the financial estimates (table E.6.7, p.167 submission, with recalculated figures table E.6.1,p46/7 Comm.). The sensitivity analyses also demonstrated that varying the base case annual mortality for int-1 patients of [redacted]% and int-2/high patients of [redacted]% to [redacted]% and [redacted]% respectively for year 1 changed the estimated cost from $20 – $30 million per year to $20 – $30 million per year, and for the upper limit used in the sensitivity analysis of 5.6% (int-1) and 20.5% (int-2/high) the estimated cost was $20 – $30 million per year. Further it was noted that this was in the context of a highly uncertain magnitude of overall survival for int-2 and high risk MF patients given the high degree of cross over in COMFORT-I and COMFORT-II.

6.30 The number of patients estimated to be treated with ruxolitinib more than doubles over the first five years of listing. The ESC considered that a doubling of the number of patients over the first 5 years seemed high and considered that the factors driving this increase, other than increased survival, remain unclear. To assist the PBAC, the ESC recommended that a summary of the methods and assumptions in the financial estimates be prepared, highlighting what has previously been accepted by the PBAC and issues that remain unresolved. This summary was provided as a PEB addendum.

6.31 In response to the ESC advice and the PEB addendum, the pre-PBAC response outlined the following revisions to the financial estimates:

- The incidence rate was reduced to 1.2/100,000, the lower bound of the incidence estimate reported by Mehta et al, 2013.
- The [redacted]% adherence factor which incorporated permanent discontinuations was no longer applied.
- A compliance factor of [redacted]% was applied in the model which was intended to account for temporary discontinuations due to adverse events or other reasons.

- The revised estimates also incorporated the further price reduction offered in the pre-PBAC response.

Revised estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated number of patients					
Intermediate-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate-2 and high risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated number of scripts					
Intermediate-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate-2 and high risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS					
Intermediate-1, intermediate-2 and high risk	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated net cost to Government (PBS/RPBS/MBS)					
Intermediate-1, intermediate-2 and high risk	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Costs reported are effective prices, net of patient co-payments. Hospitalisation costs are not included.
Source: Item 4.01 ruxolitinib Pre-PBAC Excel Section E.xls

6.32 The redacted table above shows the estimated total net cost to the PBS/MBS to be $20 - $30 million per year in year 1 and $30 - $60 million per year in years 2 to 5.

6.33 According to the revised estimates from the pre-PBAC response, at year 5, the estimated number of patients treated was less than 10,000 per year and the net cost to the PBS would be $30 – $60 million per year, as shown in the table above.

6.34 The PBAC noted the uncertainty in the financial estimates, as raised by ESC and outlined in the PEB addendum, particularly in relation to the large increase in patients over five years. The PBAC noted that to address this issue, the pre-PBAC response revised the financial estimates by reducing the incidence rate to the lower bound of the estimate provided by Mehta et al. However the PBAC noted that the number of patients still increases substantially from less than 10,000 per year in Year 1 to less than 10,000 per year in Year 5. The PBAC accepted the revised number of patients as stated in the pre-PBAC response as the upper limit of use.

6.35 The PBAC considered that ruxolitinib could potentially be used outside of the eligible population in patients with myelofibrosis but with lower symptom burden or in other chronic myeloid neoplasms.

Quality Use of Medicines

6.36 The re-submission (pp170-171) included further information on a ruxolitinib compassionate use program which enrolled patients in accordance with the COMFORT-1 trial eligibility criteria. The submission stated that participation in the program exposed clinicians to appropriate methods of identifying eligible patients, and appropriate dosing practices. The submission also outlined a series of post-listing programs which would further educate caregivers on appropriate identification of eligible patients and appropriate dosing. This was not mentioned in the July 2014 re-submission, in which the sponsor discussed the transition of 250 patients (estimated to be over 350 patients in this re-submission) on the compassionate use program to the PBS.

Financial Management – Risk Sharing Arrangements

6.37 The sponsor is willing to enter into a risk sharing arrangement, and has presented two options: a single expenditure cap (where intermediate-1 and intermediate-2 or high risk patients are grouped together) or two expenditure caps (where intermediate-1 and intermediate-2 or high risk patients have separate caps).

6.38 The PBAC accepted the total number of patients to be treated and net costs to the PBS presented in the pre-PBAC response as an upper limit of use. The PBAC considered that a risk sharing arrangement is needed to manage the total budget impact of the listing of ruxolitinib.

6.39 The PBAC considered, in the context of the less certain cost-effectiveness but likely higher persistence on treatment for the eligible intermediate-1 group, and possible use in patients with less severe disease burden, that the risk share agreement should also ensure that the maximum number of intermediate-1 patients does not exceed the number of intermediate-1 patients estimated in the pre-PBAC response.

7 PBAC outcome

7.1 The PBAC recommended the listing of ruxolitinib for the treatment of myelofibrosis.

7.2 The PBAC was satisfied that ruxolitinib provides a major advance in care for patients with poor prognosis and/or with symptoms refractory to current care.

7.3 The PBAC accepted the clinical place for ruxolitinib, noting advice from expert clinicians at the PBAC stakeholder meeting for ruxolitinib. The PBAC agreed that intermediate-1 patients with a high symptom burden should be included in the requested population, noting that no randomised controlled trials of ruxolitinib have included intermediate-1 patients.

7.4 The PBAC accepted the nominated comparator of placebo or best supportive care.

7.5 The PBAC noted the pre-PBAC response sought to validate the survival benefit from COMFORT-1 by validating the modelled survival gain in the placebo arm with historical cohort data from Price et al (2014). The PBAC considered the extent of survival benefit remains uncertain but cannot be resolved.

7.6 The PBAC accepted that in the absence of comparative evidence for the intermediate-1 population, it would be reasonable to assume that the effectiveness of

ruxolitinib for intermediate-1 patients would be the same as for intermediate-2 for the purpose of determining cost effectiveness, noting the difference in baseline mortality risk.

7.7 The PBAC considered that ruxolitinib could potentially be used outside of the eligible population in myelofibrosis with lower symptom burden or in other chronic myeloid neoplasms. The PBAC recommended a written Authority required restriction for initial use, with continuation by telephone Authority approval to mitigate this risk.

7.8 The PBAC requested that DUSC review the utilisation of ruxolitinib 12 – 24 months following listing.

7.9 The PBAC recommended that ruxolitinib should not be treated as interchangeable with any other drugs.

7.10 The PBAC advised that ruxolitinib is not suitable for prescribing by nurse practitioners.

7.11 The PBAC recommended that the Safety Net 20 Day Rule should apply for the continuation restrictions.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Intermediate-2 and high risk initiation

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
RUXOLITINIB				
Tablet 5 mg	56	0	Jakavi®	NM
Tablet 5 mg	112	0	Jakavi®	NM
Tablet 15 mg	56	0	Jakavi®	NM
Tablet 20 mg	56	0	Jakavi®	NM

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	Chronic
Severity:	High risk and Intermediate-2 risk
Condition:	Myelofibrosis
PBS Indication:	Myelofibrosis

Treatment phase:	Initiation
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	The condition must be primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.
Administrative Advice	Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) (or the Age Adjusted DIPSS).

Intermediate-2 and high risk continuation

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
RUXOLITINIB				
Tablet 5 mg	56	5	Jakavi®	NM
Tablet 5 mg	112	5	Jakavi®	NM
Tablet 15 mg	56	5	Jakavi®	NM
Tablet 20 mg	56	5	Jakavi®	NM

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Severity:	High risk and Intermediate-2 risk
Condition:	Myelofibrosis
PBS Indication:	Myelofibrosis
Treatment phase:	Continuation
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	The condition must be primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. AND Patient must have previously been treated with PBS-subsidised ruxolitinib for this condition.

Administrative Advice	Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) (or the Age Adjusted DIPSS). Note: No increase in the maximum quantity may be authorised.

Intermediate-1 risk initiation

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
RUXOLITINIB				
Tablet 5 mg	56	0	Jakavi®	NM
Tablet 5 mg	112	0	Jakavi®	NM
Tablet 15 mg	56	0	Jakavi®	NM
Tablet 20 mg	56	0	Jakavi®	NM

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	Chronic
Severity:	Intermediate-1 risk
Condition:	Myelofibrosis
PBS Indication:	Myelofibrosis
Treatment phase:	Initiation
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Clinical criteria:	The condition must be primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. AND Patient must have severe disease-related symptoms that are resistant, refractory or intolerant to available therapy.
Administrative Advice	Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) (or the Age Adjusted DIPSS).

Intermediate-1 risk continuation

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
RUXOLITINIB				
Tablet 5 mg	56	5	Jakavi®	NM
Tablet 5 mg	112	5	Jakavi®	NM
Tablet 15 mg	56	5	Jakavi®	NM
Tablet 20 mg	56	5	Jakavi®	NM

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	Chronic
Severity:	Intermediate-1 risk
Condition:	Myelofibrosis
PBS Indication:	Myelofibrosis
Treatment phase:	Continuation
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Clinical criteria:	The condition must be primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. AND Patient must have previously been treated with PBS-subsidised ruxolitinib for this condition. AND Patient must have severe disease-related symptoms that are resistant, refractory or intolerant to available therapy.
Administrative Advice	Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) (or the Age Adjusted DIPSS). Note: No increase in the maximum quantity may be authorised.

Grandfathered

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
RUXOLITINIB				
Tablet 5 mg	56	5	Jakavi®	NM
Tablet 5 mg	112	5	Jakavi®	NM
Tablet 15 mg	56	5	Jakavi®	NM
Tablet 20 mg	56	5	Jakavi®	NM

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Severity:	High risk, Intermediate-2 risk and Intermediate-1 risk
Condition:	Myelofibrosis
PBS Indication:	Myelofibrosis
Treatment phase:	Grandfathered patients
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	The condition must be primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. AND Patient must have previously received non-PBS subsidised ruxolitinib for this condition prior to [listing date].
Administrative Advice	Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) (or the Age Adjusted DIPSS). Note: No increase in the maximum quantity may be authorised.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.