7.8 RUXOLITINIB, 5mg, 15mg, 20mg tablets, Jakavi®, Novartis Pharmaceuticals Australia Pty Ltd

1 Purpose of Application

1.1 The submission requested an Authority Required listing for ruxolitinib for second line management of myelofibrosis in patients satisfying certain clinical criteria.

2 Requested listing

2.1 The main differences to the July 2013 submission are: 1) change from first line to second line listing; 2) two alternate initiation criteria; 3) an additional [redacted]% price reduction via risk sharing; 4) a new continuation criteria; and 5) six months rather than three months initial treatment.

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

Option 1 (trial based)

Condition:	Myelofibrosis
Treatment phase:	Initial
Severity	Intermediate-2 or high risk
Restriction:	Authority Required
Clinical criteria:	*Patient must be resistant, refractory, intolerant or not a candidate for available therapy* *AND* *Patient must have splenomegaly defined as a spleen palpable ≥ 5cm from the left costal margin*
Administrative Advice	*Risk of myelofibrosis is defined in accordance with the International Prognostic Scoring System (IPSS)* *No increase in the maximum quantity or number of units may be authorised* *No increase in the maximum number of repeats may be authorised*

Option 2 (clinical needs based)

Condition:	Myelofibrosis
Treatment phase:	Initial
Severity:	Intermediate-1 risk
Restriction:	Authority Required

Clinical criteria:	*Patient must be resistant, refractory, intolerant or not a candidate for available therapy* *AND* *Patient must have splenomegaly defined as a spleen palpable ≥ 5cm from the left costal margin* *OR* *Patient must have disease related symptoms (e.g. bleeding, portal hypertension, infection, thrombosis or transformation to acute myeloid leukaemia).* *AND* *Patient must have splenomegaly defined as a spleen palpable ≥ 5cm from the left costal margin*
Population criteria	*Patient must be aged less than 65 years*
Administrative Advice	*Risk of myelofibrosis is defined in accordance with the International Prognostic Scoring System (IPSS)* *No increase in the maximum quantity or number of units may be authorised* *No increase in the maximum number of repeats may be authorised*

Continuation criteria

Condition:	Myelofibrosis
Treatment phase:	Continuing
Restriction:	Authority Required
Treatment criteria:	~~Continuing Treatment of a patient previously treated with PBS subsidised ruxolitinib~~ *Patient must have previously been issued with an authority prescription for ruxolitinib*
Clinical criteria:	~~*Who has*~~ *Patient must* demonstrate~~d~~ ~~a splenic response~~ a reduction in spleen volume of at least ~~25%~~ *35%* from baseline OR *Patient must have* ~~has~~ a combined pain and fatigue score on the EORTC QLQ-C30 of ≤ 100 AND The patient *must* ~~is~~ not *be* experiencing disease progression
Administrative Advice	*Disease progression is defined as a sustained and unexplained return of splenomegaly AND a sustained and unexplained return of symptoms OR transformation to acute myeloid leukaemia* *Patients who ~~fail to demonstrate a response to ruxolitinib~~ have progressive disease with ruxolitinib are no longer eligible for PBS-subsidised ruxolitinib.* *No increase in the maximum quantity or number of units may be authorised* *No increase in the maximum number of repeats may be authorised*

2.2 Whilst trial data support superior efficacy of second-line ruxolitinib over placebo in the trial population, there is no RCT evidence to inform the efficacy of ruxolitinib in the additional 'clinical needs' based populations that are proposed. Given that patients in this group have a lesser symptom burden and/or better prognosis the benefits of treatment with ruxolitinib are likely to be less than those observed in available RCTs. The Pre-Sub-Committee Response (p1) states the sponsor is willing to consider a restriction consistent with the available evidence if the PBAC considers that extension of a listing to include these patients is not justified.

2.3 The ESC also considered the continuation criteria based on a 25% or 35% reduction in spleen volume would not be manageable in clinical practice and that the continuation rule be removed.

2.4 The economic evaluation presented is a cost-utility analysis compared with placebo.

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

3 Background

3.1 Since the July 2013 submission, ruxolitinib has been approved by the TGA (3 July 2013) for the treatment of disease related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post essential thrombocytopenia myelofibrosis.

3.2 The TGA approved starting dose of ruxolitinib is 15 mg or 20 mg twice daily, depending on patients' platelet counts; maintenance dose is based on efficacy/safety and can be between 5 mg to 25 mg twice daily.

3.3 In July 2013 the PBAC considered ruxolitinib for first line treatment in patients with intermediate-1, intermediate-2 and high risk myelofibrosis. The submission relied on pivotal trials COMFORT I and COMFORT II, which enrolled high risk and intermediate-2 risk patients. Results for overall survival (OS) reported at 112 weeks (observed in the extension study for the COMFORT II trial) were used in the modelled economic evaluation (HR=0.51; 95% CI: 0.27, 0.99). An ICER of $45,000 – $75,000/QALY was reported (extrapolating from 2 years in the trial to 10 years). The PBAC considered that the magnitude of the survival gain of ruxolitinib was hard to determine from the included trials due to design issues including the high rates of discontinuation and cross over from the control arm of the trials. The PBAC also considered there were major issues with the model, in regards to the extrapolation of survival benefit, QoL gains and health resource utilisation from the trial population to the broader population; the utilities derived from the sponsor developed standard gamble study and model structure not permitting the capture of rapid progression after discontinuation in a small minority of patients. The listing was rejected on the basis of a high and unacceptable ICER.

4 Clinical place for the proposed therapy

4.1 The clinical place for the proposed therapy for this drug is 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 is placebo and this was accepted by ESC. The change from best available therapy (BAT) to placebo between submissions was considered appropriate given the requested listing is now for a second line population.

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 (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ruxolitinib, including improved prognosis, improved quality of life due to greatly reduced morbidity, and a more manageable treatment regimen.

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

Clinical trials

6.3 The basis of the resubmission is unchanged from the July 2013 submission; although updated OS data to 3 years is presented (data up to 2 years was presented in the previous submission).

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 in base case

*Patients having a ⩾25% increase in spleen volume from the on study nadir OR splenectomy
DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised, FU=follow up; IPSS= myelofibrosis international prognostic scoring system, MF=myelofibrosis. Source: Table 1, p 3 of the commentary

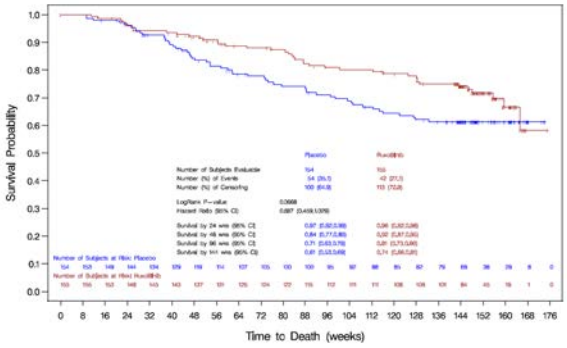
For more detail on PBAC's view, see section 7 "PBAC outcome"

Comparative effectiveness

6.4 Results of pre-planned Week 144 (3 year) results were presented in this resubmission. 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.

6.5 The results of OS reported at Week 144 in the COMFORT I and II trials are summarised in the figure below.

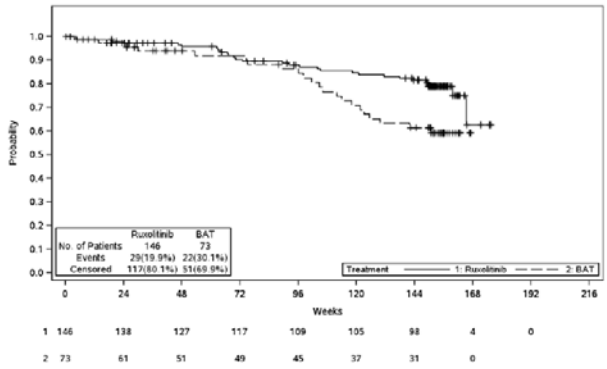
A: COMFORT I: ITT B: COMFORT I (Per Protocol , censoring at cross over)



[redacted]

Source: Figure B.6.13, p129 of the resubmission. Pg. 2659, Figure 14.4.5.1, COMFORT I Week 144 CSR; B - Pg. 2960, Figure 14.4.5.2, COMFORT I Week 144 CSR

C: COMFORT II: ITT D: COMFORT II (Per Protocol , censoring at cross over)



[redacted]

Results of overall survival reported at 144 weeks in the COMFORT I and II trials, ITT and per protocol

Source: Figure B-15, p131 of the resubmission. Pg.41, Figure 11-2, COMFORT II Week 144 CSR

6.6 The per protocol results of the COMFORT I trial were applied in the model.

6.7 The PSCR (p2) explained that the sponsor's position is that the true magnitude of OS is not likely to lie between the ITT and PP analyses, as would generally be expected. Instead the submission contends that patients crossing over in the COMFORT I trial are likely to be those with the greatest clinical need for ruxolitinib because no spontaneous resolution is expected, and they have exhausted all other treatment options. Therefore, the results from the PP analysis are suggested to be more applicable than the ITT analysis. The PSCR highlighted that the external validity of the PP model results was demonstrated with survival for the placebo arm aligning with observed survival in a historical cohort of patients with intermediate-2 and high risk myelofibrosis, as reported by Cervantes 2009. Since the preparation of the submission, another report has been published (Price et al 2014) and the PSCR also suggested that this supports the external validity of the PP model, although survival

may be overestimated in the Price et al 2014 report given patients were not limited to intermediate-2 or high risk myelofibrosis.

6.8 ESC considered sensitivity analyses using the ITT population, adjusted for cross over using RPSFT would be informative.

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

Comparative harms

6.9 At 144 weeks, the nature of adverse events does not differ greatly from the data presented for the Week 24 and Week 48 analyses of the COMFORT I and COMFORT II trials. Across both trials and all follow up periods, significantly more patients treated with ruxolitinib experienced anaemia and thrombocytopenia. The resubmission also examined the risk for developing ruxolitinib withdrawal syndrome, a phenomenon first reported by Tefferi et al (2011). No cases of rebound had occurred in the COMFORT trials. The rate of severe adverse events was similar for patients who discontinued ruxolitinib or placebo.

6.10 A summary of the comparative benefits and harms for ruxolitinib versus placebo is presented in the following table.

Summary of comparative benefits and harms for ruxolitinib and comparator

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)
COMFORT II^	46/144	0/73	41.8 (2.6, 669.7)	31.9	0	0.28 (0.21, 0.36)
OS: COMFORT I (week 144)						
ITT		RUX	PBO	Absolute Difference		HR (95% CI)
Dead*		42/155	54/154	-		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]
Median (mths)		Not reached	Not reached	Cannot estimate		-
OS: COMFORT II (week 144)						
ITT		RUX	BAT	Absolute Difference		HR (95% CI)
Dead*		29/146	22/73	-		0.48 (0.28, 0.85)
Median (mths)		Not reached	Not reached	Cannot estimate		-
PP (censoring at cross over)				Absolute Difference		HR (95% CI)
Dead*		NR	NR	-		[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)
COMFORT II	64	12	2.67 (1.5, 4.6)	43.8	16.4	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)
COMFORT II	67	10	3.35 (1.8, 6.1)	45.9	13.7	0.32 (0.2, 0.4)

*Maximum duration of follow-up: COMFORT I = 144 weeks; COMFORT II=144.5weeks

#COMFORT I, primary outcome assessed at 24 weeks, versus PBO
^COMFORT II, primary outcome assessed at 48 weeks, versus BAT
Abbreviations: RUX=ruxolitinib; BAT=best available therapy; PBO = placebo; RD = risk difference; RR = risk ratio; ITT=intention to treat, PP=per protocol
Source: Table 2, p 5 of the commentary

6.11 Based on the direct evidence presented by the resubmission, for every 100 patients treated with ruxolitinib in comparison to placebo (PBO) or best available therapy (BAT):

- Approximately 41 additional patients who are intolerant or irresponsive to BAT would experience a spleen response over a maximum duration of follow-up of 24 weeks.
- Approximately 28 additional patients would experience a spleen response over the maximum duration of follow-up of 48 weeks, compared to BAT.
- Approximately 27 additional patients would experience at least one episode of anaemia over a median duration of follow-up of 144 weeks, compared to PBO or BAT.
- Approximately 39 additional patients would experience at least one episode of thrombocytopenia episode over a median duration of follow-up of 144 weeks, compared to PBO.
- Approximately 32 additional patients would experience at least one thrombocytopenia episode over a median duration of follow-up of 144 weeks, compared to BAT.
- Approximately 7 additional patients will be alive after 48 weeks and 9 additional patients at 112 weeks compared with PBO. Due to crossover of patients from PBO to ruxolitinib 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.
- Approximately 8 additional patients will be alive after 112 weeks and 10 additional patients at 144 weeks compared with BAT. Due to crossover of patients from BAT to ruxolitinib 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.

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

Clinical claim

6.12 The submission describes ruxolitinib as superior in terms of comparative effectiveness and inferior yet manageable in terms of comparative safety over placebo.

6.13 ESC considered that although all evidence supports a conclusion of superior survival, estimating the magnitude of the benefit remains difficult. An expanded array of sensitivity analyses, including a non-pooled RPFST-cross-over correction (at the level of the COMFORT I trial) may assist in reducing the uncertainty around the OS benefit attributable to ruxolitinib.

6.14 In reply to the ESC recommendation regarding the non-pooled RPFST-cross-over correction, the sponsor advised that "A non-pooled RPFST cross-over analysis of COMFORT I estimates a hazard ratio of [redacted], which is close to that generated for the PP placebo-treated analysis of [redacted]. That is, survival estimated using RPSFT modelling methods for placebo-treated patients in COMFORT I is similar to that estimated by the PP analysis. This justifies use of the PP analysis within the base case of the economic model" (Pre-PBAC response, p3).

6.15 The PBAC agreed with ESC that, while the claim of superior comparative effectiveness was reasonable, estimating the magnitude of the benefit remains difficult.

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

Economic analysis

6.17 The resubmission presented a completely revised economic evaluation. The structure of model was changed to one that permits tracking of patients through progression of myelofibrosis and the presence of symptoms. The model is informed by individual patient data from the COMFORT I trial, applying the per protocol efficacy results.

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 • baseline state with uncontrolled pain/fatigue • spleen response but uncontrolled pain/fatigue • no spleen response and uncontrolled pain/fatigue
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 (see Section C.2.1 for more details)

Source: Table 3, p6 of the commentary

Key drivers of the model

Description	Method/Value	**Impact**
Cost of ruxolitinib	Reducing costs for ruxolitinib by 10% due to discontinuing patients not utilising full 6 months therapy.	Minor
Efficacy	In the trial based economic evaluation the use of ITT rather than PP results resulted in a doubling of the ICER ($/LY gained) over 3 years in both the COMFORT I and II trials indicating sensitivity of the results to this efficacy outcome.	Major
Health state utilities	The utilities estimated in the resubmission show a large difference in utility for individuals with or without symptom control [redacted] but only minimal difference in utility between spleen responders and non-responders [redacted] Although the approach taken by the resubmission appears appropriate, other reported utility weights in MF indicate smaller impact of symptoms on health state utilities eg, Roskell et al (2012) reported a 0.191 difference between patients with and without constitutional symptoms. This is tested in the model applying a 0.191 difference between patients with and without controlled pain/fatigue in the model.	Moderate

Source: Table 4, p6 of the commentary.

6.18 The ESC noted that the choice of utilities algorithm favoured ruxolitinib and expressed concerns as to whether the algorithm used was best for the data analysed. The model however is only moderately sensitive to changes in utilities.

Results of the stepped economic evaluation

Step and component	Ruxolitinib	Placebo	Increment
[redacted]			
Incremental cost/extra LY gained over 20 years			$[redacted]
Incremental cost/extra QALY gained over 20 years			$[redacted]

6.19 The model is most sensitive to changes in the price of ruxolitinib; therefore alternate assumptions regarding the price of ruxolitinib were tested in sensitivity analyses during the evaluation; differing time horizons and health state utilities were also analysed. For results see the table below:

Results of univariate sensitivity analyses

Variables altered in sensitivity analysis	Incremental costs	Incremental QALYs	ICER
[redacted]			

Variables altered in sensitivity analysis	Incremental costs	Incremental QALYs	ICER
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Italics represent additional sensitivity analysis conducted during the evaluation
^See Table D.1 of Attachment D for the effective prices of ruxolitinib after application of the rebates.

[redacted]

6.20 The modelled economic evaluation is based on the results of COMFORT I per protocol analyses. As pointed out by the resubmission 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. Thus ESC considered the base case ICER of $75,000 – $105,000 would represent an optimistic scenario.

6.21 Given the high clinical need for treatments for patients with myelofibrosis, the PBAC was concerned about exclusion of patients who may benefit from ruxolitinib through a restriction that reflected only trial-based entry criteria. Given the lack of specific treatment for myelofibrosis and the clinical need of symptomatic patients with poor prognosis, PBAC was willing to consider that an ICER in a higher than usual range (up to $70,000/QALY) may be justified. However, the current submission base case of $75,000 – $105,000/QALY was optimistic and unacceptable as a basis for concluding that ruxolitinib was cost-effective. Consequently, the PBS listing could not be recommended at the price offered by the sponsor.

6.22 The drug cost/patient/year based on the average cost in the COMFORT trial was $[redacted] over 48 weeks.

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

Estimated PBS usage & financial implications

6.23 This submission was considered by the Drug Utilisation Sub Committee (DUSC).

6.24 The estimated PBS usage and financial implications are presented in the tables below.

Base case estimates (adjusted during evaluation)

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated use of ruxolitinib and financial implication to PBS/RPBS					
Total eligible population (trial based restriction)	[redacted]				
Total eligible population (clinical need based restriction)	[redacted]				
Total patients likely to be treated (trial based restriction)	[redacted]				
Total patients likely to be treated (clinical need based restriction)	[redacted]				
Symptomatic int-1 patients	[redacted]				
Ruxolitinib scripts (trial based restriction)	[redacted]				
	[redacted]				
Ruxolitinib scripts (clinical need based restriction)	[redacted]				
	[redacted]				
Ruxolitinib cost^ to PBS/RPBS[d] (trial based restriction)	[redacted]				
Ruxolitinib cost to PBS/RPBS[d] (clinical need based restriction)	[redacted]				

Estimated financial implications for government health budgets

Additional cost to MBS and state governments (trial based restriction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional cost to MBS and state governments (clinical need based restriction)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost^ to government health budget (trial based restriction)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost^ to government health budget (trial based restriction)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table E.2-5, p73 of the commentary
[a]*used for delivering 5mg bd and 25mg bd dosages* [b] *used for delivering the 10mg bd dosage* [c]*used for delivering 20mg bd and 25mg bd dosages* [d] Net of patient co-payments, differs slightly to figure in the submission as they did not remove cost of copayments
^The effective price (after applying the rebate) has been used in the cost calculations.

6.25 The DUSC considered that the prevalence estimate of 4.61/100,000 used as the starting point in the submission was an overestimate. DUSC noted that this Year 1 prevalence estimate was calculated by extrapolating the age-adjusted prevalence reported in Mehta et. al. (ranging from 2.1-3.8/100,000 for the years 2008-2010), assuming that prevalence is increasing in a linear fashion over time. The DUSC considered this to be an inappropriate extrapolation, as it is not reasonable to assume that a rare condition would increase at such a rate and the incidence was not expected to increase by a comparable margin. To calculate prevalence estimates in Years 2 to 5, the submission added incident cases and subtracted deaths. While DUSC considered that the incidence and mortality parameters were based on appropriate data sources, as the calculations commenced from an overestimated Year 1 prevalence, these resulted in implausibly high prevalence across the five years. The DUSC requested that the base case estimates of use and financial implications be recalculated using a prevalence of 3.8/100,000; the upper limit of the range from Mehta et.al. The DUSC requested that this method be used to calculate prevalence for each year, not just Year 1, and that the re-estimated calculations use the trial based population and no continuation rule. The DUSC considered this would provide a closer estimate of the projected use in the trial based population.

Estimated extent of use and financial implications – re-estimates.

	Year 1	Year 2	Year 3	Year 4	Year 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients expected to meet the restriction: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible patients to be treated with ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ruxolitinib scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS (net of co-payments):	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subtotal additional cost to Government health budget:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to Govt health budgets: (PBS/RPBS + additional cost to Govt)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 2, p 4 of the DUSC advice.

6.26 The DUSC advised that there is high potential for use to occur beyond the requested restriction, as the distinction between first and second line is open to interpretation. The DUSC advised this is due to subjective, weakly defined terms such 'resistant', 'refractory', 'intolerant' and 'not a candidate for available therapy'. The DUSC also noted the potential for broad interpretation of symptom severity, and advised that this could lead to use in the majority of intermediate-1 patients, particularly due to the lack of available treatments for myelofibrosis, and the perceived benefit of treatment.

6.27 The submission states that currently more than [redacted] patients are enrolled in the compassionate access program, which has eligibility criteria in line with those of the COMFORT trials (submission, Section F, p383). Should ruxolitinib be listed, the submission assumes that these patients would be grandfathered to PBS subsidised ruxolitinib. The DUSC noted that it is unclear how long these patients continue on treatment with ruxolitinib and if they are required to meet continuation criteria as included in the proposed restriction.

6.28 The DUSC advised that the likelihood and possible extent of usage beyond the estimations in the submission was low for the trial based restriction due to overestimation of the prevalent population and high for the clinical need based restriction, as the proportion of patients estimated to meet the restriction criteria are substantially underestimated for the clinical need based restriction.

6.29 The ESC noted that a [redacted]% rebate on the ex-manufacturer price was offered ([redacted]% [redacted] compared to July 2013). PBAC had previously recommended the inclusion of a mechanism within risk sharing to obtain data (survival, durability of response and reasons for treatment failure) for patients treated with ruxolitinib in Australian clinical practice, to better inform future decisions about how this disease should be treated. This has not been addressed by the resubmission.

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

7 PBAC Outcome

7.1 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.

7.2 The PBAC noted the sponsor's request in the pre-PBAC response to limit the restriction to intermediate-2 and high risk patients, so as to ensure the restriction was consistent with the current available clinical evidence. The committee considered this inappropriate as it would exclude lower risk patients who still demonstrated a clear clinical need. The PBAC considered there is a clinical need for ruxolitinib in the treatment of myelofibrosis and that there are patients who may benefit from treatment across the risk groups.

7.3 The PBAC noted that the distinction between first and second line use was open to interpretation, as differentiating definitions such as 'resistant', 'refractory', 'intolerant' and 'not a candidate for available therapy' were highly subjective. The potential for broad interpretation of symptom severity was also noted. The PBAC, in agreement with DUSC, expressed concern that there was potential for ruxolitinib use in the

majority of intermediate-1 patients, particularly due to the lack of available treatments for myelofibrosis and the perceived benefit of treatment.

7.4 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.

7.5 The PBAC agreed with DUSC that the likelihood, and possible extent, of usage beyond the estimations in the submission was low for the trial based restriction due to overestimation of the prevalent population, and high for the clinical need based restriction, as the proportion of patients estimated to meet the restriction criteria were substantially underestimated for that restriction.

7.6 The PBAC noted that identification of patients for the ruxolitinib clinical trials (COMFORT I and II) was facilitated by the International Prognostic Scoring System (IPSS), which uses an initial risk classification. The Committee advised that the use of the Dynamic International Prognostic Scoring System (DIPSS) may be more beneficial than the IPSS in defining the appropriate patient population, as the DIPSS takes into account disease progression over time since diagnosis.

7.7 The PBAC considered that the continuation criteria based on a 25% or 35% reduction in spleen volume would not be manageable in clinical practice and advised that the continuation rule be removed.

7.8 The PBAC noted the clinical need for this product and welcomed input from individuals and organisations about the range of benefits of this treatment.

7.9 The PBAC recommended a stakeholder meeting be held between the sponsor, the Department, clinicians from applicable professional bodies, consumer representatives and PBAC members to provide clarity around the clinical place for ruxolitinib and to consider an appropriate restriction. This in turn would inform the cost-effectiveness analyses.

7.10 The PBAC noted the sponsor's willingness to enter into discussions regarding a risk share arrangement. The Committee considered it appropriate for a RSA to be in place to manage associated financial risk.

Outcome:
Deferred

8 Context for Decision

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

9 Sponsor's Comment

Novartis welcomes the opportunity for a stakeholder meeting and determining the next steps towards a PBS listing for ruxolitinib in myelofibrosis.