**6.06 RUXOLITINIB,
Tablet 5 mg, 10 mg, 15 mg, 20 mg,
Jakavi®,
Novartis Pharmaceuticals Australia Pty Ltd.**

# Purpose of Application

* 1. The submission requested an Authority Required listing for ruxolitinib for treatment of polycythemia vera (PV) in patients who are resistant or intolerant to hydroxycarbamide/hydroxyurea (HC). The PBAC has not considered ruxolitinib for this indication previously. Ruxolitinib is currently listed on the PBS for the treatment of myelofibrosis (MF)
	2. The basis for the requested listing is cost-effectiveness compared with best available therapy (BAT), which the submission assumed to be 50% HC and 50% (peg) interferon. The key components of the clinical issue addressed by the submission are presented in Table 1.

Table 1: **Key components of the clinical issue addressed by the submission**

| **Component** | **Description** |
| --- | --- |
| Population | Polycythemia vera (PV) and resistance to or intolerance of hydroxycarbamide (HC) |
| Intervention | Ruxolitinib 10 mg twice daily; up to 25 mg twice daily |
| Comparator | Best available therapy (BAT)1 |
| Outcomes | Time to response (TTR), duration of response (DoR)2 3 |
| Clinical claim | Ruxolitinib is superior to BAT in terms of TTR and DoR  |

1 Best available therapy included treatment with hydroxycarbamide (hydroxyurea), (peg) interferon, pipobroman, anagrelide, approved immunomodulators or observation. However was assumed to be hydroxyurea and peginterferon only in the submission.

2 Response was defined as haematocrit < 45% without phlebotomy and/or all of the following three items: platelet count ≤ 400 x 109/L, white blood cell count < 10 x 109/L, and absence of splenomegaly on imaging.

3 The benefits of achieving a response were assessed in the surrogate to final outcome framework, presented in Attachment 1 of submission.

Source: Table 1.1-1, p14 of the submission

# Requested listing

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Name, Restriction,****Manner of administration and form** | **Max Qty (packs)** | **Max.****Qty (units)** | **№.of****Rpts** | **Dispensed Price for Max. Qty**  | **Proprietary Name and Manufacturer** |
| Ruxolitinib 5 mg, 56 tablets | 2 | 112 | 5 | Published $5,152.13Effective $'''''''''''''''''''' | Jakavi | Novartis  |
| Ruxolitinib 10 mg, 56 tablets | 1 | 56 | 5 | Published $5,152.12Effective $''''''''''''''''''''' |
| Ruxolitinib 15 mg, 56 tablets | 1 | 56 | 5 | Published $5,152.12Effective $'''''''''''''''''''' |
| Ruxolitinib 20 mg, 56 tablets | 1 | 56 | 5 | Published $5,152.12Effective $'''''''''''''''''''''' |
| **Requested Initial Restriction**  |
| Category/Program: | General schedule |
| Prescriber type: | [ ] Dental [x] Medical Practitioners [ ] Nurse practitioners [ ] Optometrists[ ] Midwives |
| PBS Indication: | Polycythemia Vera  |
| Treatment phase: | Initial |
| Restriction Level / Method: | Authority Required – In writing |
| Clinical criteria: | The condition must be polycythemia vera,ANDPatient must be resistant to or intolerant of hydroxycarbamide /hydroxyurea (HC). |
| Prescriber Instructions: | The authority form must be made in writing and include:(1) A completed authority prescription form; and (2) A completed Polycythemia Vera Authority Application, which includes all of the following:(A) A copy of pathology report from an approved pathology authority confirming evidence of a JAK2 mutation(B) Supporting pathology reports (if applicable) |
| Administrative Advice: | Initial treatment authorisations will be limited to a maximum of 6 months of therapy. |
| Note: | Resistance to or intolerance of HC is defined as one of the following:**HC Resistance:** after 12 weeks into a course of HC therapy at a dose of at least 2 grams/day or at the patient’s maximally tolerated dose if that dose is less than 2 grams/day:1. Need for phlebotomy to keep haematocrit (HCT) <45%; OR
2. Platelet count >400 x 109/L AND white blood cell count >10 x 109/L;

OR**HC Intolerance:**1. Absolute neutrophil count <1.0 x 109/L; OR platelet count <100 x 109/L; OR haemoglobin <100 g/L (i.e. 10 g/dL) at the lowest dose of HC required to achieve a response as defined below:
* HCT <45% without phlebotomy and/or all of the following three items:
* platelet count ≤400 x 109/L,
* white blood cell count <10 x 109/L,
* and non-palpable spleen, or
1. Presence of leg ulcers or other unacceptable HC-related non-haematological toxicities (such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HC).
 |
| **Requested Continuing Restriction**  |
| Prescriber type: | [ ] Dental [x] Medical Practitioners [ ] Nurse practitioners [ ] Optometrists[ ] Midwives |
| PBS Indication: | Polycythemia vera  |
| Treatment phase: | Continuing |
| Restriction Level / Method: | Authority Required – In writing |
| Clinical criteria: | The condition must be polycythemia vera,ANDPatient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must have demonstrated a response to treatment within 6 months. |
| Prescriber Instructions: | The authority form must be made in writing and include:(1) A completed authority prescription form; and (2) A completed Polycythemia Vera Authority Application, which includes the relevant pathology reports |
| Note: | Response to PBS subsidised treatment with ruxolitinib is defined as:* HCT <45% without phlebotomy (at least 3 months since last phlebotomy); OR
* Both of the following; platelet count ≤400 x 109/L AND absence of palpable splenomegaly.

Patients must maintain a response to continue receiving treatment with ruxolitinib. |
| **Requested Grandfathering Restriction**  |
| Prescriber type: | [ ] Dental [x] Medical Practitioners [ ] Nurse practitioners [ ] Optometrists[ ] Midwives |
| PBS Indication: | Polycythemia vera  |
| Treatment phase: | Grandfathering |
| Restriction Level / Method: | Authority Required – In writing |
| Clinical criteria: | The condition must be polycythemia vera,AND Patient must be resistant to or intolerant of hydroxycarbamide (hydroxyurea),ANDPatient must have previously been treated with ruxolitinib for this condition and demonstrate an adequate response to treatment within 6 months. |
| Prescriber Instructions: | The authority form must be made in writing and include:(1) A completed authority prescription form; and (2) A completed Polycythemia Vera Authority Application, which includes all of the following:(A) A copy of pathology report from an approved pathology authority confirming evidence of a JAK2 mutation(B) Supporting pathology reports |
| Note: | Response to treatment with ruxolitinib is defined as:* HCT <45% without phlebotomy (at least 3 months since last phlebotomy); OR
* Both of the following; platelet count ≤400 x 109/L AND absence of palpable splenomegaly.

Patients must maintain a response to continue receiving treatment with ruxolitinib. |

* 1. A special pricing arrangement was proposed by the submission. All four strengths of ruxolitinib (5mg, 10mg, 15mg and 20mg) have a published DPMQ of $5152.13 and an effective DPMQ of $'''''''''', for a rebate of $''''''''''''''''' per box.
	2. The proposed definition for being resistant or intolerant to HC was based on the European LeukemiaNet (ELN) criteria. The ELN is an appropriate source for the definition for resistance or intolerance to HC. The ESC noted that the proposed definitions are a modified version of the ELN criteria from the RESPONSE-2 trial (presented in the submission as a supplementary trial). Specifically, the proposed modified definitions excluded failure to reduce splenomegaly/relieve symptoms related to splenomegaly and the requirement for no disease related symptoms (withinthe definition for complete response). As such, the ESC considered that the PBS population could potentially be different to the populations in the trials.
	3. The ESC noted that JAK2 mutation negative patients represent a minority population of PV patients and therefore considered that the proposed listing should not exclude these patients from access to treatment with ruxolitinib. The ESC noted that the current ruxolitinib listing for the treatment of MF does not include a requirement for patients to test positive for the JAK2 mutation.
	4. The proposed definition of response required for continued treatment in the requested restriction was based on the 2009 ELN response criteria but differs to the definition in the clinical trials and the European LeukemiaNet (ELN) criteria in two ways:
* The requirement for white blood cell (WBC) count ≤10 X 109/L was excluded based on input from Australian clinicians and evidence from the literature. Despite the limited evidence presented, the PBAC agreed that this was likely reasonable as improvement in WBC count is not clearly correlated to improvement in clinical outcomes; and
* The ELN criteria for complete response requires ‘normal spleen size on imaging’ but was modified to ‘absence of palpable splenomegaly’ as the submission claimed that imaging for splenomegaly is not routinely done in clinical practice. The PBAC agreed and considered this was reasonable from a practical perspective.
* Both the modified response criteria from the MAJIC trial and proposed response criteria for continued treatment excluded the requirement for no disease related symptoms (i.e. microvascular disturbances, pruritus, and headache) from the definition of complete response.
	1. The ESC noted that the proposed continuation criteria was based on a modified version of the ELN criteria from the MAJIC trial, which was then further modified in the requested PBS listing. The ESC noted that the ELN criteria for response in PV was updated in 2013 to include more clinically relevant response definitions and as a result, are more focused on improvement in disease related symptoms and reduction in hepatosplenomegaly. In this regard, the ESC considered that the exclusion of requirement for no disease related symptoms from the response criteria in the MAJIC trial (and consequently, the proposed continuation criteria) may not be in line with the direction of current clinical practice. Further, the ESC considered that allowing patients with partial response (PR) to continue ruxolitinib may not be appropriate, given there was a higher proportion of patients treated with BAT with PR compared to patients treated with ruxolitinib in the MAJIC trial (see paragraph 6.18). The option of removing the continuation criteria, as proposed in the Pre-Sub-Committee Response (PSCR), was not considered appropriate given the cost for questionable benefit and potentially long duration of therapy.
	2. The submission anticipated an additional less than 10,000 patients would require grandfathering in the first year of listing. Unlike the requested initial restriction, the proposed grandfathering restriction did not specify how resistance or intolerance to HC should be verified. This may lead to usage in patients beyond the requested restriction. The Secretariat noted that unless the initial treatment restriction proposes baseline measures of disease severity, there was no need for a grandfathering restriction as patents who at any time were assessed as resistant or intolerant to HC would qualify.
	3. In the product information (PI), it is recommended that the dose of ruxolitinib be tapered down when a patient is discontinuing treatment. However, there are no provisions in the proposed restrictions for patients to access this tapering dose in the event of a discontinuation.
	4. The ESC noted that the submission did not consider the impact of listing ruxolitinib in the PV setting on the overall treatment algorithm and whether sequential use of ruxolitinib in both PV and MF settings should be permitted. The ESC noted that no clinical evidence for sequential use of ruxolitinib was presented.

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

# Background

***Registration status***

* 1. Ruxolitinib was approved by the TGA on 14 December 2015 for the following indications:
		+ treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis; and
		+ treatment of adult patients with polycythemia vera who are resistant to or intolerant of hydroxyurea.
	2. At the time of evaluation for PBAC consideration, the clinical evaluation report, delegate overview, decision letter and risk management plan were available.

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

# Population and disease

* 1. PV is a chronic haematologic cancer and one of the classic Philadelphia chromosome-negative (BCR-ABL1–negative) group of diseases known as myeloproliferative neoplasms (MPNs), which also includes essential thrombocythemia (ET) and primary MF. Patients with PV have an increased red blood cell (RBC) mass (erythrocytosis) and often elevated WBC and platelet counts. Patients may also experience symptoms including severe night sweats, fatigue, pruritus, fever, splenomegaly and reduced health related quality of life (HRQoL), although many patients can be relatively asymptomatic. The PBAC also noted that pruritus is a common, and often debilitating, symptom. Diagnosis of PV is based on clinical presentation and laboratory tests, including the presence of Janus kinase-2 (JAK2) mutation.
	2. Patients with PV have an increased risk of thrombosis due to increased blood viscosity. This leads to increased risks of stroke, transient ischemic attack, acute myocardial infarction, angina, pulmonary embolism, peripheral arterial thrombosis, and deep venous thrombosis – which may lead to further morbidity and mortality. Patients with PV may also have an increased risk of haemorrhage, possibly influenced by elevated platelets, use of anticoagulant therapy as part of the treatment for PV and/or acquired von Willebrand disease. PV may also lead to bone marrow scarring and lead to MF which is associated with worse survival, or possibly evolve into acute myeloid leukaemia (AML) and other cancers. However, the rate of these transformations is relatively low (estimated <20% transformation at up to 20 years).
	3. Overall life expectancy for patients with PV is variable. Tefferi et al. (2013) conducted a multivariate analysis of the survival of 1,545 patients and developed a prognostic model that included age (age ≥67, 57-66 and <57 years), leucocytosis (<15 X109/L or ≥15 X 109/L) and venous thrombosis (present or absent). The median survival of low, intermediate and high risk patients was 27.8, 18.9 and 10.9 years, respectively.
	4. The goals for PV treatment include controlling haematocrit (HCT), which is the percentage of RBC in the total volume of blood, controlling WBC and platelet counts, and reducing splenomegaly. However, these are considered surrogate outcomes only, with the relevant patient outcomes being thrombosis, haemorrhage, transformation to MF or AML and overall survival.
	5. In PV, phlebotomy or venesection is often used to reduce the HCT. Phlebotomy is the removal of blood from the body, with the aim of reducing the proportion of RBC in the total blood volume. Phlebotomy may be used alongside other treatments. Additionally, in patients who can tolerate aspirin, a daily low dose aspirin is often prescribed to reduce thrombosis risks.
	6. It was proposed that ruxolitinib will be used in patients with PV who develop resistance or intolerance to HC, either before or after treatment with peginterferon.

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

# Comparator

* 1. The submission nominated best available therapy (BAT) as the main comparator, which is represented by treatment with hydroxycarbamide/hydroxyurea (HC) or peginterferon α-2a. The main arguments were that both HC and peginterferon α-2a are listed on the PBS under unrestricted listings, with either one suggested as first-line therapy in PV with the other available as second-line therapy, and there was no drug listed on the PBS specifically for the treatment in patients with PV who were resistant or intolerant to HC.
	2. The evaluation noted that neither HC nor peginterferon α-2a are specifically TGA approved for the treatment of PV. Other therapies such as busulfan were also used in the MAJIC trial (key trial supporting the submission) for second-line treatment of PV. Busulfan is a recommended alternative to HC as first-line treatment (UpToDate), and like HC and peginterferon α-2a, busulfan is also listed on the PBS with an unrestricted listing.
	3. The ESC considered the nominated comparator was appropriate, however peginterferon α-2a is not well tolerated and use was likely to remain considerably lower than continued use of HC, even with an unrestricted PBS listing.

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

# Consideration of the evidence

## Sponsor hearing

* 1. There was no hearing for this item.

## Consumer comments

* 1. The PBAC noted and welcomed the input from individuals (7) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of potential benefits of treatment with ruxolitinib, including relief of symptoms and improvement in quality of life. The comments also emphasised the need for more treatment options for PV noting there are several side effects associated with existing treatments.
	2. The Leukaemia Foundation considered there to be a high unmet need for more effective treatments for people living with PV.

## Clinical trials

* 1. The submission was based on one head-to-head randomised trial (MAJIC, n=190) and two supplementary randomised trials (RESPONSE, n=222 and RESPONSE-2, n=149) comparing ruxolitinib to BAT in patients with PV who were resistant or intolerant to HC.
	2. Details of the trials presented in the submission are provided in Table 2.

Table 2: **Trials and associated reports presented in the submission**

| **Trial ID** | **Protocol title/ Publication title** | **Publication citation** |
| --- | --- | --- |
| MAJIC | Harrison et al. Ruxolitinib compared with best available therapy for polycythaemia vera patients resistant or intolerant to hydroxycarbamide in MAJIC-an investigator-led trial. | Poster at 23rd Congress of the European Hematology Association, Stockholm, June 14-17, 2018 |
| Curto-Garcia, et al. Molecular analysis in MAJIC PV correlation with clinical end points. | Oral presentation at the 24th European Hematology Association Congress, Amsterdam, Netherlands, June 13-16, 2019 |
| RESPONSE | Randomized, open label, multicenter phase III study of efficacy and safety in polycythemia vera subjects who are resistant to or intolerant of hydroxyurea: JAK inhibitor INC424 tablets versus best available care (The RESPONSE Trial) – 48 week CSR | 05 May 2014 |
| Vannucchi et al. Ruxolitinib versus Standard Therapy for the Treatment of Polycythaemia Vera. | NEJM 2015; 372(5): 426-435.  |
| Verstovsek et al. Ruxolitinib versus best available therapy in patients with polycythaemia vera: 80-week follow-up from the RESPONSE trial. | Haematologica 2016; 101(7): 821-829. |
| Harrison et al. Comprehensive haematological control with ruxolitinib in patients with polycythaemia vera resistant to or intolerant of hydroxycarbamide.  | British Journal of Haematology 2018; 182: 276-307 |
| RESPONSE-2 | Randomised, Open Label, Multicenter Phase IIIb Study Evaluating the Efficacy and Safety of Ruxolitinib Versus Best Available Therapy in Patients With Polycythaemia Vera Who Are Hydroxyurea Resistant or Intolerant (RESPONSE-2) – 28 week CSR | 1 April 2016 |
| Passamonti et al. Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. | Lancet Oncology 2017; 18(1): 88-99 |

Source: Table 2.3-1, pp64-65 of the submission

* 1. MAJIC was an open label randomised trial which enrolled patients with both PV and essential thrombocythemia (ET), but only the PV cohort was relevant to the current submission. Patients (n=190) with high risk PV who were resistant or intolerant to HC were randomised to receive ruxolitinib (n=95) or BAT (n=95) and followed up for up to 5 years. Patients randomised to ruxolitinib who did not respond after 12 months of treatment were allowed to cross over to BAT, but patients with BAT were not allowed to crossover to ruxolitinib. BAT in MAJIC included only active treatments. The trial was powered to detect differences in the proportion of patients achieving complete response (CR) at 12 months, defined as meeting all i) HCT <45% without phlebotomy for 3 months, ii) platelet count ≤400 x 109/L, iii)white blood cell count ≤10 × 109/L and iv) normal spleen size on imaging. Partial response (PR) was defined as meeting either i) HCT <45% without phlebotomy for 3 months OR ii) platelet count ≤400 x 109/L. White blood cell count ≤10 × 109/L and normal spleen size on imaging, was considered as a secondary outcome.
	2. RESPONSE was an open label randomised trial which enrolled 222 patients with PV and image confirmed splenomegaly and were resistant or intolerant to HC based on a modified ELN criteria. Patients were randomised to receive ruxolitinib (n=110) or BAT (n=112) for up to 32 weeks. BAT in RESPONSE and RESPONSE 2 was single agent therapy (including no treatment) determined by the treating physician. The primary outcome was a composite outcome of haematocrit control (a platelet count ≤400×109/L, and a WBC count ≤10×109 per litre) and reduction of 35% in spleen volume. After 32 weeks, BAT patients were crossed over to ruxolitinib and followed for up to 256 weeks in a single arm extension phase.
	3. RESPONSE 2 was a similar trial to RESPONSE and was an open label randomised trial which enrolled 149 patients with PV but no palpable splenomegaly and were resistant or intolerant to HC based on a modified ELN criteria. Patients were randomised to receive ruxolitinib (n=74) or BAT (n=75) for up to 28 weeks. The primary outcome was the proportion of patients achieving haematocrit control (a platelet count ≤400×109/L, and a WBC count ≤10×109/L) at the end of 28 weeks. After 28 weeks, BAT patients were crossed over to ruxolitinib and followed for up to 260 weeks in a single arm extension phase.
	4. The ESC considered that the use of surrogate outcomes comprised largely of blood laboratory results to determine response to treatment in the trials may not be consistent with current clinical practice noting that the ELN response criteria for PV have been updated to include more clinically relevant measures (see paragraph 2.5)
	5. The key features of the direct randomised trials are summarised in Table 3.

Table 3**: Key features of the included evidence**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **N** | **Design/ duration** | **Risk of bias** | **Patient population** | **Outcome(s)** | **Use in modelled evaluation** |
| **Ruxolitinib vs BAT** |
| MAJIC | 190 | R,OL5 years1 | High2 | Resistant or intolerant to HC, ‘high risk’ PV3 | CR4 at 12 months, CR+PR5 at 12 months, TTR, DoR, OS | TTR, DoR and OS used to inform transitions |
| RESPONSE | 222 | R, OL32 weeks  | Low | Resistant or intolerant to HC with splenomegaly | Response (HCT <45% with no more than one phlebotomy and reduction in spleen size ≥ 35% at 32 weeks, HRQoL, OS | HRQoL used to inform utility. Adverse event rate used. |
| RESPONSE-2 | 149 | R, OL28 weeks | Low | Resistant or intolerant to HC with no splenomegaly | Response (HCT <45% with no more than one phlebotomy) at 28 weeks, HRQoL, OS | HRQoL used to inform utility. Adverse event rate used. |

BAT = Best Available Therapy, R=randomised, OL = open label, HC = hydroxycarbamide/hydroxyurea, PV = polycythemia vera, CR = complete response, PR = partial response, TTR = time to response, DoR = duration of response, OS = overall survival, HRQoL = health related quality of life

1 Primary outcome reported only at 12 months

2 High risk as open label, high attrition in long term results and potential selective reporting

3 High risk defined as one or more of: age >60 years, previous thrombosis or migraine, significant splenomegaly or platelets >1000 × 109/L

4 CR defined as meeting all of HCT <45% without phlebotomy for 3 months, AND Platelet count ≤400 x 109/L, white blood cell count ≤10 × 109/L and Normal spleen size on imaging

5 PR defined as meeting either i) HCT <45% without phlebotomy for 3 months OR ii) Platelet count ≤400 x 109/L, white blood cell count ≤10 × 109/L and Normal spleen size on imaging

Source: Constructed during evaluation

* 1. The ESC agreed with the evaluation that MAJIC was considered to have a high risk of bias as it was an open label trial that appeared to have high attrition (>40%) beyond two years of follow-up. The pre-PBAC response clarified that MAJIC had a 19% attrition rate and was an ongoing trial with a median duration of follow-up of 2.6 years and a planned duration of 5 years. Additionally, the ESC considered there was a potential for selective reporting given that data from MAJIC was available only as a conference poster (Harrison et al 2018) and a PowerPoint of an oral presentation (Curto-Garcia 2019). Both RESPONSE and RESPONSE-2, despite being open label trials, were considered to have a low risk of bias as the outcome assessors were blinded to treatment allocation until patients in BAT were allowed to cross over to ruxolitinib and the trials did not have the same risk of attrition or reporting bias as MAJIC. As such, the ESC considered that data from the RESPONSE trials, despite allowing BAT patients to crossover to ruxolitinib at less than 12 months, are more robust compared to MAJIC. The ESC considered that the submission’s use of MAJIC, over the RESPONSE trials as primary evidence, is not sufficiently justified by its longer-term follow-up given the high attrition rate (which may be due to loss of response or transformation to MF or AML).
	2. The definition of complete response (CR) and partial response (PR) in MAJIC was based on the ELN criteria for response. As discussed, this differs to the definition of response in the proposed PBS criteria, with the requirement for WBC count omitted and the requirement for spleen size altered from on imaging to on palpation (see paragraph 2.3).
	3. A key issue in the submission is whether the proposed response criteria is associated with patient relevant clinical outcomes. A summary of clinical evidence between the association of the aspects of response (a surrogate outcome) and clinical outcomes is presented in Table 4.

Table 4: Summary of association of surrogate outcome to clinical outcomes

| **Surrogate** | **Relationship to clinical outcomes** | **Comments** |
| --- | --- | --- |
| ELN response | Alvarez-Larran et al (2012) conducted a retrospective study on 261 patients with PV treated with HC (median follow-up 7.2 years, median treatment with HC for 4.4 years) and found that achieving ELN response (complete or partial) or haematocrit response did not result in better survival or less thrombosis and bleeding.  | Given that the proposed criteria for response was based on the ELN criteria, this suggests that the surrogate outcome proposed in the submission may not be clinically relevant.  |
| Haematocrit (HCT) <45% | Association with reduction in HCT to <45% was supported by evidence from the Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) trial, where 365 patients were randomised to receive either intense treatment (target HCT <45%, n=182) or less intensive treatment (HCT 45-50%, n=182). After a median 31 month follow-up, patients in low HCT group had lower death from cardiovascular or major thrombotic effect than those in the high HCT group (HR 3.91, 95% CI 1.45, 10.53) However, Ferrero et al 2019, a retrospective study of 226 patients with PV, found no differences in overall thrombosis free survival between patients with HCT of <45% and between 45-48% at a median follow up of 5.84 years, though those with an HCT of >48% was significantly associated with shorter survival and higher risk of major thrombosis.Additionally, a study by Di Nisio et al 2007 in 1638 patients with PV (median follow-up 2.8 years, total of 4393 patient years) found that patients with HCT ≤45% and patients with HCT >45% had comparable risk of death (HR 0.85, 95% CI 0.6-1.31), major thrombosis (HR 0.94, 95% CI 0.65-1.36) and total thrombosis (HR 0.97, 95% CI 0.72-1.30) | Overall, there is conflicting evidence to suggest that the threshold of 45% HCT is correlated to clinically meaningful outcomes. Additionally, the proposed response specifies that HCT <45% needs to be reached without phlebectomy, whereas the low HCT in CTYO-PV was achieved with frequent phlebotomy (average of 3.0 per patient over 6 months). Therefore it is unclear if the results of CYTO-PV would be applicable to the responses proposed in the current submission.  |
| White blood cell (WBC) count | A number of epidemiologic studies associate higher WBC count at diagnosis and worse survival. However WBC count may not necessarily change due to treatment. In CYTO-PV, there was no statistically significant increase in risk of thrombosis in patients with a WBC count 10.1 to 15 × 109/L prior to thrombosis compared to WBC count ≤10× 109/L prior to thrombosis. Alvarez-Larren et al (2012) found a lack of response in WBC to be a risk factor for survival in mono-variate analysis but lost significance when included with HC resistance in a multivariate model. | No evidence to support that improving WBC count as part of response is associated with thrombosis and OS. Additionally, WBC was recommended to be excluded from definition of response by clinicians.  |
| Platelet count <400 × 109  | Alvarez-Larran et al (2012) reported that patients with platelet count <400 × 109/L were statistically significantly less likely to experience thrombosis and bleeds. However the authors noted that the association between lack of response in platelet count and increased risk of thrombosis was unexpected and disagreed with previous studies, including Di Nisio 2007 which included data from 1638 patients for an average of 2.8 years follow-up which found no association between thrombocytosis in PV and thrombotic complications. In Tefferi et al (2013), a study in 1545 patient with PV, a multivariate prediction model for overall and leukaemia free survival was presented. Platelet count ≥450 x 109/L was not considered statistically significantly predictive (p value of 0.1 and 0.47 excluding and including abnormal karyotype as covariate, respectively) of overall survival in multivariate analysis when adjusted for age categories (57-66 and ≥67 years) | There is some biological plausibility that extreme platelet counts may increase bleeds. However there is conflicting evidence as to whether a platelet count of <400 × 109/L is correlated with any of the clinical outcomes.  |
| Splenomegaly | Bai et al (2015) (n=72, mean 6 year follow up), Abdulkarim et al (2011) (n= 150, no follow up described) reported that splenomegaly at diagnosis of PV was an independent risk factor for the development of MF. Additionally, Alvarez-Larran et al (2016) found that in one of their multivariate analysis that failure to reduce massive splenomegaly was statistically significantly correlated with increased transformation to MF (14% at 5 years vs 1.6%, p = 0.03). However it should be noted that only 7/890 patients met the criterion defined as failure to reduce splenomegaly by more than 50%, as measured by palpation after 3 months of at least 2 g/d of HC, meaning that there was only 1 case of transformation at 5 years (1/7 = 14%). In Passamonti et al (2010) (n=338, mean 3.2 year follow up), spleen size was not statistically significantly correlated with transformation. | There may be some correlation between splenomegaly at diagnosis and transformation, but it is unclear, however, if treatment to reduce or eliminate splenomegaly after diagnosis changes the risk of transformation. However it is reasonable to assume that reduction in splenomegaly in patients where it is symptomatic will improve patient quality of life.  |

Source: Attachment 1 to the submission and p88-92 of the submission

* 1. The ESC considered that, overall, the available evidence does not appear to support an association between the proposed response criteria and patient relevant outcomes:
		+ Epidemiological evidence from Alverez-Larren et al 2012 does not support an association between ELN response and overall survival;
		+ There is conflicting evidence to suggest that the threshold of 45% HCT is correlated to clinically meaningful outcomes;
		+ No evidence was provided to support that improved WBC count as part of response is positively correlated with thrombosis and OS;
		+ There is conflicting evidence as to whether a platelet count of <400 × 109/L is correlated with any of the clinical outcomes; and
		+ There is some correlation between splenomegaly at diagnosis and transformation but it is unclear if treatment to reduce or eliminate splenomegaly after diagnosis changes the risk of transformation, though it is likely to improve quality of life.
	2. Therefore, it is possible that achieving the proposed response may not lead to improvement in the relevant clinical outcomes in patients with PV.
	3. The ESC considered that quality of life for PV patients was unlikely to be impacted by partial and complete response criteria as defined above, but was affected by spleen enlargement, thrombosis, and in rare cases erythromelalgia. Reductions in phlebotomies are also likely to be impactful for patients.

## Comparative effectiveness

* 1. The proportion of patients achieving complete (CR) or partial (PR) response by 12 months in MAJIC is presented in Table 5.

Table 5: **Proportion of complete and partial responders**

| **MAJIC** | **Ruxolitinib (N = 93)** | **BAT (N = 89)** | **OR^ (95% CI)** | **RR^ (95% CI)** | **RD^ (95% CI)** |
| --- | --- | --- | --- | --- | --- |
| Complete responders, n (%) | 46 (49.5)\* | 24 (27.0) | **2.65 (1.43, 4.93)** | **1.83 (1.43, 4.93)** | **0.22 (0.09, 0.36)** |
| Partial responders, n (%) | 44 (47.3) | 59 (66.3) | **0.46 (0.25, 0.83)** | **0.71 (0.55, 0.93)** | **-0.19(-0.33,-0.05)** |
| Responders~, n (%) | 90 (96.8) | 83 (93.3) | 2.17 (0.53, 8.95) | 1.04 (0.97, 1.11) | 0.04 (-0.03, 0.10) |

Abbreviations: BAT = best available therapy; CI = confidence interval; RR = risk ratio; RD = risk difference

\* between-treatment group difference: p = 0.0009 reported in Harrison et al. (2018a) poster

^ calculated for the purpose of the submission using RevMan v5.3

~ Response comprises complete and partial response

Note: text in bold indicates statistically significant results

Source: Table 2.3-15, p92 of the submission

* 1. There were statistically significantly more patients treated with ruxolitinib who achieved CR compared to patients treated with BAT (OR 2.65; 95% CI: 1.43, 4.93) in MAJIC. However,there were statistically significantly more patients treated with BAT who achieved PR compared to patients treated with ruxolitinib (OR 0.46; 95% CI: 0.25, 0.83). The net result was that there were no statistically significant differences between the proportion of patients who responded (CR + PR) within Year 1 between treatments, with 90/93 (96.8%) and 83/89 (93.3%) of patients treated with ruxolitinib and BAT achieving CR or PR, respectively.
	2. The proposed PBS restriction for ruxolitinib in PV, however, restricts use to patients who have responded within six months. Theeconomic evaluation uses the time to response to estimate the proportion of patients who responded by six months instead of the proportion who responded within one year reported above.
	3. As the definition of ‘response’ differed between all three trials, the submission also conducted a post hoc analysis of the results from RESPONSE and RESPONSE-2 using the same criteria as MAJIC. For comparison, the proportion of patients who achieved response at a comparable time point (0.5 years, 5.74 months) in MAJIC was extracted from the economic evaluation. The results are presented in Table 6.

Table 6: *Post hoc* analysis of RESPONSE and RESPONSE-2 using response criteria from MAJIC

| **Trial** | **Ruxolitinib, n/N(%)** | **BAT\*, n/N(%)** | **OR (95%CI)** | **RR (95%CI)** | **RD (95%CI)** |
| --- | --- | --- | --- | --- | --- |
| MAJIC (up to 0.5 years) | 86/93 (92.5) | 74/89 (83.4) | 2.49 (0.89, 7.65)a | 1.11 (1.00, 1.26)a | 0.09 (-0.002, 0.19)a |
| RESPONSE (8-32 weeks)~ | '''''/110 ('''''''''''') | ''''''/112 ('''''''''') | **'''''''' (''''''''', ''''''''')** | **''''''''' ('''''''', ''''''''')** | **''''''''' (''''''''', ''''''''')** |
| RESPONSE-2 (8-28 weeks)~ | '''''/74 ('''''''''') | ''''''/74 (''''''''''') | **''''''''' (''''''''', '''''''''')** | **''''''''' ('''''''', ''''''''')** | **'''''''''' ('''''''''', '''''''')** |
| Pooled ruxolitinib vs BAT (RESPONSE and RESPONSE-2) | **'''''''' ('''''''', ''''''''')** | **'''''''''' ('''''''''', ''''''''')** | **''''''''' (''''''''', ''''''''')** |
| Heterogeneity | Tau² = '''''''''''; Chi² = '''''''''', df = '''' (P = ''''''''''''); I² = ''''% | Tau² = ''''''''''; Chi² = '''''''''''', df = '''' (P = ''''''''''); I² = '''% | Tau² = '''''''''''; Chi² = ''''''''''', df = '''' (P = ''''''''''); I² = '''% |
| Pooled ruxolitinib vs BAT (all trials)a | **''''''''' (''''''''', '''''''''')** | **''''''''' ('''''''''''','''''''')** | **'''''''''' (''''''''', ''''''''')** |
| Heterogeneitya | Chi² = '''''''''', df = ''' (P ='''''''''''''); I² = ''''''''''''% | Chi² = ''''''''''', df = '''' (P = '''''''''''''''''');I² = ''''''''''% | Chi² = '''''''''', df = '''' (P ''''''''''''''''''); I² = ''''% |

Abbreviations: BAT = best available therapy; CI = confidence interval; RR = risk ratio; RD = risk difference

Note: calculated for the purpose of the submission using RevMan v5.3

\* Subgroup of patients in the BAT arm who were receiving active treatment (observation [i.e. phlebotomy] only removed)

~ Patients in RESPONSE and RESPONSE-2 were only considered to be responders from Week 8 onwards to Week 32 and Week 28, respectively because of the effect of the pre-randomisation HCT control period

a Calculated during evaluation using StatsDirect

Bolded text indicates statistically significant differences

Source: Table 2.3-17, p99 of the submission and Jakavi (ruxolitinib) Economic Evaluation – Base case.xlsx

* 1. The results of the post hoc analysis from RESPONSE and RESPONSE-2 using the MAJIC criteria for response indicated that a statistically significantly greater proportion of patients treated with ruxolitinib achieved response. This was somewhat inconsistent with the results from MAJIC at 6 months, in which no statistically significant differences were observed between treatment arms. This could be due to differences in the BAT arm, as RESPONSE and RESPONSE-2 included ‘watch and wait’ as a BAT option whereas all patients in MAJIC received active treatments (according to protocol).
	2. The time to response (TTR) duration of response (DoR) reported in MAJIC is presented in Figure 1 and Figure 2, respectively.

Figure 1, 2: **Time to response (left) and Duration of response (right) in MAJIC**



Abbreviations: BAT = best available therapy; CR = complete response; PR = partial response

Note: Response comprised complete or partial response

Source: Figure 2.3-4, p94 and Figure 2.3-5, p94 of the submission

* 1. The submission claimed that ruxolitinib had superior efficacy in terms of faster time to response and duration of response compared to BAT. It was unclear what hypothesis or statistical tests were conducted to derive the P values. No hazard ratios were presented. As TTR was an outcome presented post hoc, it was possible that MAJIC was not powered to detect any differences. Similarly, even though DoR was a pre-specified secondary outcome, MAJIC was designed to only detect differences in CR at 12 months and therefore was not necessarily powered to detect differences in DoR. Both TTR (up to 12 months) and DoR (up to 31.2 months and extrapolated to 20 years) are used to inform the economic model.
	2. The ESC considered that DoR is a clinically significant measure given the chronic nature of PV, however, the results for DoR from MAJIC were unreliable due to the significant loss to follow-up beyond two years. For example, the proportion of patients maintaining response was 62% at Year 2 and 61% at Year 5 in the ruxolitinib arm, but the number at risk decreased from 38 at Year 2 to 1 at Year 5.
	3. While it was not specified, given the shape of the Kaplan-Meier (KM) curve, it appears that a last observation carried forward (LOCF) imputation method was used to impute missing data in DoR. A more conservative approach, such as the missing equals failure (MEF) approach would have produced vastly different results due to the large proportion of missing data (estimated to be >40% after Year 2). The ESC considered that the apparent use of LOCF imputation likely further biased the results as it is the most optimistic outcome and results in a large number of patients remaining as a responder despite no longer being ‘at risk’.
	4. The KM curve for transformation-free survival and overall survival (OS) reported in MAJIC is presented in Figure 3 and Figure 4, respectively. It is important to note that MAJIC was not powered to detect differences in transformation-free survival or OS.

Figure 3, 4**: Transformation free survival (left) and Overall survival (right) in MAJIC**

 

Abbreviations: BAT = best available therapy

Source: Figure 2.3-6, p95 and Figure 2.3-7, p96 of the submission

* 1. No statistically significant differences in transformation-free survival or OS were observed between the treatment arms in MAJIC. Additionally, no deaths were reported in any patients randomised to ruxolitinib or BAT at week 32 in RESPONSE or at week 28 in RESPONSE-2.
	2. Overall, there was no comparative evidence to suggest that patients treated with ruxolitinib had a difference in overall survival compared to patients treated with BAT. The ESC considered it was inappropriate that the submission assumed that there was a difference in overall survival in the economic model, and subsequently extrapolated the observed OS from MAJIC to 20 years. Similar to DoR, there appears to have been significant losses to follow-up for OS (e.g. >56% by Year 4) and using LOCF to impute missing data instead of MEF may introduce significant bias.
	3. There was no evidence from MAJIC, RESPONSE or RESPONSE-2 that any statistically significant differences in the incidence of thrombotic or haemorrhagic events existed between patients treated with ruxolitinib and patients treated with BAT, though the trials may not have been powered to detect any differences.
	4. Harrison et al (2018) reported that in MAJIC, the mean Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF), 10 item version (MPN-10) score for itching, fatigue, night sweats, early satiety, weight loss, bone pain, inactivity and concentration during the first 12 months were all significantly lower for patients treated with ruxolitinib compared to patients treated with BAT (all p<0.05). In RESPONSE and RESPONSE-2, a 14 item and 10 item MPN-SAF were used to assess the severity of the symptoms, respectively. Patients treated with ruxolitinib had greater reduction in all symptom clusters and reported a decrease in almost all individual symptoms compared to patients treated with BAT.
	5. Health related quality of life (HRQoL) from MAJIC was collected although no results were presented. However, RESPONSE collected HRQoL with the EORTC QLQ-C30 instrument, which the submission mapped to EQ-5D-5L using an algorithm derived from a UK patient population (McKenzie and van der Pol 2009), and which the submission noted that the PBAC had previously considered in the ruxolitinib for myelofibrosis submission in July 2013. RESPONSE-2 collected HRQoL data with the EQ-5D-5L directly, and the submission converted the two sets of EQ-5D-5L data into utilities to inform the economic model using UK tariffs. The utilities from RESPONSE applied to the proportion of patients assumed to have baseline splenomegaly (59.3%) and the utilities from RESPONSE-2 applied to the proportion of patients assumed to have no baseline splenomegaly (40.7%). The ESC considered that HRQoL data from MAJIC may be useful for validating the HRQoL data from the RESPONSE trials.
	6. Additionally, RESPONSE and RESPONSE-2 reported:
		+ Statistically significantly more patients treated with ruxolitinib achieved complete haematological remission (HCT <45%, platelet count ≤400 × 109/L and WBC count ≤100 × 109/L) compared to patients treated with BAT in RESPONSE at week 32 (RD = 0.15; 95% CI: 0.06, 0.24, p152) and in RESPONSE-2 at week 28 (RD = 0.18; 95% CI: 0.07, 0.28, p162), and HC resistance was not a treatment effect modifier; and
		+ Statistically significantly fewer patients treated with ruxolitinib required phlebotomies compared to patients treated with BAT after Week 8 up to Week 32 in RESPONSE and up to Week 28 in RESPONSE-2.

## Comparative harms

* 1. Only limited adverse event data from MAJIC was reported in Harrison et al 2018. A summary of what was reported, as well as the key drug related adverse events which were statistically significant different between treatment arms in RESPONSE and RESPONSE-2 are summarised in Table 7.

Table 7**: Key Adverse events in MAJIC, RESPONSE and RESPONSE-2**

|  | **Ruxolitinib, n/N (%)** | **BAT, n/N (%)** | **OR (95%CI)** | **RR (95%CI)** | **RD (95%CI)** |
| --- | --- | --- | --- | --- | --- |
| **MAJIC** |
| Grade 3 Anaemiaa | 6/93 (6.5) | 1/89 (1.1) | 6.07 (0.71, 282) | 5.74 (0.93, 36.0) | 0.05 (-0.004, 0.12) |
| Grade 4 thrombocytopeniaa | 1/93 (1.1) | 0/89 (0) | 2.90 (0.18, Inf) | 2.87 (0.25, Inf) | 0.011 (-0.031, 0.059) |
| Grade 3 infectiona | 8/93 (8.6) | 2/89 (2.2) | 4.09 (0.78, 40.4) | 3.83 (0.95, 15.68) | 0.064 (-0.003, 0.142) |
| Grade 4 infectiona | 2/93 (2.2) | 3/89 (3.4) | 0.63 (0.05, 5.65) | 0.64 (0.13, 3.13) | -0.012 (-0.076, 0.046) |
| **RESPONSE**  |
| Anaemia all grades | 19/110 (17.3) | 1/111 (0.9) | **22.97 (3.48, 962)** | **19.17 (2.61, 141)** | **0.16 (0.09, 0.24)** |
| Dizziness all grades | 7/110 (6.4) | 0/111 (0) | **16.16 (1.80, Inf)** | 15.14 (0.87, 262) | **0.06 (.02, 0.11)** |
| Headache all grades | 7/110 (6.4) | 0/111 (0) | **16.16 (1.80, Inf)** | 15.14 (0.87, 262) | **0.06 (.02, 0.11)** |
| **RESPONSE-2** |
| Anaemia all grades | 11/74 (14.9) | 0/75 (0) | **27.35 (3.17, Inf)** | **23.31 (1.40, 388)** | **0.15 (0.07, 0.23)** |
| Weight increased | 8/74 (10.8) | 0/75 (0) | **19.30 (1.14, 403)** | **17.23 (1.01, 293)** | **0.11 (0.03, 0.18)** |

Inf = infinity

a Values calculated with statsdirect.

Text in bold indicates statistically significant results.

Source: p9, 7 Table 2.3-54, p 173 and Table 2.3-58, p 178 of the submission

* 1. There were statistically significantly more patients treated with ruxolitinib who experienced anaemia in both RESPONSE and RESPONSE-2. Additionally, patients treated with ruxolitinib were also statistically significantly more likely to have a weight increase. However, the submission does not include these adverse events in the economic evaluation. Instead, the economic evaluation included adverse events of ≥Grade 3 severity that occurred at a rate of more than 5% per patient-year of exposure in either treatment arm in RESPONSE and RESPONSE-2, irrespective of whether the difference between ruxolitinib and BAT was statistically significant. The ESC considered not modelling statistically significant differences was likely inappropriate.
	2. In RESPONSE, the exposure-adjusted rate (AEs per 100 patient-years) for headache (13.5 vs 28.8), fatigue (11.2 vs 23.3), thrombocytopenia (7.6 vs 16.5), pruritus (11.2 vs 34.3) and dizziness (8.8 vs 15.1) were lower in ruxolitinib vs BAT arm, respectively. Conversely, the exposure-adjusted rates were higher in the ruxolitinib arm for anaemia (15.5 vs 5.5), dyspnoea (8.8 vs 2.7), weight increase (7.6 vs 1. 4), herpes zoster (6.5 vs 0) and hypertension (6.5 vs 4.1). It was unclear if these differences were statistically significant.
	3. In RESPONSE-2, the exposure-adjusted rates were higher (difference ≥10) in the ruxolitinib group compared to BAT group for anaemia (19.2 vs 4.5) and weight increased (12.8 vs 2.3). The exposure-adjusted rates were lower (difference ≥10) in the ruxolitinib group compared to BAT group for thrombocytopenia (3.2 vs 13.6), upper respiratory tract infection (3.2 vs 15.9), and pruritus (12.8 vs 34.0). It was unclear if these differences were statistically significant.
	4. The ESC expressed concerns over the safety profile of ruxolitinib, with respect to the higher proportion of grade 3 infections in the ruxolitinib arm of MAJIC, particularly given the long-term toxicity of ruxolitinib is unknown.

## Benefits/harms

* 1. There was insufficient detail for efficacy from MAJIC to populate a benefit and harms table or to provide a meaningful event per 100 patients statement. However, in summary:
		+ Harrison et al (2018) claimed that patients treated with ruxolitinib had superior time to response (p=0.0061) and duration of response (p=0.0000) compared to patients treated with BAT. It was unclear what hypotheses were tested or which statistical tests were conducted to derive the p-values which show statistically significant differences. No hazard ratios were reported;
		+ There was no evidence for any difference in overall survival for up to six years (p=0.5550) or transformation-free (i.e. not developing into myelofibrosis or acute myeloid leukaemia) survival for up to five years (p=0.2290) between patients treated with ruxolitinib and patients treated with BAT. It was unclear what hypotheses were tested or which statistical tests were conducted to derive the p-values which show no statistically significant difference. No hazard ratios were reported; and
		+ There was no statistically significant differences in the incidence of adverse events in MAJIC at a median duration of follow up of 31.2 months.
	2. The adverse events which were statistically significantly different between treatments in RESPONSE and RESPONSE-2 are summarised in Table 8.

Table 8**: Summary of comparative harms for Ruxolitinib and BAT in supplementary evidence**

|  |
| --- |
| **Harms**  |
|  | **Ruxolitinib****n/N** | **BAT****n/N** | **RR****(95% CI)** | **Event rate/100 patients**  | **RD****(95% CI)** |
| **Ruxolitinib** | **BAT** |
| **Anaemia (all grades)** |
| RESPONSE1 | 19/110 | 1/111 | 19.17 (2.61,141) | 17.3 | 0.09 | 0.16 (0.09, 0.24) |
| RESPONSE-22 | 11/74 | 0/75 | 23.31 (1.40, 388) | 14.9 | 0 | 0.15 (0.07, 0.23) |
| **Dizziness (all grades)** |
| RESPONSE1 | 7/110 | 0/111 | 15.14 (0.87, 262) | 6.4 | 0 | 0.06 (0.02, 0.11) |
| **Headache (all grades)** |
| RESPONSE1 | 7/110 | 0/111 | 15.14 (0.87, 262) | 6.4 | 0 | 0.06 (0.02, 0.11) |
| **Weight increased** |
| RESPONSE-22 | 8/74 | 0/75 | 17.23 (1.01, 293) | 10.8 | 0 | 0.11 (0.03, 0.18) |

1 at 32 weeks

2 at 28 weeks

HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio

Source: Table 2.3-54, p 173 and table 2.3-58, p 178 of the submission

* 1. On the basis of direct evidence presented by the submission in the RESPONSE and REPOSNE-2 trials, for every 100 patients treated with ruxolitinib in comparison to BAT and over 28-32 weeks:
* Approximately 15-16 additional patients would have anaemia (all grades).
* Approximately 6 additional patients would have dizziness (all grades).
* Approximately 6 additional patients would have headache (all grades).
* Approximately 11 additional patients would have experienced weight increases.

## Clinical claim

* 1. The submission described ruxolitinib as superior in terms of effectiveness in terms of time to response (TTR) and duration of response (DoR) compared with BAT and non-inferior in terms of safety compared to BAT.
	2. The evaluation considered the therapeutic conclusion presented in the submission was partially supported by the evidence presented in Section 2 of the submission as:
		+ While the included trials (MAJIC, RESPONSE and RESPONSE-2) may not have been powered to detect differences in TTR and DoR, there was a consistent difference in the time to response favouring quicker TTR in patients treated with ruxolitinib compared to patients treated with BAT and longer DoR across all the included trials; and
		+ It is likely that patients treated with ruxolitinib will experience better symptom improvement and HRQoL, though this is not captured in the proposed response criteria; however
		+ There were statistically significantly more events of anaemia and weight gain in patients treated with ruxolitinib than in patients treated with BAT in RESPONSE-2. The exposure adjusted rates of anaemia, dyspnoea, weight gain, herpes zoster and hypertension were higher in patients treated with ruxolitinib compared to patients treated with BAT in RESPONSE, though the inverse was true for headache, fatigue, thrombocytopenia and dizziness. Therefore, rather than claiming non-inferiority on safety, it may be more appropriate to describe ruxolitinib as having a different safety profile to BAT.
	3. However, the association between the proposed surrogate outcome (response based on HCT, platelet and WBC count and splenomegaly) and the relevant clinical outcomes for patients with PV (thrombosis, haemorrhage, transformation to MF or AML, and OS) may not be supported. While there is biological plausibility in associating the surrogate outcomes with clinical outcomes, the association does not appear to be supported by available evidence. Therefore, it is possible that achieving the proposed response criteria may not lead to improvement in the relevant clinical outcomes in patients with PV.
	4. The ESC considered that overall the superiority claim was not adequately supported. The pivotal trial evidence (MAJIC) was highly biased, the supporting RESPONSE and RESPONSE 2 trials relied on post-hoc analyses, there were no statistically significant differences overall in the proportion of partial or complete responders at 12 months and more partial responders in the BAT treatment arm at 12 months.
	5. The ESC noted that while there was some evidence of improvement in disease related symptoms, the magnitude of improvement was not reported and it was unclear what the MCID for these outcomes would be.
	6. The PBAC agreed with the ESC and considered that the clinical importance of the difference in safety profiles between ruxolitinib and BAT was unclear given the lack of long-term safety data. The PBAC considered the non-inferior safety claim was not adequately supported.
	7. The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data.

## Economic analysis

* 1. The ESC considered it was uncertain whether the ‘responder’ and ‘non-responder’ health states included in the model accurately capture the clinical and patient-reported outcomes of interest from treatment with ruxolitinib and BAT, given there was no difference in quality of life (QoL) between these groups and no evidence of OS gains. This places uncertainty over the entire model structure, assumptions and thus results. Overall, the economic model does not form a reliable basis for decision making.
	2. The ESC considered it was unclear which outcomes in PV treatment are most patient-relevant and whether quality of life differences could be captured with this condition. The clinical benefit may be associated with overall survival, for which there is no evidence of significant improvement with ruxolitinib.
	3. A stepped economic evaluation based on direct randomised trials (MAJIC, RESPONSE and RESPONSE-2) and implementing a modelled evaluation was presented. A summary of the model structure is presented in Table 9.

Table 9**: Summary of model structure and rationale**

| **Component** | **Description** | **Justification/comments** |
| --- | --- | --- |
| Type of analysis | Cost-utility analysis | Trial evidence showed that ruxolitinib was superior to Best Available Therapy (BAT) in Time To Response (TTR) and Duration of Response (DoR). Reasonable only if surrogate outcome is accepted. The ESC noted that response was not associated with quality of life (QoL) in the presented trial evidence, and considered it may not be in practice either. The ESC noted that there was no significant difference in OS demonstrated between ruxolitinib and BAT in the MAJIC trial. The ESC therefore considered that, currently, the appropriateness of cost-utility is questionable. |
| Outcomes | Life years (LY) and Quality Adjusted Life Years (QALY) | Quality of life data reported in RESPONSE and RESPONSE-2 used to inform model. The ESC noted that QoL data was collected in MAJIC but it was not presented. The ESC also noted there was no difference in QoL between responder and non-responders, but that a QoL gain for ruxolitinib responders was assumed based on correlation between QoL and treatment received. The ESC considered this may not have been appropriate. The ESC also considered it was not appropriate to model any OS differences as there is no evidence that treatment with ruxolitinib or maintaining surrogate response improves survival.  |
| Time horizon | 20 years in base case, 5 years in MAJIC trial | Published long-term survival studies show that long term survival in PV at 20 years is 57%. Time horizon is longer than Canadian and Irish models (15 years). Extrapolation of data may be unreliable and was inappropriate due to non-significant OS results.  |
| Methods used to generate results | Markov model | Reasonable |
| Health states | Non-responder (initial), responder, second time non-responder and death | The ESC considered the relationship between responder states and clinical and patient outcomes was uncertain. |
| Cycle length | 28 days | Consistent with monthly follow-up in MAJIC, but may be inconsistent with real world follow-up. The submission assumes quarterly visits.  |
| Transition probabilities | The Kaplan-Meier estimates for TTR, DoR and overall survival (OS) are derived directly from the MAJIC trial. Parametric distributions are fitted to the observed Kaplan-Meier survival estimates to derive time-dependent transition probabilities to enable extrapolation beyond the follow-up of MAJIC to the time horizon of the economic evaluation. Select adverse events from RESPONSE and RESPONSE-2 were included.  | There was no statistically significant difference in OS, therefore it was inappropriate to model any differences. Selection of adverse events were not based on statistically significant differences, so it was also likely inappropriate to include in the model.  |
| Software package | Microsoft Excel | Appropriate |

Source: Table 3.1-1, p205 of the Submission

* 1. The submission presented a Markov model with four health states: non-responder (initial), responder, second time non-responder and death (Figure 5). All patients start in the non-responder (initial) state, and in each cycle a proportion of the cohort move into the responder state based on the treatment dependent TTR estimates from MAJIC. Patients were only able to move into the responder state within the first six cycles when treated with ruxolitinib (consistent with requested restriction) and in the first 13 cycles when treated with BAT (consistent with MAJIC). At the end of six cycles in the ruxolitinib arm and 13 cycles in the BAT arm, any patients remaining in the non-responder (initial) are assumed to be treated with BAT (subsequent) until death.

Figure 5: Structure of economic model



Source: created during evaluation using Jakavi (ruxolitinib) Economic Evaluation – Base case.xlsx

* 1. A proportion of patients in the responder state move to the second time non-responder state each cycle based on the treatment dependent DoR estimates from MAJIC. Second time non-responders are assumed to be treated with BAT (subsequent) and cannot move back into the responder state. Patients remaining in the responder state are assumed to remain on treatment with the same drug as they were randomised to. In each cycle, patients may die in any of the health states, with the same risk of mortality irrespective of response, but dependent on the treatment they were randomised to.
	2. Additionally, the submission claimed that transformation to MF or AML was not included as a health state as there was no information on how many responder and non-responders experienced disease transformation. However, the submission subsequently assumed that 10% of all patients in non-responder (initial) and second time non-responder would transform to MF and require treatment with ruxolitinib until they die.
	3. Response in the model was not associated with improved utility. The ESC noted that, instead, patients treated with ruxolitinib (utility = ''''''''''') were assumed to have a higher utility than patients treated with BAT (utility = ''''''''''''), which included all non-responders and patients who respond to BAT. This was supported by the results of RESPONSE and RESPONSE-2, as patients treated with ruxolitinib on average reported improvement in almost all symptom scores whereas patients treated with BAT on average reported no change or slight worsening in all symptom scores. Additionally, patients treated with ruxolitinib had better HRQoL and fewer phlebotomies on average compared to patients treated with BAT. The ESC noted there appeared to belarger differences in utility values between ruxolitinib and BAT treatment arms in RESPONSE compared to RESPONSE-2. The ESC considered that, while this could be attributed to differences between the trial populations (for e.g. baseline splenomegaly), it was uncertain if any differences in utilities between ruxolitinib and BAT arms are attributable to treatment with ruxolitinib (particularly given this cannot be explained by ‘responder’ health state differences). The ESC considered it was unclear why ruxolitinib responders would have an improvement in QoL over BAT responders and considered the application of this assumption in the model to be poorly justified.
	4. The ESC considered that QoL may not differ significantly between patients who do and no not respond to treatment in clinical practice as in general, only more serious disease related symptoms such as severe splenomegaly, thrombosis and haemorrhage (which are rare events) would have a noticeable impact on QoL.
	5. The only function of the responder health state was to determine what treatments were used in the cohort and associated costs. In the ruxolitinib responders, they continue to use ruxolitinib ($''''''''''/cycle) and in the BAT responders, they continue to use BAT ($''''''''''''/cycle). All non-responders (initial and second time) are assumed to be treated with BAT (subsequent), which incorporates 10% ruxolitinib for MF due to the assumed transformation, and have a cost of $''''''''''''''/cycle. The ESC considered that the inclusion of transformation to MF in the model was inappropriate noting the no evidence was provided to support the assumption of 10% transformation to MF and there were no changes in OS or QALY for patients who experience transformation to MF. The ESC noted that incorporation of ruxolitinib costs for transformation to MF favours ruxolitinib as it increases the cost of treatment in non-responders and the submission modelled a larger proportion of non-responders in BAT compared to ruxolitinib.
	6. A summary of the key drivers of the model is presented in Table 10.

Table 10: **Key drivers of the model**

| **Description** | **Method/Value** | **Impact** |
| --- | --- | --- |
| Difference in OS | Submission assumes that there was a difference in the OS in patients treated with ruxolitinib and BAT at 6 years which is extrapolated to 20 years. This is despite:• MAJIC not being designed to detect differences in OS;• There was no statistically significant differences between patients treated with ruxolitinib and patients treated with BAT (p=0.5550); and • There is no evidence that the response criteria in MAJIC (or ELN response) is correlated with improved OS.It was inappropriate to have modelled any difference in OS between treatment arms. | High, favours ruxolitinib. Assuming no difference in OS increases ICER by 88-89%. |
| Proportion of patients receiving peginterferon α-2a | In the base case, the submission assumed that patients treated with BAT were treated 50:50 with peginterferon α-2a to HC. This was likely an overestimate, as the ratio for HC to peginterferon in MAJIC, RESPONSE and RESPONSE-2 were 61:39, 16:84 and 21:79, respectively. | High, favours ruxolitinib. Assuming 39:61, 16:84 and 21:79 ratio of peginterferon to HC, the ICER increases by 13%, 40% and 34% respectively.  |
| OS extrapolation | The submission assumed that the Weibull parametric function was the best fit for the extrapolation for OS, based on visual inspection against published OS curves. However, three different OS curves from the literature were sourced, and it could be argued that all the extrapolations except for Exponential and Gompertz fit visually (Figure 6). However this will be an issue only if it was deemed appropriate to model OS differences. | Moderate. The Weibull functional form has the lowest ICER of all the functions. The ICER increases by 6% with Gompertz, up to 38% with Gamma.  |
| OS not associated with response | The submission assumed that the survival of patient is dependent only on the treatment they were randomised to and is independent on the actual treatment received. That is, patients who started on ruxolitinib but became a non-responder and assumed to be treated with BAT will still have the same OS as patients who did respond to ruxolitinib. This is implausible, and is a result of the model assuming a difference in OS when there was no statistical significance as well as being a structural issue.  | Moderate. Assuming that patients who were treated with ruxolitinib who did not respond had the same OS as patients treated with BAT increases ICER by 22%. |
| Cost of ruxolitinib | The submission assumed that the cost of ruxolitinib was $''''''''''''' per 28 days, irrespective of dose. However, there are several reasons why this may be an underestimate:• More than one pack/tablet form may be required to deliver a dose. The recommended dose of ruxolitinib for PV is 5-25mg twice daily, but only tablets of 5mg, 10mg, 15mg and 20mg are available. Therefore, at a minimum, a patient on 25mg will need 5mg + 20mg tablets. Additionally, given that patients are expected to titrate their doses, a dose of 15mg may be given as 5mg + 10mg. These combinations will increase the price per 28 days of treatment;• The model assumes that patients will discontinue every cycle. However patients will not visit doctors for a response assessment every month, leading to an underestimate of the duration of treatment; and • It is recommended that the dose of ruxolitinib be tapered down if discontinuing, but the submission does not account for the cost of the tapering dose.Therefore it is possible that the cost of ruxolitinib per 28 days will exceed $'''''''''''''. | Moderate. Assuming that the cost of ruxolitinib per 28 days to be $''''''''''''' instead of $'''''''''''''' increases the ICER by 24%.  |

Source: Constructed during evaluation

Figure 6: Comparison of extrapolated OS from MAGIC with published OS curves from literature



Source: constructed during evaluation using information from Jakavi (ruxolitinib) Economic Evaluation – Base case.xlsx

* 1. While it may have been inappropriate to model adverse events which were not statistically significant, this had minimal impact on the model (+2% on ICER). Similarly, changing the time horizon led to relatively small changes in the ICER (increasing to 30 years led to 2% decrease and decreasing to 15 years led to 6% increase).
	2. The results of the stepped economic evaluation is presented in Table 11.

Table 11**: Results of the stepped economic evaluation**

| **Data** | **Costs** | **Health outcomes** | **Incremental cost-effectiveness ratio** |
| --- | --- | --- | --- |
| **Ruxolitinib** | **BAT** | **Increment** | **Ruxolitinib** | **BAT** | **Increment** |
| Step 1: MAJIC (time horizon 5 years)a | ''''''''''''''''' | ''''''''''''''''' | '''''''''''''''''' | ''''''''''' LY | '''''''''' LY | '''''''''' LY | $''''''''''''''''''''/LYG |
| '''''''''' QALY | '''''''''''' QALY | ''''''''''' QALY | $'''''''''''''''''/QALY |
| Step 2: MAJIC extrapolated to 20 years, background mortality and ruxolitinib continuation criteria  | ''''''''''''''''''''' | '''''''''''''''''' | '''''''''''''''''' | '''''''''' LY | '''''''''' LY | ''''''''''' LY | $''''''''''''''''''''/LYG |
| '''''''''' QALY | '''''''''' QALY | '''''''''' QALY | $'''''''''''''''''/QALY |
| Step 3: MAJIC extrapolated to 20 years, background mortality, ruxolitinib continuation criteria and all resource use | '''''''''''''''''''''''' | ''''''''''''''''' | ''''''''''''''''''' | ''''''''''' LY | ''''''''''' LY | '''''''''''' LY | $''''''''''''''''/LYG |
| ''''''''''' QALY | '''''''''' QALY | ''''''''''' QALY | $'''''''''''''''/QALY |

a values extracted during evaluation.

Source: Table 3.8-1, p 246 of the submission and ‘results’ sheet in Jakavi (ruxolitinib) Economic Evaluation – Base case.xlsx

* 1. It should be noted that the results in Step 1 were dependent on modelling a non-statistically significant difference in OS between patients treated with ruxolitinib and BAT and is likely inaccurate. The ESC considered that the available data does not adequately support the modelled OS difference between the ruxolitinib and BAT arms. The PSCR argued that while MAJIC was not powered to detect a difference in OS, a randomised clinical trial that is sufficiently powered to detect a difference in OS may not be feasible given the rarity of the condition. The PSCR argued that it is reasonable and clinically plausible to conclude treatment with ruxolitinib is associated with a small survival benefit compared to BAT as there was a trend towards improvement in OS in the later part of the OS curve in MAJIC. The ESC maintained that the extrapolation of OS from MAJIC was highly uncertain particularly given the limited long-term comparative data available on the trial.
	2. Extrapolating from 5 years (Step 1) to 20 years (Step 2) reduced the cost per LY gain by more than 70% and cost per QALY gain by 38%, indicating that the extrapolation had a significant effect on ICER. The extrapolation relied on some potentially inappropriate assumptions (e.g. patients treated with ruxolitinib that did not respond after 6 months are still considered to have better OS than patients who responded but treated with BAT) and uncertain extrapolations from MAJIC (e.g. DoR extrapolated with high loss to follow-up, OS extrapolated with high loss to follow-up and no statistically significant difference). This contributes to the uncertainty in the ICERs calculated.
	3. Adding resource use costs such as MBS costs and subsequent treatment costs from Step 2 to Step 3 led to a decrease in the incremental costs and hence a lower ICER. The utilisation of treatments (particularly peginterferon) and transformation to MF in non-responders were not informed by any evidence and were likely inappropriate and/or overestimated. Overall, there appears to be a lot of uncertainty around the Step 3 ICER and it is likely that the Step 3 ICER is underestimated, favouring ruxolitinib.
	4. The ESC noted the results were highly sensitive to the assumption of 50% of patient in BAT receiving peginterferon (see multivariate sensitivity analyses in Table 12). This was much higher than in the MAJIC (39%), RESPONSE (16%) and RESPONSE-2 (21%) trials, and may be much higher than in clinical practice (~5-10%). The PSCR argued that the ratio of peginterferon use would likely increase in the future given the recent unrestricted benefit listing of peginterferon and noting that peginterferon is a recommended first-line cytoreductive treatment in treatment guidelines. The ESC noted that in clinical practice, given it is not well tolerated, peginterferon would only be used for a small subset of patients who are younger or pregnant and considered this use more likely represents less than 10% of BAT in clinical practice. The PBAC considered the range of 16–39% of peg-interferon use from the clinical trials may be reasonable.
	5. Overall, the ESC considered that the economic model did not form a reliable basis for decision making as it incorporated responder health states that do not correlate to clinical outcomes and therefore, do not adequately capture the benefits, if any, oftreatment. The ESC considered a model that more reliably estimates cost-effectiveness could incorporate responder health states defined by patient relevant outcomes. While the ESC noted that the current clinical evidence as presented by the submission, does not adequately support an improvement with ruxolitinib treatment over treatment with BAT for key clinical outcomes (thrombosis, haemorrhage, transformation to MF or AML, and OS), identifying alternative clinical outcomes from the available evidence may address this issue. The ESC also considered that as most PV patients who respond to treatment may not experience significant QoL changes, an alternative model structure would be more appropriate.
	6. The ESC noted the ‘scenario analysis’ presented by the submission where patients were assumed to be treated with ruxolitinib even if there is no response. The PSCR (p1) stated that the intent of the submission in proposing continuation criteria was to ensure use of ruxolitinib is maintained only in patients who continue to benefit. The PSCR stated that, if there is no clear relationship between ‘response’ and improvement in QoL, then patients may be required to discontinue treatment prematurely, thus prompting the submission’s alternative scenario where the discontinuation criteria were removed. The ESC considered that the removal of continuation treatment criteria and thus allowing patients to continue treatment without response was not clinically appropriate especially considering the potentially long duration of therapy. The ESC considered that the lack of correlation between a response and improvement in patient relevant outcomes may have been due to the use of response criteria from MAJIC.
	7. A range of univariate sensitivity analyses were presented by the submission around extrapolation of DoR and OS, utilities, time horizon and discount rates. As discussed, the OS extrapolation was a driver of the model, and using other parametric functions can increase the ICER by 6-38%. Using other parametric functions for DoR extrapolation led to a decrease in ICER by 7-15%, but this was a result of the assumptions and structure of the model. For example, patients in the ruxolitinib cohort, even if they lost response quicker and discontinued treatment from ruxolitinib earlier (therefore incurring fewer costs) and have a shorter period of utility benefit, were still assumed to have an OS benefit compared to patients in the BAT cohort. This is implausible and indicates potential issues with the model structure. Using only RESPONSE utilities lowered the ICER by 8% and using only RESPONSE-2 utilities increased the ICER by 15%.
	8. Additional univariate and multivariate sensitivity analyses were conducted during the evaluation. These included sensitivity around assumptions behind the OS, proportion of HC to peginterferon α-2a and testing the cost of ruxolitinib. The results of these analyses were discussed in Table 10. Additionally, a scenario where transformation to MF was removed was tested and led to a +7% in ICER. Multivariate sensitivity analyses conducted during the evaluation are presented in Table 12.

Table 12: **Multivariate sensitivity analyses conducted during evaluation**

| **Data** | **Costs** | **Health outcomes** | **Incremental cost-effectiveness ratio** | **Diff** |
| --- | --- | --- | --- | --- |
| **Ruxolitinib** | **BAT** | **Increment** | **Ruxolitinib** | **BAT** | **Increment** |
| Base case | '''''''''''''''''''' | $'''''''''''''''' | '''''''''''''''''''' | '''''''''''' LY | '''''''''' LY | ''''''''''' LY | $''''''''''''''''/LY | 0% |
| '''''''''''' QALY | '''''''''''' QALY | ''''''''''' QALY | $'''''''''''''''/ QALY | 0% |
| Assume 39% peginterferon in BAT and BAT (subsequent), no OS difference (apply BAT OS to both) | ''''''''''''''''''''' | $''''''''''''''' | '''''''''''''''''' | '''''''''' LY | ''''''''''' LY | '''LY | NA | NA |
| ''''''''''' QALY | '''''''''' QALY | '''''''''' QALY | $'''''''''''''''''''/ QALY | +122% |
| Assume 39% peginterferon in BAT and BAT (subsequent), BAT OS applied to all non-responders, remove ruxolitinib for MF | ''''''''''''''''''''' | $'''''''''''''''' | ''''''''''''''''''' | ''''''''''' LY | ''''''''''' LY | '''''''''' LY | $''''''''''''''''''''''/LY | +106% |
| ''''''''''' QALY | ''''''''''' QALY | '''''''''' QALY | $''''''''''''''''/ QALY | +53% |
| Assume 16% peginterferon in BAT and BAT (subsequent), No OS difference (both use BAT OS), remove ruxolitinib for MF and no adverse event modelling | ''''''''''''''''' | $'''''''''''''''''' | ''''''''''''''''''''' | '''''99 LY | '''''''''' LY | ''''LY | NA | NA |
| '''''''''' QALY | '''''''''' QALY | '''''''''' QALY | $'''''''''''''''''''/ QALY | +223% |

Diff=difference

Source: Constructed during evaluation

The redacted table shows ICERs in the range of $45,000/QALY - $200,000/QALY.

* 1. Peginterferon discontinuation was not estimated during the evaluation as data about a reasonable duration of use in PV was unavailable. However, as the result is likely to be a reduction in peginterferon use, the effect on ICER should be similar to changing the proportion of peginterferon to HC as above.
	2. Overall, the ESC considered the economic model does not form a reliable basis for decision making.

## Drug cost/patient/year: $''''''''''''

* 1. At the proposed effective DPMQ of $''''''''' for 56 x 10 mg ruxolitinib capsules, the total cost of treatment per patient per year is $''''''''''''' ($'''''''''' x [365.25/28]). The drug cost per patient for ruxolitinib and BAT are presented in Table 13. Despite the likely intention of the submission to make the cost of ruxolitinib consistent across all doses, the cost per 28 days for each recommended dose is actually variable (from $'''''''/28days up to $'''''''''/28 days).
	2. For HC, at the recommended daily dose of 30mg/kg/day and an average of 77.6kg body weight, an average daily dose of 2,327 mg per day was estimated. Using the DPMQ of $63.20 for 100 × 500mg capsules, the cost of treatment per patient year was $1047.77. It was assumed that 50% of all BAT patients use HC.
	3. For peginterferon α-2a, at the recommended daily dose of 180 mcg/week, using the DPMQ of $1272.42 for 4 ×180mcg/0.5mL injections, the cost per patient year was estimated to be $16,541. It was assumed that 50% of all BAT patients use peginterferon α-2a.
	4. As noted above, the ESC did not consider the 50:50 split between HC and peginterferon was a valid assumption. The use of peginterferon is likely to be less than 10% in clinical practice.

Table 13**: Drug cost per patient for proposed and comparator drugs**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Ruxolitinib****Trial dose and duration** | **Ruxolitinib****Model** | **Ruxolitinib****Financial estimates** | **BAT****Trial dose and duration** | **BAT****Model**  | **BAT****Financial estimates** |
| Median dose | 10mg BD | 10mg BD | NR | NR | HC: 2,327 mg daily Peginterferon α-2a: 180mcg/week  |
| Mean duration | NR | NR | NR | NR | NR | NR |
| Cost/patient/28 days | ''''''''''''''''' | ''''''''''''''' | '''''''''''''''' | NR | $675.231 | $675.23 |
| Cost/patient/year  | '''''''''''''''''' | '''''''''''''''''''' | '''''''''''''''''' | NR | HC: $1047.77Peginterferon α-2a: $16,5411 |

1 There was a slight discrepancy between the 28 day cost of BAT and the total cost of BAT per year, as the submission assumed that the cost of 4 weeks of peginterferon α-2a in the model to be $1,268.07 instead of $1,272.42.

BD = twice daily, NR = not reported

Source: constructed during evaluation

## Estimated PBS usage & financial implications

* 1. This submission was considered by DUSC.
	2. The estimated financial implications for listing ruxolitinib for patients with PV who are resistant or intolerant to HC is presented in Table 14.

Table 14**: Estimated use and financial implications**

|  | **2020** | **2021** | **2022** | **2023** | **2024** | **2025** |
| --- | --- | --- | --- | --- | --- | --- |
| **Estimated used and financial impact of ruxolitinib**  |
| Prevalent eligible population1 | ''''''''''''' | - | - | - | - | - |
| Incident eligible population 2 | - | '''''' | ''''''' | '''''' | ''''' | ''''''' |
| Estimated prevalent patient commencing treatment 3 | ''''''''' | '''''''' | '''''''''' | '''''''''' | ''''''''' | ''''''''' |
| Estimated incidence patients commencing treatment 4 | ''' | ''''' | '''''' | ''''' | ''''''' | ''''''' |
| Grandfathered patients 5 | ''''''''' | - | - | - | - | - |
| Total commencing patients | ''''''''' | ''''''''' | ''''''''' | '''''''''' | ''''''''' | ''''''''' |
| Total ruxolitinib (PV) PBS scripts 6 | '''''''''''''' | ''''''''''''''' | ''''''''''''' | '''''''''''''''' | ''''''''''''''' | '''''''''''''''''' |
| Total ruxolitinib (PV) RPBS scripts6 | ''''''''' | '''''''''' | '''''''''' | '''''''''' | ''''''''' | '''''''''' |
| Total ruxolitinib (PV) scripts | ''''''''''''' | '''''''''''' | '''''''''''''''' | ''''''''''''''''' | ''''''''''''''''' | '''''''''''''''' |
| Total PBS cost (effective) minus copayment 7 | ''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' |
| Total RPBS cost (effective) minus copayment 7 | ''''''''''''''''''''''' | '''''''''''''''''''' | '''''''''''''''''''''''' | '''''''''''''''''''' | ''''''''''''''''''''' | ''''''''''''''''''''' |
| **Total cost (effective) minus copayment**  | **''''''''''''''''''''''** | **'''''''''''''''''''''''''** | **''''''''''''''''''''''''** | **''''''''''''''''''''''''''** | **''''''''''''''''''''''''** | **''''''''''''''''''''''** |
| **Estimation of change in use and financial impact of other medicines** |
| HC packs offset 8 | '''''''''''''' | '''''''''''''''' | ''''''''''''''' | '''''''''''''''' | ''''''''''''''' | '''''''''''''''' |
| Peginterferon α-2a packs offset 8 | '''''''''''''''' | '''''''''''''''' | ''''''''''''''' | ''''''''''''''' | '''''''''''''''' | '''''''''''''' |
| Ruxolitinib (MF) packs offset 8 | ''''''' | ''''''''''' | ''''''''''' | '''''''''' | '''''''''' | ''''''''''' |
| Total packs offset | '''''''''''''' | '''''''''''''''' | '''''''''''''''''''' | '''''''''''''''''' | ''''''''''''''''''' | ''''''''''''''''''' |
| Total cost HC offset minus copayments 9 | ''''''''''''''''''''''''' | '''''''''''''''''''''''' | '''''''''''''''''''''' | ''''''''''''''''''''''' | ''''''''''''''''''''''' | ''''''''''''''''''''''' |
| Total cost peginterferon (published) offset minus copayments 10 | '''''''''''''''''''''''''' | '''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | '''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''' |
| Total cost ruxolitinib (MF) (effective) offset minus copayments 11 | '''''''''''''''''''''''''' | '''''''''''''''''''''''''' | ''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' |
| **Total cost of medicines offset (published)** | **''''''''''''''''''''''''** | **'''''''''''''''''''''** | **'''''''''''''''''''''''** | **'''''''''''''''''''''''''** | **''''''''''''''''''''''''** | **'''''''''''''''''''''''''** |
| **Estimated financial impact for PBS/RPBS** |
| **Net impact on PBS/RPBS (effective ruxolitinib, published interferon)** | **'''''''''''''''''''''''** | **''''''''''''''''''''''** | **'''''''''''''''''''''** | **'''''''''''''''''''''''** | **'''''''''''''''''''''''** | **'''''''''''''''''''''** |
| **Estimated financial impact for the health budget** |
| Total ruxolitinib (PV) scripts | ''''''''''''''' | ''''''''''''''' | ''''''''''''''' | '''''''''''''''' | ''''''''''''''''' | '''''''''''''''' |
| Total BAT scripts | ''''''''''''' | '''''''''''''''' | '''''''''''''''' | ''''''''''''''' | '''''''''''''''' | '''''''''''''''''' |
| Net change | '''''''''''''''' | '''''''''''''''' | '''''''''''''''' | ''''''''''''''' | ''''''''''' | '''''''''' |
| Change in follow up, FBC, LFT and iron study  12 | ''''''''''''''''' | '''''''''''''' | '''''''''''''' | ''''''''''''''' | '''''''''''' | '''''''''''''' |
| Change in phlebotomy 13 | '''''''''' | ''''''''''''''' | ''''''''''''''' | ''''''''''''''''' | '''''''''''''''' | ''''''''''''''' |
| Change in follow up, FBC, LFT and iron study costs | '''''''''''''''''''' | ''''''''''''''''''''' | ''''''''''''''''''''''' | ''''''''''''''''''''' | ''''''''''''''''''''''' | '''''''''''''''''''''''' |
| Change in phlebotomy costs | '''''''''''''''''''''' | ''''''''''''''''''''''''' | '''''''''''''''''''''''' | ''''''''''''''''''''''' | ''''''''''''''''''''''' | ''''''''''''''''''''''' |
| **Total change MBS costs** | **''''''''''''''''** | **'''''''''''''''''''** | **'''''''''''''''** | **''''''''''** | **'''''''''''''''** | **''''''''''''''''** |
| Total change on PBS/RPBS costs(effective ruxolitinib, published interferon) | ''''''''''''''''''''''''''' | ''''''''''''''''''''''' | '''''''''''''''''''''''' | '''''''''''''''''''''''''''' | '''''''''''''''''''''''''' | '''''''''''''''''''''''' |
| **Net health budget costs** | **'''''''''''''''''''''''** | **''''''''''''''''''''** | **'''''''''''''''''''''** | **'''''''''''''''''''** | **''''''''''''''''''''** | **''''''''''''''''''''** |

1 Estimated current year population multiplied by prevalence of PV (30/100,000), proportion treated with HC (77.3%) and proportion intolerant/resistant to HC (24.0%).

2 Estimated current year population multiplied by incidence of PV (1.36/100,000), proportion treated with HC (77.3%) and proportion intolerant/resistant to HC (24.0%).

3 Estimated prevalent patient multiplied by additional prevalent patients treated each year, starting at an additional '''''''% in year 1 decreasing to '''''''% by year 6.

4 Estimated incident patients multiplied by uptake rate for incident patients (85%)

5 Assumption

6 Estimated total commencing patients in each year multiplied by expected number of packs of ruxolitinib (PV) derived from the economic model in year 1, then added to expected number of packs used by patients who commenced in previous years, then multiplied by proportion of ruxolitinib (PV) PBS scripts (97.5%) or RPBS scripts (2.5%)

7 Assume each ruxolitinib (PV) script costs $'''''''''''''', minus average PBS copayment of $15.51 (97.5%) and RPBS copayment of $5.34 (2.5%)

8 Estimated total commencing patients in each year multiplied by expected number of packs of HC, peginterferon or ruxolitinib (MF) not used derived from the economic model in year 1, then added to expected number of HC, interferon or ruxolitinib (MF) packs not used by patients who commenced in previous years

9 Assume each HC script costs $63.20, minus average PBS copayment of $16.45 (97.4%) and RPBS copayment of $5.38 (2.6%)

10 Assume each peginterferon script costs $1,272.42 minus average PBS copayment of $25.49 (97.4%) and RPBS copayment of $5.38 (2.6%)

11 Assume each ruxolitinib (PV) script costs $''''''''''''''''''''', minus average PBS copayment of $15.51 (97.48%) and RPBS copayment of $5.34 (2.52%)

12 Combination of estimated total commencing patients in each year multiplied by expected number each service(oncologist follow up, FBC, LFT, iron study) in year 1 derived from the economic model, then added to expected number of services used by patients who commenced in previous years

13 Estimated total commencing patients in each year multiplied by expected number of phlebotomy avoided in year 1 derived from the economic model, then added to expected number of phlebotomy avoided by patients who commenced in previous years

Source: Constructed during evaluation

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than 10 million per year.

* 1. No justification for the assumption of less than 10,000 grandfathered patients in Year 1 of listing was provided.
	2. There were uncertainties around the prevalence and incidence of PV as well as the proportion of patients treated with, resistant to or intolerant to HC as:
* Prevalence rate was based on Orpha.net, an online portal for rare diseases and orphan drugs. As Orpha.net includes mainly data from Europeans, it may not be applicable to Australia.
* The incidence of PV was based on the average incidence between 2003-2014 from AIHW 2014 Australian Cancer Database and Australian Population. While this source is appropriate, Baade et al 2019 calculated an age-adjusted incidence rate of 0.9/100,000 using the same data.
* The proportion of patients treated with HC (77.3%) was based on Alvarez-Larran et al 2016, from a retrospective Spanish registry between July 2011 to June 2015. Values identified in the literature ranged from 31.4% to 88%.
* The proportion of patients resistant or intolerant to HC (24%) was based on Alvarez-Larran et al 2012, data from 5 institutes in Spain. Parasuraman et al 2016, a US study, that had the largest sample size (N=1,309) reported 27.5% of patients as intolerant to HC, and a further 29.3% discontinued due to inadequate response, representing a total of 56.8% intolerant or resistant to HC. The DUSC noted that the evaluation had incorrectly reflected the numbers from Parasuraman et al 2016. The 27.5% of patients reported as intolerant to HC and the 29.3% who discontinued due to inadequate response should have been applied to the group of patients who discontinued (n=229; 17.5% of total population), not the overall population (N=1,309). Therefore, the proportion reported as intolerant or resistant to HC in Parasuraman et al 2016 was approximately 10%.
	1. The submission utilises the number of prescriptions used/offset and services used/offset predicted by the economic model to inform the financial estimates. The assumed number of additional prescriptions and MBS services used and offset is presented in Table 15. As discussed, the proportion of patients using peginterferon was overestimated in the economic model, and there was no evidence to support differential transformation to MF depending on surrogate response. This will lead to an overestimated cost offset for BAT in the financial impact estimates

Table 15: **Expected change in prescriptions and MBS services per year**

|  | **Ruxolitinib (PV)** | **HC** | **Peginterferon** | **Ruxolitinib (MF)** | **Follow up visit, FBC, LFT, Iron study** | **Phlebotomy** |
| --- | --- | --- | --- | --- | --- | --- |
| Year 1 | ''''''''''''' | ''''''''''''' | ''''''''''' | ''''''''''' | ''''''''''' | ''''''''''''' |
| Year 2 | '''''''''' | ''''''''''''' | ''''''''''''' | ''''''''''' | '''''''''' | '''''''''''' |
| Year 3 | ''''''''''' | ''''''''''''' | ''''''''''''' | ''''''''''' | ''''''''''' | ''''''''''''' |
| Year 4 | '''''''''' | ''''''''''''' | '''''''''''' | ''''''''''''' | '''''''''''' | ''''''''''''' |
| Year 5 | ''''''''''' | '''''''''''''' | '''''''''''''' | ''''''''''''' | ''''''''''' | '''''''''''''' |
| Year 5 | '''''''''' | '''''''''''' | '''''''''''' | '''''''''''''' | '''''''''' | ''''''''''''' |

HC = hydroxycarbamide/hydroxyurea FBC = full blood count, LFT = liver function test

Source: Table 4.1-7, p261 and Table 4.1-8, p262 of the submission.

* 1. The submission estimated that the cost of listing ruxolitinib for patients with PV who are intolerant or resistant to HC will have a net cost of less than$10 million in Year 1 of listing and up to less than $10 million by Year 6 of listing.
	2. The overall financial estimate was likely to be underestimated as the number of packs of peginterferon α-2a offset was likely vastly overestimated. Between July 2018 – June 2019, only 654 items of peginterferon α-2a (11037X) were processed on the PBS, whereas the submission assumed that 3,864 packs would be offset in Year 1 of listing (2020). This seems implausible and leads to an overestimated offset for BAT and lower overall impact on the health budget. Assuming a ratio of 16:84 peginterferon to HC (as observed in RESPONSE), the overall financial impact increases to less than $10 million in Year 1 increasing to $10 - $20 million in Year 6, an increase of more than 40% each year.
	3. Additionally, peginterferon α-2a has a special pricing arrangement which was not available to the sponsor, therefore the cost of BAT offset is overestimated.
	4. DUSC considered the eligible population presented in the submission to be overestimated, but the overall costs to be underestimated. The main issues are:
* The assumptions used to derive eligible patient numbers (prevalence rate, incidence rate, proportion treated with HC and proportion intolerant or resistant to HC) were all likely overestimated, leading to an overestimated number of eligible patients. This was exacerbated in Year 1 by the additional less than 10,000 grandfathered patients, for which no justification was provided.
* It was unclear why uptake in prevalent patients ('''''% in Year 1; cumulative uptake of '''''% by Year 6) would require such a long time to ramp up to the same level as incident patients ('''''% in each of Years 2-6). DUSC considered '''''% uptake from the prevalent pool in Year 1 was too low, considering these patients are resistant or intolerant to HC. However, the unclear therapeutic advantage, with no impact on survival or transformation, but some risks, may limit uptake.
* The estimated prescription and MBS offsets relied on an economic model with little face validity (i.e. the economic model relies on an overall survival benefit, which was not supported by the MAJIC trial).
* The number of packs of peginterferon α-2a offset was likely vastly overestimated.An overestimate of the number of peginterferon α-2a offsets will lead to an underestimated overall cost of listing ruxolitinib.
* Offsets for ruxolitinib in myelofibrosis are unlikely to be realised if ruxolitinib has no impact on survival or transformation in PV.
* There was no link between continuation criteria and outcomes, which would likely lead to long-term use in the eligible population with up to 30-year survival.

## Quality Use of Medicines

* 1. No information around quality use of medicines (QUM) was included in the submission. However, there may be QUM issues around the titration of the dose from 5mg to 25mg twice daily, as well as the possible combination of tablets used to achieve the desired dose. Additionally, it is recommended that ruxolitinib be tapered down gradually in the event of a discontinuation. However, provision for this tapering dose has not been provided in the requested restriction.

## Financial Management – Risk Sharing Arrangements

* 1. No risk sharing arrangements were proposed. However a special pricing arrangement, with a rebate of $''''''''''''''''' per pack, was proposed (Published DPMQ = $'''''''''''''''', effective DPMQ = $'''''''''''').

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

# PBAC Outcome

* 1. The PBAC did not recommend the listing of ruxolitinib for the treatment of patients with polycythemia vera (PV) who are resistant to, or intolerant of, hydroxyurea. The PBAC considered that the evidence from the key trial did not clearly support a benefit in terms of clinically relevant outcomes or overall survival. Further, the PBAC considered that the economic model did not provide a reliable basis for assessing the cost-effectiveness of ruxolitinib as the clinical benefits modelled were not supported by evidence.
	2. The PBAC noted that the European LeukemiaNet (ELN) criteria for response in PV was updated in 2013 to include more clinically relevant response definitions and, as a result, are more focused on improvement in disease related symptoms and reduction in hepatosplenomegaly. The PBAC agreed with the ESC and considered that the exclusion of requirement for no disease related symptoms from the response criteria in the MAJIC trial (and consequently, the proposed continuation criteria) may not be in line with the direction of current clinical practice. However, the PBAC also considered that the impact of treatment on symptoms can be subjective. The pre-PBAC response argued that ruxolitinib improves quality of life (QoL) by improved symptom control but acknowledged that this is not captured by the response criteria. The PBAC advised that a requested listing and restriction in this setting with continuation criteria in line with modified ELN criteria was acceptable.
	3. In accordance with treatment guidelines, the PBAC considered that the clinical place of ruxolitinib in therapy should be for patients who have failed treatment with other available therapies and/or for those with extreme pruritus or symptoms of splenomegaly.
	4. The PBAC considered the nominated main comparator of best available therapy (BAT) to be appropriate, noting that peginterferon α-2a use was likely to be considerably lower than hydroxyurea, i.e. less than 50%.
	5. The PBAC considered the pivotal trial (MAJIC) supporting the proposed listing to be unreliable given the high risk of bias. The PBAC agreed with the ESC that there was potential for selective reporting bias given the trial data was only available as conference abstracts from poster and PowerPoint presentations, noting that QoL data was collected but not presented. The PBAC was also concerned with its open label design, the limited median follow-up of 2.6 years, the duration of response (DoR) secondary outcome not being clearly defined, limited safety data, and no magnitude of effect on patient-reported symptoms.
	6. The PBAC agreed with the ESC advice that association between the proposed surrogate outcome (response based on HCT, platelet and WBC count and splenomegaly) and the relevant clinical outcomes for patients with PV (thrombosis, haemorrhage, transformation to MF or AML, and OS) were not supported by the available evidence. Therefore, it is possible that achieving the proposed response criteria may not lead to improvement in the relevant clinical outcomes in patients with PV.
	7. With respect to MAJIC, the PBAC noted that, overall, there were no statistically significant differences at 12 months between the proportion of patients who responded between treatments, with 96.8% and 93.3% of patients treated with ruxolitinib and BAT achieving complete response (CR) or partial response (PR) respectively. With respect to the submission’s claim of superior efficacy in terms of faster time to response (TTR) and DoR compared to BAT, the PBAC noted that it was unclear what hypothesis or statistical tests were conducted to derive the P values and no hazard ratios were presented. Further, the PBAC agreed with the ESC and considered that DoR is a clinically significant measure given the chronic nature of PV; however, the results for DoR from MAJIC were unreliable due limited follow-up beyond two years.
	8. The PBAC noted the supplementary evidence presented in the submission, i.e. the RESPONSE and RESPONSE-2 trials. Despite being open label trials and allowing for cross-over from BAT to ruxolitinib, the PBAC agreed with the ESC and considered this data to be more robust compared to MAJIC.
	9. The PBAC noted that the results of the post hoc analysis from RESPONSE and RESPONSE-2 using the MAJIC criteria for response indicated that a statistically significantly greater proportion of patients treated with ruxolitinib achieved response. However, the PBAC noted this was somewhat inconsistent with the results from MAJIC at 6 months, in which no statistically significant differences were observed between treatment arms, and considered this could be due to differences in the BAT arm, as RESPONSE and RESPONSE-2 included ‘watch and wait’ as a BAT option whereas all patients in MAJIC received active treatments (according to protocol).
	10. The PBAC considered that the responder outcomes were inconsistent across the MAJIC and RESPONSE/RESPONSE-2 trials and the translation into longer term benefits was unsupported. The PBAC noted that no statistically significant differences in transformation-free survival or overall survival (OS) were observed between treatment arms in MAJIC. However, the PBAC also noted that data from the RESPONSE trials indicated that ruxolitinib provides a greater benefit over BAT in terms of a reduction in splenomegaly, number of phlebotomies necessary for haematocrit (HCT) control, and is associated with a decrease in the number of thrombotic events. The PBAC considered the latter two to be relevant clinical outcomes for PV patients regardless of spleen volume.
	11. On balance, the PBAC considered that the clinical claim of superior comparative effectiveness was not adequately supported, and that clinically meaningful outcomes for the purposes of a PBS restriction and economic model would need to be more clearly defined.
	12. The PBAC considered that the clinical importance of the difference in safety profiles between ruxolitinib and BAT was unclear given the lack of long-term safety data. The PBAC considered the non-inferior safety claim was not adequately supported.
	13. The PBAC considered that the economic model relied on responder health states that do not correlate to clinically relevant outcomes and therefore do not adequately capture the benefits, if any, of treatment. Noting that the model also relies on OS, the PBAC considered this to be inappropriate given that no OS benefit was demonstrated in the MAJIC trial. The PBAC noted that, assuming no difference in OS between treatments, the ICER increases by 88-89%. The PBAC considered there was uncertainty over the entire model structure, assumptions and thus results, and regarded the ESC advice that the economic model does not form a reliable basis for decision making. Further, the PBAC agreed with the ESC that it was not reasonable to assume that the proportion of patients using peginterferon 180mcg to hydroxycarbamide/hydroxyurea (HC) would be 50:50. The pre-PBAC response argued that peginterferon use is expected to be higher than that seen in the RESPONSE trials, and is more likely to reflect the 39% seen in MAJIC. The PBAC considered the range of 16–39% of peginterferon use from the clinical trials to be more reasonable than the 50% assumed by the submission.
	14. The PBAC agreed with DUSC that the certainty around the financial estimates was low, and considered the eligible population presented in the submission to be overestimated, but the overall costs to be underestimated. The PBAC noted that peginterferon has a special pricing arrangement which was not available to the sponsor, and therefore the cost of BAT offset is overestimated. The PBAC also agreed with DUSC that with no link between continuation criteria and outcomes, this would likely lead to long-term use in the eligible population with up to 30-year survival.
	15. The pre-PBAC response requested that the PBAC consider a restriction which allows for treatment with ruxolitinib as long as the benefit-risk ratio remains positive. The sponsor acknowledged that QoL is not correlated with partial response (ELN 2009), and argued that the impact of continuing patients on treatment with ruxolitinib has a marginal impact on the ICER (increasing from $45,000/QALY - $75,000/QALY to $45,000/QALY - $75,000/QALY without continuation criteria). Further, the pre-PBAC response proposed a risk sharing arrangement (RSA) whereby the Commonwealth expenditure is capped based on estimates that incorporate discontinuation criteria (ELN 2009 criteria), taking into account comments from DUSC to remove the less than 10,000 grandfathered patients from the eligible population and a faster rate of uptake in the prevalent population (to reach '''''% before Year 6). The sponsor acknowledged the ESC’s view that removing the continuation criteria was inappropriate given the cost for questionable benefit and potentially long duration of therapy, and stated that it would also be amenable to incorporating improvement in disease specific symptoms as part of the continuation criteria in addition to the proposed RSA. The PBAC considered that the pre-PBAC response did not provide sufficient details on the proposed RSA and that the financial estimates remained uncertain.
	16. The PBAC advised that a resubmission should consider use of the RESPONSE trials as the primary clinical evidence in support of a proposed listing. No OS benefit has been demonstrated with any PV treatment and as such the more clinically meaningful outcomes will include reductions in vascular events and thrombosis. A cost-minimisation analysis should be considered, with the use of peginterferon in the BAT arm reflecting the trial evidence. The PBAC considered that more data on the sequential use of ruxolitinib in both PV and MF settings would be informative, noting the DUSC advice that cost offsets are unlikely. The PBAC advised that continuation criteria in line with modified ELN criteria would be acceptable, incorporating improvement in disease specific symptoms.
	17. The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

1. Context for Decision

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

1. Sponsor’s Comment

Novartis is disappointed with the PBAC outcome given the clinical need for patients with polycythemia vera and will continue to evaluate all options for access to ruxolitinib for this population.