Public Summary Document

Product: Ruxolitinib, tablets, 5 mg, 15 mg and 20 mg, Jakavi®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission requested an Authority required listing for the treatment of disease-related symptoms in patients with intermediate or high-risk primary (idiopathic) myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

The submission was considered under TGA/PBAC parallel processes. At the time of consideration by the PBAC in July 2013, the Clinical Evaluation Report,TGA Delegate's Overview and the Australian Committee on Prescription Medicines (ACPM) recommendation were available.

2. Background

This was the first consideration by the PBAC of ruxolitinib for myelofibrosis.

3. Registration Status

Ruxolitinib was TGA registered on 3 July 2013 for the treatment of disease related splenomegaly or symptoms in patients with primary myelofibrosis, post polycythemia vera myelofibrosis or post essential thrombocythemia myelofibrosis.

4. Listing Requested and PBAC's View

Authority required

Treatment of disease-related symptoms in patients with intermediate or high-risk (IPSS/DIPSS) primary (idiopathic) myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

Note: ruxolitinib is to be continued for as long as the clinician determines the patient is deriving a clinical benefit

The PBAC noted that the requested restriction was broader than the trial population but not as broad as the TGA registered indication.

The PBAC considered that the requested restriction would allow access to ruxolitinib treatment for intermediate risk level-1 primary myelofibrosis patients who were not included in the COMFORT 1 and COMFORT II clinical trials. These patients have a better prognosis and on average a lower symptom burden, so benefit from treatment will be less than for high risk or intermediate risk level-2 patients.

The PBAC also considered that restricting treatment to the trial population or to high and intermediate risk level-2 patients may disadvantage symptomatic patients with an otherwise good prognosis.

5. Clinical Place for the Proposed Therapy

Myelofibrosis is a rare condition of variable prognosis and severity. It is a myeloproliferative neoplasm of haemopoietic stem cells that can arise de novo or develop as part of the evolution of two related conditions, polycythemia vera and essential thrombocythemia. The disease causes fibrosis or scarring of the bone marrow, with failure of normal blood cell production, and enlargement of the spleen and liver. An inappropriate production of multiple pro-inflammatory cytokines can occur and this results in debilitating systemic symptoms (itch, sweats, bone pain, severe lethargy).

Myelofibrosis causes premature mortality through bone marrow failure, cachexia, and development of acute myeloid leukaemia. Systemic symptoms, pain and anorexia due to massive splenomegaly, and dependence on frequent blood transfusions can severely reduce a patient's quality of life. The only curative treatment is allogeneic bone marrow transplantation, and this is only possible for a small subgroup of patients. No other treatment has been shown to alter the natural history of myelofibrosis.

There is an unmet clinical need for new therapies of patients with myelofibrosis that carries a poor prognosis and / or is causing severe symptoms uncontrolled by current treatment.

The submission proposed ruxolitinib as a first line treatment for myelofibrosis.

6. Comparator

The submission nominated Best Available Therapy (BAT), including a range of active therapies such as hydroxyurea and placebo for no treatment as the comparator.

The PBAC accepted BAT as the appropriate comparator.

7. Clinical Trials

The submission presented two randomised trials comparing ruxolitinib with BAT (COMFORT-II; n=219; randomised 2:1) and with placebo (COMFORT-I; n=309; randomised 1:1). COMFORT-II was an open label, randomised controlled trial whereas COMFORT-I was a double blind, placebo controlled trial. Both trials enrolled patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis, however COMFORT-I restricted enrolment to patients who were refractory to treatment with/unable to tolerate BAT. The starting dose of ruxolitinib depended on the baseline platelet count, whilst BAT could include a single agent, a combination of agents or no therapy.

The details of the published clinical trials presented in the submission are shown in the following table:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Direct randomised trial		

COMFORT-II Harrison et al	JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis.	NEJM 2012; 366(9):787-798.
Supplementary randomised trial		
COMFORT-I Verstovsek et al.	A double-blind, placebo controlled trial of ruxolitinib for myelofibrosis.	NEJM 2012; 366(9):799-807.

Crossover from BAT to ruxolitinib was permitted during the 48 weeks of the COMFORT-II trial if spleen growth was greater than 25% and patients were able to continue in an extension trial with ruxolitinib when they discontinued from COMFORT-II. Overall, 72.6% and 61.6% of patients randomised to ruxolitinib and BAT respectively, enrolled in the extension study. All patients enrolled in the extension study were treated with ruxolitinib.

COMFORT-II was an open label trial. The outcome assessment (detection of spleen volume reduction via MRI or CT) was done by a blinded assessor. More BAT patients discontinued prematurely (57.5% compared to 37.5% in ruxolitinib treated patients), potentially due to the open label nature of the trial.

There was significant crossover in the COMFORT-II extension (post the 48 week trial period) which had a significant impact on overall survival results.

For COMFORT-I, early unblinding and cross over to ruxolitinib prior to 24 weeks occurred if spleen growth was greater than 25% and return of symptoms for patients on placebo.

8. Results of Trials

The primary outcome of the trials was a greater than or equal to 35% spleen volume reduction at 48 and 24 weeks in COMFORT-II and -I, respectively.

The proportion of patients achieving a greater than or equal to 35% spleen volume reduction was statistically significantly greater for those treated with ruxolitinib compared with those treated with BAT or placebo. Both trials also reported the results for overall survival, although neither trial was powered to detect a difference in this outcome.

The results for the primary outcome, patients with ≥35% spleen volume reduction in COMFORT-II and COMFORT-I are shown in the following table:

Trial	Ruxolitinib n/N (%)	Comparator n/N (%)	Risk difference RD (95% CI)	Odds Ratio OR (95% CI)	NNT (95%CI)
COMFORT-II*	41/144 (28.5)	0/72 (0)	0.285 (0.209, 0.361)	58.1 (3.52, 960)	4 (3, 5)
COMFORT-I^	65/155 (41.9)	1/154 (0.7)	0.412 (0.334, 0.491)	110.5 (15.1, 810)	2 (2, 3)

*The comparator was Best Available Therapy (BAT) and results reported at 48 weeks from baseline

^The comparator was placebo and results reported at 24 weeks from baseline

The results for overall survival 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). These analyses are described as being unplanned in the clinical trial reports, and

were conducted without adjusting the level of significance from 5%, despite "multiple looks" at the data. This increased the likelihood of a spurious positive result. In addition, there is confounding due to significant cross-over in the extension study.

The PBAC considered the magnitude of the survival benefit cannot be accurately determined because of issues with the trial design:

- COMFORT-I and COMFORT-II had low statistical power to detect survival differences
- crossover in COMFORT-II extension (post 48 week trial period),
- in COMFORT-II more BAT treated patients discontinued prematurely than ruxolitinib patients (57.5% versus 37.5%)
- short follow up (COMFORT-I one year, COMFORT-II two years)

With regard to comparative harms, the following table summarises some of the most commonly occurring adverse events reported in the COMFORT-II and -I trials:

Commonly occurring adverse events in COMFORT-II and -I

Preferred term Maximum grade	**COMFORT-II**			**COMFORT-I**		
	Ruxolitinib (N=146) n (%)	**BAT (N=73) n (%)**	**OR (95%CI)**	**Ruxolitinib (N=155) n (%)**	**Placebo (N=151) n (%)**	**OR (95%CI)**
Any preferred term	118 (80.8)	14 (19.2)	17.8 (8.7, 36.3)	115 (74.2)	84 (55.6)	2.3 (1.3, 3.7)
Grade 3	32 (21.9)	1 (1.4)	20.2 (2.7, 151.2)	31 (20)	25 (16.6)	1.3 (0.7, 2.3)
Grade 4	2 (1.4)	0	2.5 (0.1, 53.7)	12 (7.7)	0	26.4 (1.6, 449.9)
Thrombocytopenia	62 (42.5)	1 (1.4)	53.1 (7.2, 392.9)	47 (30.3)	8 (5.3)	7.8 (3.5, 17.1)
Grade 3	9 (6.2)	0	10.2 (0.6, 177.0)	10 (6.5)	1 (0.7)	10.3 (1.3, 81.8)
Grade 4	1 (0.7)	0	1.5 (0.1, 37.7)	1 (0.6)	0	2.9 (0.1, 72.8)
Anaemia	45 (30.8)	3 (4.1)	10.4 (3.1, 34.8)	38 (24.5)	9 (6.0)	5.1 (2.4, 11.0)
Grade 3	13 (8.9)	0	14.9 (0.9, 253.7)	10 (6.5)	5 (3.3)	2.0 (0.7, 6.0)
Grade 4	0	0	NA	6 (3.9)	0	13.2 (0.7, 235.9)

The submission provided additional safety information beyond the trial data. The two year update of COMFORT-II showed that there were no new adverse events observed that were not reported in the first 48 week of the trial and a Development Safety Update Report (DSUR) indicated that there do not appear to be any major safety issues associated with ruxolitinib.

Ruxolitinib causes anaemia and thrombocytopenia in a significant minority of patients. Return of myelofibrosis symptoms and accelerated changes in blood count abnormalities have been recognised after discontinuation of the drug.

9. Clinical Claim

The submission described ruxolitinib as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over best available therapy.

The PBAC accepted the clinical claim of superior efficacy demonstrated in spleen response (a greater than or equal to 35% reduction in spleen size), quality of life (QoL) measures and likely in overall survival, although the magnitude of survival benefit is uncertain.

The PBAC noted the trend of the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire and Fundamental Assessment of Cancer Therapy - Lymphoma favours ruxolitinib, and expert clinician and consumer opinion that the improvements in quality of life could be highly significant for patients with severe symptoms. While the existing evidence suggests that there may be survival benefits with ruxolitinib, due to the high number of cross-over and confounding factors from the analysis of overall survival in the COMFORT-II extension study, it is uncertain what the magnitude of this benefit may be.

The PBAC did not accept the claim for equivalence in comparative safety. Patients randomised to ruxolitinib experienced significantly more drug related adverse events than patients treated with either BAT (in COMFORT-II) or placebo (in COMFORT-I). There were also significantly more cases of thrombocytopenia and anaemia in ruxolitinib treated patients compared to BAT treated patients in COMFORT-II.

10. Economic Analysis

The submission presented a modelled economic evaluation (cost utility approach/cost effective approach) based on the claim of superior efficacy.

The submission presented an ICER between $45,000 - $75,000 /QALY based on the survival outcomes reported in the extension study to the COMFORT-II trial, applied to patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis and extrapolated to 10 years duration (from 2 years in the extension study) and applying utility weights from a Sponsor-developed standard gamble study.

The model structure reflects the proposed treatment algorithm, with ruxolitinib representing a first line treatment option in addition to BAT, and with BAT considered as a second line treatment option following treatment with ruxolitinib. The model does not consider whether patients actually respond to ruxolitinib or BAT. The model is based on four treatment states – Alive on BAT, Alive on ruxolitinib, Alive on BAT post ruxolitinib and dead. Patients were assigned a utility value depending on the treatment state they are in, and it was assumed that patients on ruxolitinib will have symptom reductions (and assigned the related utility) compared to patients on BAT.

Overall survival associated with ruxolitinib is modelled by applying the hazard ratio reported at 112 weeks to an historical estimation of overall survival in MF patients. In the ruxolitinib arm, patients are either alive or dead. A constant proportion of patients is assumed to continue treatment with ruxolitinib each cycle and the remaining alive patients are assumed to move onto BAT. Patients in the BAT arm are either alive and on treatment or dead.

In the ruxolitinib group, patients who discontinued from ruxolitinib and transitioned to BAT are assumed to have the same survival outcomes as those who are still on ruxolitinib, which is a higher likelihood of survival compared to those in the BAT group with no ruxolitinib treatment. If all patients in the RUX group discontinued ruxolitinib after 1 month and moved onto BAT, the ICER is reduced by 77%, all else being equal. This assumption is a key driver of the model.

Another key driver of the model is the utilities applied to each treatment state.

The PBAC considered an analysis prepared during the evaluation that used the submission's model, but changed the following:

- Time horizon 3 years
- HR=0.48 (from 0.51 in the original model)
- Discontinuation rate = 0.0290 (from 0.0230 in the original model)
- Applying Roskell utilities:
  - 0.754 reported for responders to patients on "RUX"
  - 0.670 reported for non-responders to patients on "active BAT", on "no active treatment", and on "BAT post RUX"

The PBAC noted that this analysis illustrated the sensitivity to the assumed utilities. The ICER for this analysis was greater than $200,000 per LYG and per QALYG.

The PBAC considered there were major issues with the modelled evaluation with regard to:

- extrapolation of survival benefit, QoL gains and health resource utilisation from the trial population to the broader population;
- the assumption that patients exposed to ruxolitinib retain a survival benefit after cessation of ruxolitinib,
- the assumption that all patients on ruxolitinib have similar quality of life to an asymptomatic patient,
- utility gain estimates: the QoL instruments do not adequately capture the incapacity experienced by untreated MF patients, and lack of justification from clinical data for the health states assigned in the standard gamble study that underpins the model. The PBAC considered that in this case it would be more informative to use the values from Roskell et al (2012) (a published mapping of the EORTC QLQ-30 results from COMFORT-II to utilities), as the utilities derived from the sponsor developed standard gamble study were problematic. One concern was whether a general population would have adequate understanding of the health states being considered, and
- Transition states do not capture the issue of rapid progression after discontinuation in a small minority of patients.

The PBAC therefore considered the ICER between $45,000 - $75,000 /QALY unreliable because of uncertainties around its applicability to the proposed PBS population, multiple modelling issues, and its sensitivity to the survival gains and utilities assumed.

11. Estimated PBS Usage and Financial Implications

The PBAC considered the estimated number of patients treated per year by Year 5 to be uncertain, depending on the population included in the restriction and the enforceability of that restriction.

The submission's estimated net cost (amended during the evaluation) to the Government over the first five years of listing was between $30 million - $60 million.

The submission estimated a total net cost to the PBS between $30 million to $60 million over the first 5 years. This increases to between $60 million - $100 million depending on the approach used for estimating patient numbers.

The PBAC considered the financial estimates unreliable and a likely underestimate.

The PBAC noted the submission proposed a price reduction off the cost of each pack at the ex-manufacturer price level as part of a risk-sharing agreement. The modelled economic evaluation and the financial impacts estimated by the submission were based on the proposed effective price of ruxolitinib.

12. Recommendation and Reasons

The PBAC rejected the submission requesting PBS listing of ruxolitinib for treatment of myelofibrosis on the basis of a high and unacceptable ICER.

The PBAC considered the ICER between $45,000 - $75,000/QALY unreliable because of modelling issues and sensitivity to assumed survival and utility gains. The PBAC considered that the ICER was highly underestimated. This underestimation was compounded by the inherent assumption that the broader population proposed in the PBS-listing would gain similar incremental benefit as the poorer prognosis patients entered into the clinical trials.

The PBAC acknowledged that a high clinical need exists for an effective treatment for some patients with myelofibrosis. The PBAC considered ruxolitinib to be an advance in therapy for patients with a poor prognosis and/or with symptoms refractory to current care, through improved quality of life. However, the PBAC considered that a substantial price reduction would be required to achieve acceptable cost-effectiveness.

The PBAC considered there may be survival benefits, though the magnitude of that benefit cannot be reliably estimated from the data available and may only apply to patients with poor prognosis, as studied in the clinical trials.

The PBAC considered that the proposed restriction would not adequately limit access to patients with a genuine need for treatment with ruxolitinib. The pivotal trials COMFORT I and COMFORT II included only high risk and intermediate-2 risk patients and the restriction as requested would allow access to intermediate-1 patients. It is unknown whether this population would derive the same benefit from treatment as the study population, or whether intermediate-1 patients with mild symptoms would gain any benefit. However, the PBAC also recognised that some patients with severe symptoms refractory to BAT, but with a more favourable prognosis, could benefit from treatment with ruxolitinib through symptom relief, and that exclusion of these patients from PBS-subsidy would be problematic. The PBAC

therefore considered that that cost-effectiveness of ruxolitinib can only be determined with acceptable accuracy once the population for PBS subsidy is further refined.

The PBAC accepted that the appropriate comparator was Best Available Therapy (BAT).

The PBAC noted that the sponsor had offered a Risk Share Agreement to address the uncertainties associated with the likely population and market uptake. The PBAC recommended the inclusion of mechanism within a risk-share arrangement 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 rare disease should be treated.

Overall, the PBAC considered the estimates of use and financial impact were likely to be underestimates due to unreliability in the assumptions used to estimate the number of patients treated and the potential for leakage beyond the intended population to asymptomatic or only mildly symptomatic patients and to patients with low risk disease.

The PBAC noted and welcomed the input received from individuals (15), health care professionals (2) and patient support organisations (1) via the Consumer Comments facility on the PBS website. Most notably, comments cited improvement in quality of life, less hospital visits and more independence as benefits associated with treatment with ruxolitinib.

The PBAC noted that the submission meets the criteria for an independent review.

Outcome:
Rejected

13. 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.

14. Sponsor's Comment

Novartis looks forward to working with the PBAC towards a PBS listing of ruxolitinib in myelofibrosis.