7.10 RUXOLITINIB,
Tablet 5 mg,
Tablet 10 mg,
Tablet 15 mg,
Tablet 20 mg,
Jakavi®,
Novartis Pharmaceuticals Australia Pty Ltd

1. Purpose of submission
	1. The Category 2 resubmission requested Authority Required (STREAMLINED) listing for ruxolitinib for the treatment of adult patients with polycythaemia vera (PV) who are resistant to or intolerant of hydroxycarbamide (hydroxyurea) (HC/HU).
	2. Listing was requested on the basis of a cost-utility analysis versus best available therapy (BAT).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

|  |  |
| --- | --- |
| **Component** | **Description** |
| Population | Adult patients with Polycythemia vera (PV) who are resistant to or intolerant of hydroxycarbamide/hydroxyurea (HC/HU) |
| Intervention | Ruxolitinib 10 mg twice daily; up to 25 mg twice daily |
| Comparator | Best available therapy (BAT)a |
| Outcomes | Response b rate, duration of response, event-free c survival, overall survival and safety |
| Clinical claim | In treatment of PV, ruxolitinib is superior to BAT in terms of comparative effectiveness. Ruxolitinib has a different safety profile to BAT.  |

Source: Table 1.1 Key components of the clinical issue addressed by the resubmission, p13 of the submission.

Abbreviations: mg, milligram.

a BAT includes treatment with HC/HU, peginterferon α-2a or observation.

b Response was defined as HCT <45% without venesection and/or all of the three items: platelet count ≤ 400 x 109/L, WBC < 10 x 109/L, and absence of splenomegaly on imaging

c Event-free is reduction in the risk of patient relevant outcomes such as thrombosis, haemorrhage, and progression to MF or AML.

Blue shading indicates information previously seen by the PBAC.

1. Background

***Registration status***

* 1. Ruxolitinib was Therapeutic Goods Administration (TGA) registered on 14 December 2015 for treatment of adult patients with PV who are resistant to or intolerant of HC/HU.
	2. Ruxolitinib is also registered for:
* the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis (MF), post-PV MF or post-essential thrombocythaemia MF; and
* the treatment of patients aged 12 years and older with chronic graft versus host disease (GVHD) who have inadequate response to corticosteroids and treatment of patients aged 12 years and older with acute GVHD who have inadequate response to corticosteroids.

***Previous PBAC consideration***

* 1. Table 2 summarises the key matters of concern highlighted at the November 2019 Pharmaceutical Benefits Advisory Committee (PBAC) meeting.

**Table 2: Summary of key matters of concern**

| **Component** | **Matter of concern** | **How the resubmission addresses it** |
| --- | --- | --- |
| Proposed listing | ELN criteria for response in PV (updated 2013) included more clinically relevant response definitions (Para 7.2, Nov 2019 Public Summary Document (PSD)). | Addressed. Resubmission response criteria have incorporated modified response criteria (per Para 7.2, Nov 2019 PSD) now referring to 'absence of palpable splenomegaly'; WBC counts were excluded. |
| Clinical place in therapy | The clinical place of ruxolitinib should be for patients who have failed treatment with other available therapies and/or for those with extreme pruritus or symptoms of splenomegaly (Para 7.3, Nov 2019 PSD). | Not addressed – the resubmission argued advisory board feedback recommended against specifying patients with extreme pruritus or symptoms of splenomegaly. The resubmission did not assume patients with HC/HU resistance or intolerance would have failed peginterferon a-2a.  |
| Clinical effectiveness | MAJIC did not support a benefit for clinically relevant outcomes or OS (Para 7.1, Nov 2019 PSD).The association between response and relevant clinical outcomes (thrombosis, haemorrhage, transformation to MF or AML, and OS) was not supported by the available evidence (Para 7.6 Nov 2019 PSD).RESPONSE trials indicated that venesections and thrombotic events were relevant clinical outcomes for PV patients (Para 7.10 Nov 2019 PSD).The claim of superior comparative effectiveness not adequately supported (Para 7.11 Nov 2019 PSD).Results for DoR from MAJIC were unreliable due limited follow-up beyond 2 years (Para 7.7, Nov 2019 PSD).  | Partially addressed. The resubmission presented updated results for MAJIC, RESPONSE and RESPONSE-2 trials. Median follow-up was partially reported:MAJIC: 4.8 y (range n.r.) [4.9 y (ruxolitinib arm) (range n.r.); 4.8 y (BAT arm) (range n.r.)]RESPONSE: median n.r. (range n.r)RESPONSE-2: 67 mo (IQR: 65-70 mo)However, updated data for EFS, PFS, OS and haemorrhagic events showed no statistically significant differences across treatment arms. EFS was a post hoc outcome for MAJIC newly presented in this resubmission. |
| Clinical effectiveness | The pivotal trial (MAJIC) was considered unreliable given high risk of bias […], open label design, limited median follow-up of 2.6 y, DoR secondary outcome not clearly defined, limited safety data, and no magnitude of effect on patient-reported symptoms (Para 7.5, Nov 2019 PSD). | Partially addressed. Resubmission presented updated results for MAJIC trial with longer follow up, and a publication and CSR, minimising the risk of selective reporting bias. Previous concerns regarding the open label design and definition of duration of response remain. |
| Clinical effectiveness | The clinical importance of the difference in safety profiles (ruxolitinib vs BAT) was unclear given the lack of long-term safety data. The non-inferior safety claim was not adequately supported (Para 7.12, Nov 2019 PSD). | Addressed. Updated safety data was presented with up to 5 years follow up.The resubmission revised their safety claim from non-inferior to “different safety profile”.  |
| Economic model | The model relied on responder health states that did not correlate to clinically relevant outcomes and did not capture the benefits of treatment. Model reliance on OS was inappropriate given MAJIC demonstrated no OS benefit (Para 7.13, Nov 2019 PSD). | Partially addressed. The economic model has been updated to a four state Markov model. Health states include progression-free disease on ruxolitinib, progression-free on BAT, a progressed state (includes MF, AML and MDS), and death. These states reflect clinically relevant progression of PV. The ESC considered this issue was partially addressed as while the PFS health states were now more objective, the trial did not demonstrate a significant difference in this outcome for patients treated with ruxolitinib. In addition, the ESC noted the updated results continued to demonstrate no OS benefit and considered the model reliance on this outcome remained inappropriate.  |
| Economic model | A cost minimisation analysis should be considered, with the use of peginterferon α-2a in the BAT arm reflecting the trial evidence given that the clinical evidence suggests no OS benefit and as such the more clinically meaningful outcomes will include reductions in vascular events and thrombosis (Para 7.16, Nov 2019 PSD).  | Partially addressed with the updated clinical data and model structure. However, the model continued to assume an OS treatment benefit which is not supported by longer term clinical evidence. Given the potential change of in the use of peginterferon α-2a use in clinical practice, a cost-minimisation analysis could be considered.  |
| Financial impact | Low certainty around the financial estimates in that the eligible population was overestimated, but the overall costs were underestimated (Para 7.14, Nov 2019 PSD). | Not addressed. The resubmission changed the financial estimates modelling approach to model the incident and prevalent patients together and included assumptions which could not be verified; thus the patient numbers and financial estimates were considered unreliable and uncertain.  |
| Financial impact | DUSC considered the assumptions used to derive eligible patient numbers (prevalence rate, incidence rate, proportion treated with HC/HU and proportion intolerant or resistant to HC/HU) 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 (Para 6.82, Nov 2019 PSD). | Partially addressed. Both the incidence and prevalence rates have been updated using AIHW cancer data; proportion intolerant or resistant to HC/HU has been revised from 24% to 22.5%, grandfathered patients (n=|| ||1) included into the prevalent population, and uptake rates adjusted. Despite the revisions made in the resubmission, it was likely that the number of eligible patients is overestimated. |
| Financial impact | 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) (Para 6.82, Nov 2019 PSD). | Not addressed. The financial estimates continued to rely on outputs from the economic model which in turn relied on a number of assumptions not adequately supported by clinical evidence which increases the risk of uncertainty. |
| Financial impact | No link between continuation criteria and outcomes, would likely lead to long-term use in a population with up to 30-year survival (Para 7.14, Nov 2019 PSD). | Not addressed. Long term use remains likely. |

Source: Compiled during the evaluation.
AIHW, Australian Institute of Health and Welfare; AML, acute myeloid leukaemia; BAT, best available therapy; CR, complete response; CSR, clinical study report; CUA, cost utility analysis; DoR, duration of response; DUSC, Drug Utilisation Sub Committee; EFS, event-free survival; ELN, European LeukemiaNet; HC/HU, hydroxycarbamide/hydroxyurea; MBS, Medicare Benefits Schedule; MDS, myelodysplastic syndrome; MF, myelofibrosis; mo, month; n.r, not reported; OR, odds ratio; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; PFs, progression-free survival; PR, partial response; PSD, public summary document; PV, polycythaemia vera; WBC, white blood cells; yr, year.

*The redacted values correspond to the following ranges:*

*1 < 500*

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

1. 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** |
| 5 mg, 56 tablets10 mg, 56 tablets15 mg, 56 tablets20 mg, 56 tablets | 1111 | 56565656 | 5555 | Published: $4,912.60Effective:$|||| | Jakavi®Novartis Pharmaceuticals Australia Pty Ltd |  |

|  |  |
| --- | --- |
| **Category / Program:** | GENERAL - General Schedule (Code GE) |
| **Prescriber type:** | [ ] Dental [x] Medical Practitioners [ ] Nurse practitioners [ ] Optometrists [ ] Midwives |
| **Episodicity:** | Chronic |
| **Condition:** | Polycythemia vera |
| **PBS Indication:** | Chronic polycythemia vera |
| **Treatment phase:**  | Initial treatment |
| **Restriction Level / Method:** | [ ] Restricted benefit[ ] Authority Required - In Writing[ ] Authority Required - Telephone[ ] Authority Required - Emergency[ ] Authority Required - Electronic[x] Streamlined |
| **Population criteria:** | Patient must be 18 years of age or over |
| **Clinical criteria:** | Patient must be resistant to hydroxycarbamide (hydroxyurea); orPatient must have an intolerance to hydroxycarbamide (hydroxyurea) of a severity necessitating permanent treatment withdrawal; orPatient must have a contraindication to hydroxycarbamide (hydroxyurea) as defined in the TGA-approved Product Information; ANDPatient must not have previously received PBS-subsidised treatment with this drug for this condition. |
| **Prescriber Instructions:**  | The authority application must be made in writing and must include:(1) A completed authority prescription form; and (2) A completed Polycythemia Vera Authority Application, which includes confirmation that the patient is resistant to, or intolerant of, hydroxycarbamide (hydroxyurea). Hydroxycarbamide (hydroxyurea) resistance is defined as a minimum of 12 consecutive weeks treatment at a dose of at least 1.5 grams/day or at the maximum tolerated that still results in one of the following: (i) the need to reduce haematocrit levels to below 45% through phlebotomy; or(ii) a platelet count greater than 400 x 109/L and a white blood cell count greater than 10 x 109/L If intolerance to hydroxycarbamide (hydroxyurea) treatment develops during the relevant period of use which is of a severity necessitating permanent treatment withdrawal, the application must provide details of the nature and severity of this intolerance. |
| **Note:**  | NoteSpecial Pricing Arrangements apply.NoteNo increase in the maximum quantity or number of units may be authorised.NoteNo increase in the maximum number of repeats may be authorised. NoteAny queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.auApplications for authority to prescribe should be forwarded to: Department of Human ServicesComplex Drugs Reply Paid 9826 HOBART TAS 7001 |

|  |  |
| --- | --- |
| **Category / Program:** | GENERAL - General Schedule (Code GE) |
| **Prescriber type:** | [ ] Dental [x] Medical Practitioners [ ] Nurse practitioners [ ] Optometrists [ ] Midwives |
| **Episodicity:** | Chronic |
| **Condition:** | Polycythemia vera |
| **PBS Indication:** | Chronic polycythemia vera |
| **Treatment phase:**  | Continuing treatment |
| **Restriction Level / Method:** | [ ] Restricted benefit[ ] Authority Required - In Writing[ ] Authority Required - Telephone[ ] Authority Required - Emergency[ ] Authority Required - Electronic[x] Streamlined |
| **Population criteria:** | Patient must be 18 years of age or over |
| **Clinical criteria:** | Patient must have previously received PBS-subsidised treatment with this drug for this condition. AND Patient must have demonstrated a response to treatment within 12 months defined as:* Maintained a haematocrit level of less than 45% without relying on phlebotomy and which was measured at least 12 weeks after the most recent phlebotomy procedure (if performed) to reduce red blood cell levels; or
* Patient must have demonstrated, or maintained a normal platelet count of less than or equal to 400 x 109/L; or
* Patient must have an absence of palpable splenomegaly

Patient must maintain a response to continue receiving treatment with ruxolitinib. |
| **Prescriber Instructions:**  | The authority application must be made in writing and mustinclude:(1) A completed authority prescription form; and (2) A completed Polycythemia vera Authority Application, which includes the relevant pathology reports |
| ***Administrative Advice:*** | NoteSpecial Pricing Arrangements apply.NoteNo increase in the maximum quantity or number of units may be authorised.NoteNo increase in the maximum number of repeats may be authorised.NoteAny queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.auApplications for authority to prescribe should be forwarded to: Department of Human ServicesComplex Drugs Reply Paid 9826 HOBART TAS 7001 [concept ID 7753; Complex Authority Required flag] |

* 1. The resubmission requested initial and continuing treatment as Authority Required (STREAMLINED) listings. The requested authority level is different to that of the ruxolitinib listing for MF which is Authority Required (Written) for initial treatment and an Authority Required (Telephone/Electronic) listing for continuing therapy.
	2. A Special Pricing Arrangement (SPA) was proposed (dispensed price for maximum quantity [DPMQ] $4,912.60 published price; $| | effective price). The same pricing was requested across all strengths. The proposed effective price represents a | |% reduction of the price proposed in the previous submission (which requested a DMPQ $5,152.12 published price, $| | effective). The proposed effective ex-manufacturer price (EMP) for PV is $| | across all strengths. The EMPs for the current MF listings are $| | for the 5 mg strength and $| | for the 10 mg, 15 mg and 20 mg strengths. The EMPs for the current acute and chronic GVHD listings are $| | and $| | respectively for the 5 mg strength and $| | and $| | respectively for the 10 mg strength. The pre-PBAC response offered a reduced EMP of $| | for PV across all strengths.
	3. Most patients receiving ruxolitinib would be expected to require a moderate rate of month-to-month dose adjustments over the long term. Hence, patients would likely need more than one tablet strength dispensed (most likely a second script for the 5 mg strength) in order to manage these adjustments. The most common reasons for dose adjustment are anaemia, thrombocytopenia, and pruritus (as observed in the RESPONSE trial).
	4. The resubmission proposed a continuation at 12 months (instead of the previously used 6 months) based on the MAJIC trial, where patients who achieved a complete response (CR) or partial response (PR)[[1]](#footnote-2) with ruxolitinib within the first 12 months continued the treatment as long as at least a PR was maintained. Evidence from the MAJIC trial showed that 90 patients (97%) in the ruxolitinib arm achieved an overall response by the 12-month analysis (Table 5). The resubmission also argued that the full ELN (European LeukemiaNet) response criteria were too restrictive for clinical practice, as they were designed for clinical trials. Therefore, the proposed response criteria include meeting at least one of the following: haematocrit (HCT) < 45% without venesection for 3 months; platelet count ≤ 400 x 10^9/L; or absence of palpable splenomegaly.
	5. The proposed response criteria for treatment continuation include the wording ‘absence of palpable splenomegaly’ which was proposed as an alternative for ‘normal spleen size on imaging’ given that imaging for splenomegaly is not routinely performed in clinical practice. White blood cell (WBC) counts were also excluded from the response criteria. These changes are consistent with feedback from PBAC on the previous submission (paragraph 7.2, ruxolitinib, public summary document (PSD), November 2019 PBAC meeting).
	6. Based on the proposed continuation criteria, PV patients would need up to 12 months treatment under the initial treatment restriction. As it is currently worded, a patient would only be able to access a single script offering six months treatment in the initial treatment phase (given the criterion “Patient must not have previously received PBS-subsidised treatment with this drug for this condition”).
	7. No grandfathering restriction was requested (compared with the previous submission which requested a grandfather restriction for the first year of listing). The submission anticipated that there would be approximately <500 adult PV patients who would be expected to receive ruxolitinib prior to listing on the PBS.

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

1. Population and disease
	1. PV is myeloproliferative neoplasm (MPN) characterised by proliferation of one or more of the lineages in the bone marrow, mainly the erythroid lineage (causing erythrocytosis), but also that of granulocytes (leukocytosis) and megakaryocytes (thrombocytosis). Cell proliferation is accompanied by overproduction of inflammatory cytokines which results in a chronic inflammatory state. Splenomegaly can result from sequestration of excess cells in the spleen.
	2. The main features of PV – erythrocytosis and thrombosis risk – are managed with regular venesection and low dose aspirin. A subset of PV patients defined as high risk[[2]](#footnote-3) will require cytoreductive therapy to manage their symptoms. PV in high risk patients is accompanied by debilitating symptoms and increased risk of thrombosis and cardiovascular events. Other key features are pruritus and constitutional symptoms (pain, migraine and fatigue). PV patients also experience anaemia and haemorrhages.
	3. PV may eventually terminate in bone marrow failure due to MF, or transformation to acute myeloid leukaemia (AML). The twenty-year rate of transformation to MF is approximately 16% and to AML is 4%. For a haematological malignancy, PV is a relatively long-lived disease with a median survival in low-risk patients reported as 27.8 years. However, survival in high-risk patients has been reported as median 10.9 years (Tefferi et al., 2013).
	4. The most commonly used cytoreductive agents are HC/HU and peginterferon α-2a. About 10–15% of patients with PV who are treated with HC/HU develop an intolerance to the drug. The resubmission did not provide a figure for the proportion of patients who are likely to have failed peginterferon α-2a. Patients who have failed both these agents have a high symptom burden but limited treatment options.
	5. For the previous submission, PBAC considered that the place in therapy for ruxolitinib should be for patients who have failed treatment with other available therapies (namely HC/HU or peginterferon α-2a) and/or for those with extreme pruritus or symptoms of splenomegaly (para 7.3, ruxolitinib, PSD, November 2019 PBAC meeting). Current National Comprehensive Cancer Network (NCCN) recommendations (the most commonly used guidelines in Australia for treatment of MPNs) describe both HC/HU and peginterferon α-2a as equally preferred regimens without distinguishing between them (whereas ruxolitinib is considered “useful in certain circumstances” only).
	6. Ruxolitinib is an oral protein kinase inhibitor of Janus Associated Kinases (JAK), JAK1 and JAK2. In normal bone marrow, JAK signalling mediates cytokines and growth factors that are important for haematopoiesis and immune function. Ruxolitinib binds to the kinase domain of JAK1 and JAK2, thus inhibiting signalling and in turn myeloid cell proliferation (Harrison et al., 2012).

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

1. Comparator
	1. The resubmission nominated BAT as the comparator. This was accepted by PBAC for the previous submission and remained unchanged.
	2. For the previous submission, PBAC noted that peginterferon α-2a use as a proportion of BAT was likely to be considerably lower than HC/HU, i.e. less than 50% (para 7.4, ruxolitinib, PSD, November 2019 PBAC meeting). However, changes in peginterferon α-2a use have occurred since 2019.
	3. Based on engagement with consultant haematologists during the evaluation, it was understood that peginterferon α-2a use may have increased, driven by two factors:
* The change in PBS listing of peginterferon α-2a to an unrestricted benefit in August 2018 making it more accessible for this indication
* Publication of clinical studies suggesting that peginterferon α-2a may confer a survival benefit and reduction in risk of transformation to MF (Abu-Zeinah et al, 2021; Kiladjian et al., 2022; Gisslinger et al., 2023)[[3]](#footnote-4).
	1. The resubmission noted the sponsor’s PV Advisory Board (comprising three Australian consultant haematologists) advised that peginterferon α-2a use in clinical practice is lower than HC/HU, at approximately 20% – 30% of patients diagnosed with PV (who require cytoreductive therapy). The resubmission’s economic model used an assumption of 47% peginterferon α-2a as a proportion of BAT based on treatment distribution in the BAT arm of the MAJIC trial.

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

1. Consideration of the evidence

Sponsor hearing

* 1. The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease and the benefits of ruxolitinib shown in the trial. The clinician noted that a higher proportion of patients treated with ruxolitinib in the MAJIC trial achieved a molecular response (defined as a >50% reduction in JAK2V61F variant allele fraction) and stated that risk reduction is likely greater in those who achieve a molecular response.[[4]](#footnote-5) The clinician stated that peginterferon α-2a was more likely to be used than HC/HU in younger patients and raised the possibility of ruxolitinib being used second-line for such patients.

Consumer comments

* 1. The PBAC noted and welcomed the input from individuals (11), health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The PBAC noted the comments from individuals who would like to access the medicine to treat their own health condition described the impact of PV on their quality of life (QoL) and the contribution of side-effects from currently available treatments on reducing QoL. The comments also noted the time and cost burden on patients needing to travel from rural areas for venesections and to see specialists. The comments from individuals noted potential supply concerns with peginterferon α-2a and highlighted the need for alternative treatment options. The input from individuals with the condition and their families described the advantages of ruxolitinib being in tablet form as opposed to peginterferon α-2a which is an injection that needs to be kept cold. Input from a health care professional who had experience in treating patients with ruxolitinib for PV described benefits in terms of reduced complication rates (such as clots) and improvements in symptom burden.
	2. Input from the Leukaemia Foundation stated that current BAT is largely focused on prevention of thrombosis with more options needed that treat the underlying cause of the disease. The Leukaemia Foundation input noted that ruxolitinib has shown efficacy in reducing spleen volume, controlling haematocrit and improving symptoms of disease by directly targeting JAK1 and JAK2 signalling pathways.
	3. Input from MPN Alliance Australia described the impact of PV on patient’s QoL, including the fear that their disease will progress to MF or AML. The input described patients experiences with current treatment options and highlighted supply concerns with peginterferon α-2a. The input noted that ruxolitinib would provide an important treatment option for the relatively small percentage of PV patients who can no longer have first line cytoreduction therapy due to intolerance or failing efficacy.
	4. Input from the Australasian Leukaemia & Lymphoma Group (ALLG) described how patients with PV are at higher risk of cardiovascular-related complications, disease transformation and early mortality. The input described how the burden of frequent hospital visits, along with symptoms and complications significantly impact on patients QoL. The input outlined the issues associated with the treatment options currently available and highlighted the need for alternative therapies. The input described ruxolitinib as a suitable second-line treatment and acknowledged that use would likely be restricted to patients who are resistant or intolerant to HC/HU. The ALLG advocated for a pragmatic continuation criteria[[5]](#footnote-6) to ensure patients can continue to receive ruxolitinib whilst clinical benefit persists. The ALLG argued that sequential use of ruxolitinib in both the PV and MF settings should be permitted.

Clinical trials

* 1. The resubmission was based on one head-to-head randomised trial comparing ruxolitinib to BAT: MAJIC (n=190), and two supplementary randomised trials comparing ruxolitinib to BAT: RESPONSE (n=222) and RESPONSE-2 (n=149).
	2. The resubmission maintained the use of MAJIC as the primary evidence and presented the RESPONSE trials as supporting evidence to demonstrate superior response, DoR, QoL and to reinforce the safety claim. These trials were reviewed by the PBAC at the November 2019 meeting. At the November 2019 meeting the MAJIC trial data was only available as conference abstracts from poster and PowerPoint presentations (para 7.5, ruxolitinib, PSD, November 2019 PBAC meeting). Since the previous PBAC consideration a full peer-review publication from Harrison et al., 2023 and the clinical study report (CSR) from the MAJIC trial were available, allowing for a more thorough assessment. The resubmission presented updated data from all three trials with a longer follow up period of 5 years each (compared to 2.6 years for MAJIC, 32 Weeks for RESPONSE and 28 weeks for RESPONSE-2 trials presented in the previous submission).
	3. Details of the trials presented in the resubmission are provided in Table 3.

Table 3: **Trials and associated reports presented in the resubmission**

| Trial ID | Protocol title/ Publication title | Publication citation |
| --- | --- | --- |
| MAJIC | A Randomised study of best available therapy versus JAK Inhibition in patients with high risk Polycythaemia Vera or Essential Thrombocythaemia who are resistant or intolerant to HydroxyCarbamide. University of Birmingham.  | CSR; 28 March 2023 |
|  | Harrison et al. Ruxolitinib Versus Best Available Therapy for Polycythemia Vera Intolerant or Resistant to Hydroxycarbamide in a Randomized Trial. | Journal of Clinical Oncology, 2023; 41(19), 3534‐3544. |
|  | 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 |
|  | 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) - Protocol | 16 February 2016 |
| RESPONSE | Kiladjian, et al. Long-term efficacy and safety of ruxolitinib versus best available therapy in polycythaemia vera (RESPONSE): 5-year follow up of a phase 3 study. | The Lancet Haematology, 2020; 7(3), e226‐e237 |
|  | 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) – 256 week CSR | 23 August 2018 |
|  | 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(2): 279‐284 |
|  | 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) - Protocol | 24 March 2016 |
|  | Passamonti et al. Ruxolitinib versus best available therapy in inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): 5-year follow up of a randomised, phase 3b study. | The Lancet Haematology, 2022; 9(7), e480‐e492. |
|  | 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) – 260 week CSR | 7 April 2020 |
| RESPONSE-2 | 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 |
|  | Griesshammer et al. Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly: 80-week follow-up from the RESPONSE-2 trial. | Annals of Hematology 2018; 97(9): 1591-1600 |

Source: Table 2.4, pp59-60 of the resubmission.

Abbreviations: CSR, clinical study report; JAK2, Janus associated kinase; PV, polycythaemia vera

Blue shading indicates information previously seen by the PBAC.

* 1. The resubmission justified the selection of MAJIC as the pivotal study stating that it provides up to 5 years of head-to-head evidence of comparative efficacy with limited crossover while the majority of patients randomised to BAT had crossed over to ruxolitinib from Week 32 in RESPONSE and from Week 28 in RESPONSE-2. The resubmission stated that the benefit of ruxolitinib compared with BAT was not captured beyond the time-point of crossover in RESPONSE and RESPONSE-2 trials, thereby introducing a high risk of bias and confounding the comparability of the ruxolitinib vs BAT. All patients crossed over from BAT to ruxolitinib or discontinued by Week 80 in these trials. The resubmission presented the results of primary outcomes for both arms and only presented long term results (after Week 80) for the ruxolitinib arm.
	2. A recent publication of a systematic review and meta-analysis comparing ruxolitinib and BAT for patients with PV and patients with PV resistant or intolerant to HC/HU was identified during the evaluation (Roca Mora et al., 2024).[[6]](#footnote-7) The systematic review and meta-analysis considered data across six studies including the MAJIC, RESPONSE, and RESPONSE-2 trials. A subgroup analysis carried out for patients intolerant or resistant to HC/HU is presented in paragraphs 6.40 and 6.46.
	3. The key features of the direct randomised trials are summarised in Table 4.

**Table 4: 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 years | High a | Resistant or intolerant to HC/HU, ‘high risk’ PV b | CRc at 12 months, CR+PRd at 12 months and 5 years, DoR, thromboembolic and haemorrhagic event rates, EFS, TEFS, HEFS, PFS, OS, venesections, QoL, AEs | DoR, QoL, PFS, OS, venesections used to inform transitions.  |
| RESPONSE | 222 | R, OL256 weeks  | High a | Resistant or intolerant to HC/HU with splenomegaly | Response (HCT <45% with no more than one venesection and reduction in spleen size ≥ 35% at 32 weeks and 256 weeks, DoR, thromboembolic and haemorrhagic event rates, OS, QoL, venesections, AEs | QoL used to inform utility in SA. Thromboembolic events and AEs used. |
| RESPONSE-2 | 149 | R, OL260 weeks | High a | Resistant or intolerant to HC/HU with no splenomegaly | Response (HCT <45% with no more than one venesection) at 28 weeks and 260 weeks, DoR, thromboembolic and haemorrhagic event rates, OS, QoL, venesections, AEs | QoL used to inform utility. Thromboembolic and haemorrhagic events, and AEs used. |

Source: Produced during the evaluation

Abbreviations: AEs, adverse events; BAT, Best Available Therapy; CR, complete response; DoR, duration of response; EFS, event-free survival; HCT, haematocrit control; HC/HU, hydroxycarbamide/hydroxyurea; HEFS, haemorrhagic event-free survival OL, open label; PFS, progression-free survival; PR, partial response; PV, polycythemia vera; OS, overall survival, QoL, quality of life; R, randomised; SA, sensitivity analysis; TEFS, thromboembolic event-free survival.

a High risk as open label and high attrition in long term results.

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

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

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

Blue shading indicates information previously seen by the PBAC.

* 1. The resubmission acknowledged that MAJIC was an open-label study and argued that as the clinical efficacy and safety endpoints were based on objective measurements the risk of bias was minimised. Despite the resubmission presenting full-peer reviewed evidence for the MAJIC trial that provided additional data and transparency and minimised the risk of selective reporting bias, the high risk of attrition bias due to discontinuation remained (32.6% in ruxolitinib and 24.2% in BAT) and there were some concerns of risk of detection bias due to the lack of blinding of outcome assessors (participants and investigators). As such, the evaluation considered the trial had an overall high risk of bias and considered that previous concerns raised by PBAC regarding the open label design and the high risk of bias of the MAJIC trial remained.
	2. The resubmission presented updated evidence for MAJIC, a publication from Harrison et al., 2023 and the CSR, which included a longer median follow-up of 4.8 years (data cut at April 2022) and 4.9 years (data cut at March 2023), respectively. The Harrison et al., 2023 paper also included QoL data. The resubmission included both sources to support the clinical effectiveness and safety claim. Given that both data sources were of the same trial and the analyses from the CSR were from a later data cut, the results from the CSR were the focus of the evaluation and data from the Harrison et al., 2023 publication was used to corroborate and/or supplement the results where needed.
	3. In November 2019, both RESPONSE and RESPONSE-2 trials, 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 the BAT arm were allowed to cross over to ruxolitinib and the trials did not have the same risk of attrition or reporting bias as MAJIC (para 6.11, ruxolitinib, PSD, November 2019 PBAC meeting). While the risk of bias is low for outcomes assessed before patients crossed over (at Week 32 in RESPONSE and Week 28 in RESPONSE-2), the overall risk of bias of these trials was potentially high for long term outcomes due to the risk of detection bias from unblinding after the crossover point. In addition, the evaluation considered there was a high risk of attrition bias due to discontinuation by 5 years of follow-up in RESPONSE (34.7% in ruxolitinib and 100% in BAT) and RESPONSE-2 (20.3% in ruxolitinib and 100% in BAT). Given that long term outcomes are presented and assessed in this resubmission, the evaluation considered the overall risk of bias to be high for these trials.
	4. In terms of baseline patient demographics for all included trials, there were minimal changes since the previous submission, except for the MAJIC trial which analysed 87 patients in the BAT arm (decreased from 89 patients in previous submission) due to two patients not receiving assigned treatment (classified as BAT therapies) as per protocol. Therefore, all analyses (including outcomes) of the BAT arm have changed slightly in this trial.

Comparative effectiveness

**MAJIC results**

* 1. The proportion of patients achieving CR or PR response by 12 months and the best response across five years in MAJIC are presented in Table 5.

**Table 5: Proportion of patients achieving response in MAJIC**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MAJIC** | **Ruxolitinib (N = 93)** | **BAT (N = 87)** | **ORa (95% CI)** | **RRa (95% CI)** | **RDa (95% CI)** |
| **New evidence presented in this resubmission** |
| **Response across 5 Years**  |
| Complete response, n (%)  | 63 (68) | 51 (59) | 1.48 (0.81, 2.73) | 1.16 (0.92, 1.45) | 0.09 (-0.05, 0.23) |
| Overall response b, n (%)  | 90 (97) | 85 (98) | 0.71 (0.12, 4.33) | 0.99 (0.94, 1.04) | -0.01 (-0.06, 0.04) |
| No response  | 3 (3) | 2 (2) | 1.42 (0.23, 8.69) | 1.40 (0.24, 8.20) | 0.01 (-0.04, 0.06) |
| **Response within 12 months** |
| Complete response, n (%)  | 40 (43) | 23 (26) | **2.10 (1.12, 3.94)** | **1.63 (1.07, 2.48)** | **0.17 (0.03, 0.30)** |
| Partial response, n (%)  | 50 (54) | 58 (67) | 0.58 (0.32, 1.06) | 0.81 (0.63, 1.03) | -0.13 (-0.27, 0.01) |
| Overall response b, n (%)  | 90 (97) | 81 (93) | 2.22 (0.54, 9.18) | 1.04 (0.97, 1.11) | 0.04 (-0.03, 0.10) |
| No response  | 3 (3) | 6 (7) | 0.45 (0.11, 1.86) | 0.47 (0.12, 1.81) | -0.04 (-0.10, 0.03) |
| **Evidence from previous submission - Response within 12 months** |
| **MAJIC** | **Ruxolitinib (N = 93)** | **BAT (N = 89)** | **ORa (95% CI)** | **RRa (95% CI)** | **RDa (95% CI)** |
| Complete response, 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 response, 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)** |
| Overall response b, 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) |

Source: Table 2.16, p89 of resubmission (based on MAJIC CSR), Table 2.14, p88 of resubmission (based on Harrison et al., 2023) and Table 2.3-15, p92 of previous submission (based on Harrison et al., 2018a poster)

Abbreviations: BAT, best available therapy; CI, confidence interval; OR, odds ratio; RD, risk difference; RR, risk ratio

a Calculated for the resubmission using the Mantel-Haenszel statistical method with a fixed effect model. Previous submission calculation used RevMan v5.3.

b Overall response comprises complete and partial response

Note: Results in **bold** indicate statistically significant difference (p<0.05)

Blue shading indicates information previously seen by the PBAC.

* 1. At 12 months, there was a statistically significantly higher proportion of patients treated with ruxolitinib who achieved CR (43%), compared to patients treated with BAT (26%) (OR 2.10; 95% CI: 1.12, 3.94). However, there was no statistically significant differences in the overall response (CR + PR) between patients treated with ruxolitinib (97%) and BAT (93%) (OR 2.22; 95% CI: 0.54, 9.18). There were small differences in the reported outcomes at 12 months between this and the previous submission (based on a small change to the number analysed in the BAT arm).
	2. Across the first 5 years, there were no statistically significant differences in CR and overall response between the two treatment arms. While overall response remained similar across the 12-month and 5-year period, the proportion of patients achieving CR improved in both groups between 12 months (43% in ruxolitinib and 26% in BAT) and 5 years (68% in ruxolitinib and 59% in BAT).
	3. The Kaplan-Meier (KM) curve of DoR in MAJIC are presented in Figure 1. A KM curve for DoR in MAJIC was presented in the November 2019 submission but no hazard ratios were presented.

**Figure 1: Duration of response in MAJIC**



Source: Figure 2.6, p91 of resubmission (based on MAJIC CSR)

Abbreviations: BAT, best available therapy; CI, confidence interval; CSR, clinical study report; HR, hazard ratio; PV, polycythaemia vera.

* 1. Patients treated with ruxolitinib in MAJIC achieved more durable CR or PR compared to those who had received BAT (Hazard Ratio [HR] = 0.14, 95% CI: 0.07, 0.30) at 5 years of follow-up. With longer follow up (5 years), the proportion of patients who maintained either CR or PR remained at 88% in the ruxolitinib arm and 41% in the BAT arm. However, data at year 5 was informed by a small number of patients (i.e. up to 1 and 8 in the BAT and ruxolitinib arms respectively). The PBAC noted that the duration of response at 3 years was informed by a larger number of patients (29 and 62 in the BAT and ruxolitinib arms respectively. At 3 years, the PBAC noted that the proportion of patients who maintained either CR or PR was 91% in the ruxolitinib arm and 55% in the BAT arm.
	2. The KM curves of thromboembolic event-free survival (TEFS) and haemorrhagic event-free survival (HEFS) presented in the resubmission are shown in Figure 2. KM curves of TEFS and HEFS were not presented in the previous submission.

**Figure 2: Thromboembolic event-free survival (left) and haemorrhagic event-free survival (right) in MAJIC**

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Source: Figure 2.15 and 2.16, p97, 98 of resubmission (based on MAJIC CSR).

Abbreviations: BAT, best available therapy; CI, confidence interval; CSR, clinical study report; HR, hazard ratio; PV, polycythaemia vera.

* 1. An improvement in TEFS was observed in patients treated with ruxolitinib compared with patients treated with BAT (HR 0.57, 95% CI: 0.32, 0.99) at 5-year of follow up (based on MAJIC CSR), noting the wide 95% CIs approached the null. This was not observed in HEFS (HR 0.86, 95% CI: 0.49, 1.51), noting this trial was not powered to detect any differences in either of these outcomes.
	2. The thromboembolic and haemorrhagic events reported in MAJIC, RESPONSE and RESPONSE-2 in previous submission and at 5-year of follow up are summarised in Table 6.

**Table 6: Incidence of thrombotic and haemorrhagic events in the included trials**

|  |  |  |  |
| --- | --- | --- | --- |
| **Trial** | **Ruxolitinib n/N(%)** | **BAT n/N(%)** | **HR (95% CI); P-value**  |
| **New evidence presented at 5-year follow up in all trials** |
| **Thromboembolic events (any grade)** |
| MAJIC a  | 10/93 (10.8) | 17/87 (19.5) | 0.57 (0.32, 0.99); p=0.05  |
| RESPONSE b | 5 (1.2) | 6 (8.2) | NR |
| RESPONSE-2 c | 5 (1.5) | 2 (3.7) | NR |
| **Haemorrhagic events (any grade)** |
| MAJIC d | 12/93 (12.9) | 16/87 (18.4) | 0.86 (0.49, 1.51); p=0.60  |
| RESPONSE e | NR (5.6) | NR | NR |
| RESPONSE-2 c | 22 (6.6) | 8 (15.0) | NR |
| **Evidence presented in previous submission at 2.6 years, 32 weeks, 28 weeks of follow up in MAJIC, RESPONSE and RESPONSE-2 trials, respectively** |
| **Trial** | **Ruxolitinib n/N(%)** | **BAT n/N(%)** | **OR (95% CI)** | **RR (95% CI)** | **RD (95% CI)** |
| **Thrombotic events (any grade)** |
| MAJIC | 10 f/93 (10.8) | 10 f/89 (11.2) | 0.95 (0.36, 2.70) | 0.96 (0.43, 2.14) | -0.01 (-0.10, 0.09) |
| RESPONSE | 1/110 (0.9) | 6/111 (5.4) | 0.16 (0.003, 1.37) | 0.17 (0.03, 1.04) | -0.04 (-0.09, 0.00) |
| RESPONSE-2 | 1/74 (1.4) | 3/75 (4.0) | 0.33 (0.03, 3.24) | 0.34 (0.05, 2.30) | -0.03 (-0.08, 0.03) |
| **Haemorrhagic events (any grade)** |
| MAJIC | 9/93 (9.7) | 8 g/93 (8.6) | 1.14 (0.37, 3.57) | 1.13 (0.47, 2.72) | 0.01 (-0.08, 0.10) |
| RESPONSE | 22/110 (20.0) | 17/111 (15.3) | 1.38 (0.65, 2.97) | 1.31 (0.74, 2.31) | 0.05 (-0.06, 0.15) |
| RESPONSE-2 | 10/74 (13.5) | 9/75 (12.0) | 1.15 (0.44,3.00) | 1.13 (0.50, 2.56) | 0.02 (-0.09, 0.12) |

Source: Table 43, p52 of MAJIC CSR, p94 of RESPONSE CSR, p11, p117 of RESPONSE-2 CSR, Kiladjian et al., 2020, Harrison et al., 2018, Table 2.3-39, p154, Table 2.3-40, p155, Tables 2.3-49 and 2.3-50, p165 of previous submission.

Abbreviations: BAT, best available therapy; CI, confidence interval; HR, hazard ratio; NR, not reported.

a Based on MAJIC CSR. 14 events occurred in 10 patients with ruxolitinib and 22 events occurred in 17 patients with BAT.

b Reported by Week 256 in Kiladjuan et al., 2020. Data corresponds to exposure-adjusted rates per 100 patient-year

c Reported by Week 260 in Passamonti et al., 2022. Data correspond to exposure-adjusted rate per 100 person-years. Haemorrhagic events was reported as bleeding (haemorrhages).

d Based on MAJIC CSR. 15 events occurred in 12 patients with ruxolitinib and 18 events occurred in 16 patients with BAT.

e Data corresponding to exposure-adjusted rate per 100 person-years (p94 of RESPONSE CSR). Number of events were not reported for either arm in the RESPONSE CSR or Kiladjian et al., 2020.

f 12 events in 10 patients

g 9 events in 8 patients

Blue shading indicates data previously seen by the PBAC.

* 1. Although, on average, the incidence of thromboembolic and haemorrhagic events were numerically higher in patients treated with BAT across the three trials, these differences were not statistically significant. Overall, by the end of 5-year follow up period the proportions of events increased in the BAT arm. In the MAJIC trial, the number of thromboembolic and haemorrhagic events increased by 8.3% and 9.8% in the BAT arm, respectively, between 2.6-year and 5-year follow up periods. Similar trends were observed in the RESPONSE and RESPONSE-2 trials although at lower rates (2.8-3.0%), noting these were adjusted by exposure per 100 patients-years. The adjusted incidence of thromboembolic and haemorrhagic events from the RESPONSE and RESPONSE-2 trials were used in the economic evaluation.
	2. The updated results of PFS and OS are presented in Table 7. HRs were not reported in the previous submission. The KM curves for PFS and OS are shown in Figure 3.

**Table 7: Results of progression-free survival and overall survival in MAJIC**

|  |  |  |
| --- | --- | --- |
|  | **Ruxolitinib****N=93** | **BAT****N=87** |
| **PFS** |
| Number of events | 22 | 27 |
| Median survival | Not reached | Not reached |
| Survival percentage  |
| 1 year (95% CI) | 96% (89, 98) | 95% (88, 98) |
| 3 years (95% CI) | 84% (74, 90) | 75% (63, 83) |
| 5 years (95% CI) | 76% (65, 84) | 64% (51, 74) |
| HR (95% CI; p-value) | 0.64 (0.35, 1.14; p=0.13) |
| **OS** |
| Number of events | 17 | 17 |
| Median survival | Not reached | Not reached |
| Survival percentage  |
| 1 year (95% CI) | 100% | 99% (92, 100) |
| 3 years (95% CI) | 88% (79, 93) | 87% (77, 93) |
| 5 years (95% CI) | 83% (72, 89) | 75% (61, 84) |
| HR (95% CI); p-value | 0.72 (0.35, 1.48; p=0.38) |

Source: Table 2.17, p102 of resubmission (based on CSR)

Abbreviations: BAT, best available therapy; CI, confidence interval; CSR, clinical study report; HR, hazard ratio; OS, overall survival; PFS, progression-free survival;

**Figure 3: Progression-free (left) and overall survival (right) in MAJIC**

** **

Source: Figure 2.18 and 2.20, p100, 102 of resubmission (based on MAJIC CSR).

Abbreviations: BAT, best available therapy; CI, confidence interval; CSR, clinical study report; HR, hazard ratio; PV, polycythaemia vera.

* 1. The number of PFS events was higher in the BAT arm compared to the ruxolitinib arm (27 vs 22), while the number of events was the same for OS (17 for both arms). No statistically significant differences in PFS and OS were observed between the treatment arms in MAJIC. This aligns with results presented in the previous submission. The PFS KM curves appear to separate after 1.5 years and the PFS rates at 3- and 5-years were numerically higher in the ruxolitinib arm compared to BAT; 84% vs 75% and 76% vs 64% respectively. The 5-year OS rates were 83% in the ruxolitinib arm and 75% in the BAT arm, noting the 95% CIs were overlapping. The Pre-Sub-Committee Response (PSCR) stated that the absence of a statistically significant difference in PFS and OS was due to the low number of disease progression events and deaths over the 5-year follow-up in MAJIC and noted that the trial was not powered to demonstrate a difference in these outcomes. The ESC agreed with the PSCR that this was not unexpected, given the natural history of PV where median survival of patients varies between 10.9 years (high-risk patients) and 27.8 years (low-risk patients).
	2. The KM curves of EFS for both Harrison et al., and the CSR are shown in Figure 4. EFS was newly presented in this resubmission and has additional potential for bias due to being defined post-hoc.

**Figure 4: Event-free survival in MAJIC for all minor and major thromboembolic/haemorrhagic events (CSR)(left) and for major thromboembolic/haemorrhagic events (Harrison et al.) (right)**

****

Source: Figure 2.9 and Figure 2.11, p94-95 of resubmission.

Abbreviations: BAT, best available therapy; CI, confidence interval; CSR, clinical study report; EFS, event-free survival, HR, hazard ratio; RUX, ruxolitinib.

* 1. The definition of EFS differed between the MAJIC CSR and Harrison et al., 2023 with the former including all minor and major thromboembolic/haemorrhagic events while the latter only includes major events. These results suggest that while ruxolitinib was not associated with a statistically significant reduction in EFS (both minor and major events combined) (HR 0.65, 95% CI: 0.41, 1.02 from CSR), ruxolitinib was associated with a statistically significantly lower risk for major EFS (major thromboembolic/haemorrhagic events) (HR 0.58, 95% CI: 0.35, 0.94 from Harrison et al., 2023) compared to BAT. Further, additional analysis presented in the MAJIC CSR for major EFS, also indicated a statistically significant difference for ruxolitinib (HR 0.60, 95% CI: 0.37, 0.97; p=0.04).
	2. The results of venesections and venesection-free survival (VFS) are presented in Table 8. Venesections was an exploratory outcome, not pre-specified in the protocol.

**Table 8: Results of venesections in MAJIC presented in the resubmission**

|  |  |  |
| --- | --- | --- |
| **Venesections** | **Ruxolitinib (N=93)** | **BAT (N=87)** |
| Number of venesections during trial a | 97 | 338 |
| Number of venesections during treatment b | 77 | 298 |
| Number of patients who received at least one venesection, n (%)a | 30 (32.3) | 49 (56.3) |
| Median (range) per patient b | 0 (0, 13) | 1 (0, 25) |
| Average treatment length, median (range) in months b | 52 (1, 73) | 42 (1,73) |
| **Venesection-free survival** a |
| HR (95% CI) | **0.51 (0.40, 0.64)** |

Source: Table S7A, supplement to Harrison et al., 2023, p102 of resubmission and Table 2.18, p103 of resubmission (based on CSR)

Abbreviations: BAT, best available therapy; CI, confidence interval; HR, hazard ratio.

a Based on MAJIC CSR

b Based on Harrison et al. 2023.

* 1. The number of venesections during treatment (based on Harrison et al., 2023) and the proportion of patients who received at least one venesection (based on MAJIC CSR) were substantially higher in the BAT arm compared with the ruxolitinib arm (298 vs 77 and 56.3% vs 32.3%, respectively). There was a significant difference in the VFS with ruxolitinib compared with BAT (HR 0.51; 95% CI: 0.40, 0.64) (based on MAJIC CSR). The ESC noted that the number of venesections was not a pre-specified outcome of the MAJIC trial, but considered that a reduction in venesections may be clinically relevant for some patients.
	2. Updated results of patient-reported symptom scores from the Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF) based on Harrison et al., 2023 are presented in Figure 5.

**Figure 5: Symptom responses: change in total symptom scores based on MPN-SAF in MAJIC**



Source: Figure 2.24, p107 of resubmission (based on Harrison et al., 2023)

Abbreviations: BAT, best available therapy; CI, confidence interval; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; RUX, ruxolitinib.

Note: Shaded areas indicate 95% CIs.

* 1. Of the 115 patients with MPN-SAF total symptom score (TSS) scores at baseline and at least one additional time point, a significantly greater proportion of patients in the ruxolitinib arm (61%) had TSS reduction of 50% or greater in at least one time point compared to the BAT arm (30%) (p=0.001). Regarding specific symptoms, there was statistically significant symptom reduction for ruxolitinib compared with BAT at more than five time points for fatigue, early satiety, night-sweats, itching, bone pain, and weight loss (p<0.05). This aligns with the MPN-SAF results presented in the previous submission, which also reported significant differences in the specified symptoms which are likely to be patient relevant. However, minimum clinically important differences (MCIDs) were not nominated for these outcomes. No EuroQol-5 Dimensions (EQ-5D) data from MAJIC were reported in either Harrison et al., 2023 or MAJIC CSR.

**RESPONSE and RESPONSE-2 results**

* 1. The primary outcomes of response in the RESPONSE and RESPONSE-2 trials are summarised in Table 9. The number and proportion of responses in each arm have not changed since previous submission. Calculations of OR, risk ratio (RR) and risk difference (RD) have slightly changed likely due to differences in analytical approaches, but these remain very similar to those previously considered by PBAC which were also statistically significant.

**Table 9: Primary outcomes of response in RESPONSE at week 32 and RESPONSE-2 at week 28**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** | **Ruxolitinib, n/N(%)** | **BAT, n/N(%)** | **ORa (95% CI)** | **RRa (95% CI)** | **RDa (95% CI)** |
| **RESPONSE** |
| Primary composite outcome (spleen + HCT) at week 32 | 25/110 (22.7) | 1/112 (0.9) | **32.65 (4.34, 245.77)** | **25.45 (3.51, 184.62)** | **0.22 (0.14, 0.30)** |
| ≥35% spleen volume reduction at week 32 | 44/110 (40.0) | 1/112 (0.9) | **74.0 (9.96, 549.74)** | **44.8 (6.28, 319.51)** | **0.39 (0.30, 0.48)** |
| HCT <45% at week 32 | 66/110 (60.0) | 22/112 (19.6) | **6.14 (3.36, 11.21)** | **3.05 (2.04, 4.58)** | **0.40 (0.29, 0.52)** |
| **RESPONSE-2** |  |  |  |  |  |
| HCT <45% at Week 28 | 46/74 (62.2) | 14/75 (18.7) | **7.16 (3.39, 15.11)** | **3.33 (2.01, 5.52)** | **0.43 (0.29, 0.58)** |

Source: Table 2.19, p108 and Table 2.20, p116 of resubmission.

Abbreviations: BAT, best available therapy; CI, confidence interval; HCT, haematocrit; OR, odds ratio; RD, risk difference; RR, risk ratio

a Calculated for the resubmission using the Mantel-Haenszel statistical method with a fixed effect model. Previous submission calculation used Statsdirect. There were very small differences in the point estimates and 95% CI from previous submission.

Note: Results in **bold** indicate statistically significant difference (p<0.05)

Text in italics indicate values calculated during evaluation of previous submission.

Blue shading indicates data previously seen by the PBAC.

* 1. Statistically significantly more patients treated with ruxolitinib responded with reduction in spleen volume and/or HCT <45% in both RESPONSE and RESPONSE-2 compared to patients treated with BAT at up to Week 32 (RESPONSE) or Week 28 (RESPONSE-2). This aligns with the complete response results from MAJIC at 12 months, however it is inconsistent with the partial response and overall response results from MAJIC, in which no statistically significant differences were observed between treatment arms (Table 5). The inconsistency of results between trials was previously noted by PBAC in the November 2019 meeting who 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) (para 7.9, ruxolitinib, PSD, November 2019 PBAC meeting).
	2. The resubmission presented 5-year follow up results of secondary outcomes of RESPONSE and RESPONSE-2 trials predominately for the ruxolitinib group only, due to all patients being assigned to the BAT arm crossing over to ruxolitinib or discontinuing by Week 80 for both trials (Table 10).

**Table 10: Summary of response rate of ruxolitinib at 5 years of follow up in RESPONSE and RESPONSE-2- trials**

|  | **Response rate, % (95% CI)** |
| --- | --- |
| **RESPONSE (at Week 224)** | **Ruxolitinib (N=110)** |
| Primary composite outcome (spleen + HCT)  | 74 (51, 88) |
| ≥35% spleen volume reduction | 72 (34, 91) |
| HCT <45% | 73 (60, 83) |
| Complete haematological remission | 55 (32, 73) |
| Clinico-haematological response | 67 (54, 77) |
| **RESPONSE-2 (at Week 260)** | **Ruxolitinib (N=74)** |
| HCT <45% | 22 (13, 33) |
| Complete haematological remission | 12 (6, 22) |

Source: Sections 2.5.1.2 and 2.5.1.3 of resubmission, Kiladjan et al., 2020 and Passamonti et al., 2022.

Abbreviations: CI, confidence interval; HCT, Haematocrit control.

* 1. The 5-year follow up results indicate that a large proportion (over 55%) of patients treated with ruxolitinib maintained response by Week 224 in RESPONSE trial. However, a smaller proportion of patients (12-22%) maintained response by Week 260 in the RESPONSE-2 trial. This suggests that PV patients with splenomegaly (included in RESPONSE) may have a better sustained response than those without splenomegaly (included in RESPONSE-2) in the long term. Overall, there is no comparative evidence to suggest any differences in response between patients treated with ruxolitinib and BAT in the RESPONSE trials after week 80.
	2. No statistically significant differences in OS were observed between the treatment arms in RESPONSE and RESPONSE-2 trials. This aligns with results from MAJIC trial (para 6.26).
	3. The KM curves of EFS in the RESPONSE 2 trial are presented in Figure 6. EFS was not analysed in the RESPONSE trial. Rates of transformation to MF and AML for RESPONSE trial were presented as description only in Kiladjian et al., 2020.

**Figure 6: Event-free survival in in the RESPONSE-2 trial (full set analysis)**



Source: Figure 2.38, p121 of resubmission.

Abbreviations: CI, confidence interval; NR, not reached.

Note: Median follow-up for event free survival was 19.5 months (interquartile range (IQR): 7.5–60.8).

* 1. In the RESPONSE-2 trial, of the 74 patients in the ruxolitinib group, 4 patients (5%) had an event of MF, AML, or death by week 260 (5 years), compared with 3 patients (4%) in the BAT group at Week 80. Median duration of EFS was not reached in the ruxolitinib, BAT, or crossover groups. Among patients in the ruxolitinib group, EFS at 260 weeks was 94% (95% CI: 85%, 98%). Patients in the BAT group at Week 80 were not eligible to enter the extended treatment period and hence EFS at 260 weeks was not assessed. In the RESPONSE trial, the rates of transformation to MF and AML (per 100 patient-years) at 5-year of follow up were 2.1 and 0.2 in the ruxolitinib group, 1.8 and 0.6 in the crossover population, and 1.4 and 0.0 in the BAT group, respectively. Overall, there was limited comparative evidence to suggest any difference in EFS or transformation between patients treated with ruxolitinib and BAT.
	2. The number of venesections were reported for the ruxolitinib arm in the RESPONSE trial and for both arms in the RESPONSE-2 trial. In RESPONSE, 78 (83%) of 94 of the evaluable patients treated with ruxolitinib required no venesections and only 6 (6%) patients needed three or more after week 80 up until the Week 256 visit. In the RESPONSE-2 trial, fewer venesections from baseline were required in the ruxolitinib arm compared to BAT arm (36 vs 106, respectively) at Week 80 ( RESPONSE-2 CSR).
	3. In the RESPONSE and RESPONSE-2 trials, a Pruritus Symptom Impact Scale and the MPN-SAF TSS was used to assess the severity of the symptoms. In both trials, improvements in pruritus were reported by a higher proportion of patients in the ruxolitinib group than the BAT group and these improvements were maintained with ruxolitinib by the end of treatment. In the RESPONSE-2 trial there were significantly more patients treated with ruxolitinib who reported at least 50% improvement in the MPN-SAF TSS compared to patients treated with BAT (45% vs 16%; OR: 4.36; 95% CI: 1.88, 10.12).
	4. QoL data were collected using the European Organization for the Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) in RESPONSE and the EuroQol-5 Dimension-5 levels (EQ-5D-5L) in RESPONSE-2. In RESPONSE, the improvements in EORTC QLQ-C30 scores were sustained in some patients by Week 256 with a mean improvement from baseline of +9.49. In RESPONSE-2 the change from baseline in the EQ-5D-5L Visual Analogue Scale (VAS) scores showed numerical improvement in ruxolitinib arm compared with BAT arm, while the change from baseline in the EQ-5D-5L health index scores were similar between the ruxolitinib and BAT arms. The differences reported were not statistically significant.

**Systematic Review and meta-analysis (Rocca Mora et al., 2024)**

* 1. The efficacy findings of patients resistant or intolerant to HC/HU presented in the systematic review and meta-analysis (Rocca Mora et al., 2024)[[7]](#footnote-8) showed that patients treated with ruxolitinib achieved a significantly higher rate of complete haematological response (RR 2.28; 95% CI: 1.36, 3.84; p < 0.01; I2 = 45%), and a significant improvement of MPN-SAF score reduction of >50% (RR 3.19; 95% CI: 1.21, 8.46; p = 0.02; I2 = 77%) and Patient Global Impression of Change (PGIC) score (RR 6.86; 95% CI: 3.45, 13.63; p < 0.01; I2 = 41%) when compared to BAT. There were no significant differences between groups in the rates of death (RR 0.48; 95% CI: 0.20, 1.11; p = 0.09; I2 = 59%) progression to MF (RR 0.60; 95% CI: 0.32, 1.12; p = 0.11; I2 = 12%), progression to AML (RR 1.46; 95% CI: 0.12, 17.96; p = 0.77; I2 = 53%), and pruritus (RR 0.83; 95% CI: 0.3, 2.25; p = 0.71; I2 = 69%). Overall, the efficacy results from Rocca Mora et al., 2024 were broadly consistent with the results observed in the included trials.

Comparative harms

* 1. The resubmission presented safety data assessed at the final 5-year follow-up in MAJIC, RESPONSE and RESPONSE-2. Due to significant crossover in RESPONSE and RESPONSE-2, safety data were presented as exposure-adjusted rates to account for the different durations of exposure to ruxolitinib and BAT. A summary of AEs and transformation from MAJIC are presented in Table 11.

**Table 11: Summary of adverse events and transformation in MAJIC**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Ruxolitinib N=93, n (%)** | **BAT N=87, n (%)** | **OR a (95%CI)** | **RR a (95%CI)** | **RD a (95%CI)** |
| **AEs reported at 5-year follow up**  |
| Grade ≥3 AE | 55 (59) | 45 (52) | 1.35 (0.75, 2.44) | 1.14 (0.88, 1.49) | 0.07 (-0.07, 0.22) |
| Serious AE | 54 (58) | 48 (55) | 1.13 (0.62, 2.03) | 1.05 (0.81, 1.36) | 0.03 (-0.12, 0.17) |
| Deaths | 15 (16) | 17 (20) | 0.79 (0.37,1.70) | 0.83 (0.44, 1.55) | -0.03 (-0.14, 0.08) |
|  **Transformation reported at 5-year follow up**  |
| Any transformation | 9 (10) | 11 (13) | 0.74 (0.29, 1.88) | 0.77 (0.33, 1.76) | -0.03 (-0.12, 0.06) |
| AML | 4 (4) | 0 (0) | 8.80 (0.47, 165.87) | 8.43 (0.46, 154.24) | 0.04 (-0.00, 0.09) |
| Myelodysplastic Syndrome | 0 (0) | 1 (1) | 0.31 (0.01, 7.67) | 0.31 (0.01, 7.56) | -0.01 (-0.04, 0.02) |
| MF | 5 (5) | 10 (11) | 0.44 (0.14, 1.34) | 0.47 (0.17, 1.31) | -0.06 (-0.14, 0.02) |
| **AEs reported at 1 year follow up** |
|  | **Ruxolitinib, n/N(%)** | **BAT, n/N(%)** | **OR (95%CI)** | **RR (95%CI)** | **RD (95%CI)** |
|  Grade 3 Anaemia | 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 thrombocytopenia | 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 infection | 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 infection | 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) |

Source: Table 2.21, p126 of resubmission, Table 2.22, p127 of resubmission, Harrison et al., 2023 and p97 of previous submission

Abbreviations: AE, adverse event; AML, acute myeloid leukaemia; BAT, best available therapy; CI, confidence interval; Inf, infinity; MF, Myelofibrosis; OR, odds ratio; RD, risk difference; RR, risk ratio.

a Calculated for the resubmission using the Mantel-Haenszel statistical method with a fixed effect model.

Note: Text in italics indicate values calculated with statsdirect during evaluation of previous submission.

Blue shading indicated values previously seen by PBAC.

* 1. By the end of the 5-year follow up period, more than half of the patients in the safety population experienced a Grade 3-5 AE and serious adverse event (SAE) in each treatment group in MAJIC. The proportions of patients who either experienced a Grade 3-5 AEs, SAE or death were similar across arms with no significant differences.
	2. Whilst overall the percentage of transformations in the two treatment groups in MAJIC were similar (10% in ruxolitinib vs 13% in BAT), a higher percentage of BAT patients experienced myelofibrosis (11% vs 5%), and for the ruxolitinib-arm, AML was more prevalent (4% vs 0%).
	3. The key adverse events in RESPONSE and RESPONSE-2 are summarised in Table 12.

**Table 12: Summary of adverse events in RESPONSE and RESPONSE-2**

|  |  |  |
| --- | --- | --- |
| **AEs** | **Ruxolitinib (%)** | **BAT (%)** |
| **New evidence presented in the resubmission- Adjusted AEs per 100 patient-years** |
| **RESPONSE a** |
| Anaemia all grades |  8.9 | 5.4 |
| Dizziness all grades | 4.0 | 15.0 |
| Headache all grades | 5.8 |  28.5 |
| Anaemia Grade 3-4 | 0.9 | 0.0 |
| Infections all grades | 18.9 | 59.8 |
| Infection Grade 3-4 | 3.5 | 4.1 |
| Transformation to MF | 2.1 | 1.4 |
| Transformation to AML | 0.2 | 0.0 |
| **RESPONSE-2 b** |
| Anaemia all grades | 8.7 | 5.6 |
| Weight increased | 5.7 | 1.9 |
| Anaemia Grade 3-4 | 0 | 1.9 |
| Infections all grades | 14.7 | 33.7 |
| Infection Grade 3-4 | 2.1 | 3.8 |
| Transformation to MF | 0.6 | 1.9 |
| **Evidence presented in previous submission** |
|  | **Ruxolitinib, n/N (%)** | **BAT, n/N (%)** | **OR (95%CI)** | **RR (95%CI)** | **RD (95%CI)** |
| **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)** |

Source: p127-128 of resubmission, Kiladjian et al., 2020, Passamonti et al., 2022, Table 2.3-54, p 173 and table 2.3-58, p 178 of previous submission

Abbreviations: AEs, adverse events; AML, acute myeloid leukaemia; BAT, best available therapy; CI, confidence interval; Inf, infinity; MF, myelofibrosis; OR, odds ratio; RD, risk difference; RR, risk ratio.

a Adverse events occurring at a rate of ≥5 per 100 patient-years of exposure in any group, regardless of relationship to study drug. Adjusted rates were calculated as the number of patients with events per 100 patient-year of exposure. Exposure for ruxolitinib=428·4 patient-years. Exposure for BAT=73·6 patient-years.

b Adjusted rates were calculated as the number of patients with events per 100 patient-year of exposure. Median exposure was 260 weeks (IQR 257–261) in the ruxolitinib group and 28 weeks (28–40) in the best available therapy group.

Blue shading indicated values previously seen by PBAC.

* 1. The 5-year follow up results showed that exposure-adjusted rates of anaemia (all grades) were higher with ruxolitinib compared to BAT. The differences in weight gain between arms continued to be higher with ruxolitinib compared to BAT, while infections (all grades) are more prominent with BAT compared with ruxolitinib.
	2. The safety findings reported in Rocca Mora et al., 2024[[8]](#footnote-9) for patients resistant or intolerant to HC/HU showed significantly lower thromboembolism rates (RR 0.42; 95% CI: 0.19, 0.92; p = 0.03; I2 = 44%), yet significantly increased rates of anaemia (RR 2.75; 95% CI: 1.01, 7.50; p = 0.05; I2 = 50%), and herpes zoster infections (RR 3.63; 95% CI 1.22 to 10.83; p = 0.02; I2 = 0%) with the use of ruxolitinib. There were no significant differences between groups in the rates of thrombocytopenia (RR 0.98; 95% CI: 0.38, 2.55; p = 0.97; I2 = 30%), and nonmelanoma skin cancer (NMSC) (RR 1.83; 95% CI: 0.46, 7.31; p = 0.39; I2 = 65%). Overall, the safety results from Rocca Mora et al. 2024 were broadly consistent with the results observed in the included trials.

***Benefits/harms***

* 1. On the basis of direct comparison evidence presented by the resubmission for MAJIC, for every 100 patients treated ruxolitinib and BAT over a median follow up of 4.9 years:
* Approximately 17 additional patients would achieve complete response within 12 months (Table 5), however there was no difference in partial response or overall response (complete response + partial response). Patients treated with ruxolitinib achieved more durable CR or PR compared to those treated with BAT.
* There was no evidence for any significant difference in PFS, OS, EFS, transformation, haemorrhagic events, grade ≥3 AEs and SAEs for up to 5 years between patients treated with ruxolitinib and patients treated with BAT.
	1. It was not possible to quantify the benefits and harms based on the RESPONSE and RESPONSE-2 trials as the resubmission presented long-term data predominately for the ruxolitinib group only.

Clinical claim

* 1. The resubmission claimed that ruxolitinib was superior in terms of effectiveness and had a different safety profile that was manageable, compared to BAT.
	2. The evaluation considered the claim of superior effectiveness was partially supported by the clinical evidence presented in the resubmission because:
* While the MAJIC trial reported significant improvements with ruxolitinib in terms of haematological response (para 6.17) and durability of response across the 5-year follow up (para 6.20), it remains uncertain how this translates to other relevant clinical outcomes for patients with PV, such as PFS, haemorrhagic events and OS, as no significant differences were observed for these outcomes between treatment arms in this trial.
* However, the incidence of thromboembolic and haemorrhagic events were numerically lower in patients treated with ruxolitinib across trials, with MAJIC showing an improvement in TEFS (HR 0.57, 95% CI: 0.32, 0.99; p=0.05) and a significant difference in major EFS (HR 0.60, 95% CI: 0.37, 0.97; p=0.04) which included major thromboembolic and haemorrhagic events.
* MAJIC reported that patients treated with ruxolitinib had significant improvements in the number of venesections and symptoms based on the MPN-SAF TSS over the 5-year follow up period compared to BAT. RESPONSE and RESPONSE-2 also showed that over time, patients treated with ruxolitinib experienced significant improvements in pruritus symptoms and MPN-SAF TSS, and fewer venesections on average compared to patients treated with BAT.
* All three trials were considered to be at high overall risk of bias for long term outcomes given the high rate of attrition and detection bias due to discontinuation and unblinding (of outcome assessors) in all trials. Additionally, post hoc analyses of exploratory outcomes in MAJIC such as EFS, venesections and VFS are less rigorous and have additional potential for bias versus outcomes pre-specified in the protocol. Previous concerns raised by PBAC regarding the open label design and the high risk of bias of the MAJIC trial remain.
	1. The ESC acknowledged the limitations of the clinical evidence and that no significant differences in PFS or OS were reported. However, the ESC considered that, although uncertain, the claim of superior effectiveness was supported by the significant improvements in major EFS, the reductions in venesections and the improvements in duration of response and MPN-SAF TSS reported for ruxolitinib compared to BAT.
	2. The evaluation considered the claim of different safety profile was adequately supported. In MAJIC, there were no significant differences in Grade ≥3 AEs, SAEs and deaths reported by the 5-year follow up. However, differences in AE profiles were evident between ruxolitinib and BAT. RESPONSE and RESPONSE-2 trials reported a higher exposure-adjusted rates of anaemia (all grades) and weight increase with ruxolitinib vs BAT, although the inverse occurred with infections (all grades). Overall, the ESC agreed with the resubmission claim that ruxolitinib has a different safety profile compared to BAT, and considered that this is likely to be manageable.
	3. The PBAC agreed with the ESC that although uncertain, the claim of superior comparative effectiveness was reasonable based on the significant improvements in major EFS, the reductions in venesections and the improvements in duration of response reported for ruxolitinib compared to BAT.
	4. The PBAC also agreed with the ESC that ruxolitinib has a different safety profile compared to BAT, and that this is likely to be manageable in clinical practice.

***Economic analysis***

* 1. The resubmission presented a stepped economic evaluation of ruxolitinib compared to BAT in adults with PV who are resistant or intolerant to HC/HU. The economic evaluation was based on direct randomised trials (MAJIC, RESPONSE and RESPONSE-2 trials) and implemented a modelled evaluation. The economic evaluation was presented as cost-utility/cost-effectiveness analysis.
	2. Compared to the July 2019 submission, the key changes in the resubmission model were:
* Updated model structure that was based on progression events, AML, MF, and death, with Pre progression, Progressed and Dead health states. The updated model structure limited the value of comparisons with the model used in the previous submission.
* Transition probabilities for progression events are based on PFS data from the MAJIC trial combined with KM curves from the literature. Time to response and duration of response were not directly considered in the economic model.
* OS in the economic model was based on both assumed difference in OS within the updated 5-year follow up data from the MAJIC trial and survival following transition into MF or AML/MDS based on the literature.
* Updated utility data based on the EQ-5D-5L data from the RESPONSE-2 trial.
* The effective DPMQ was updated to $| | per cycle (| |% reduction from the previous submission).
	1. A summary of the key components of the economic model are presented in Table 13.

**Table 13: Summary of model structure, key inputs and rationale**

| **Component** | **Summary** |
| --- | --- |
| Treatments | Ruxolitinib vs BAT |
| Time horizon | 20 years in the economic model vs 5 years in the MAJIC trial |
| Outcomes | Life years and QALYs |
| Methods used to generate results | Markov state-transition model  |
| Health states | 4 health states: Progression-free on ruxolitinib; Progression-free on BAT; Progressed disease (three substates: low/intermediate-1 MF, intermediate-2/high MF, and AML/MDS); Dead (absorbing state) |
| Cycle length | 28 days |
| Transition probabilities  | Progression-free on ruxolitinib to Progression-free on BAT was based on TTD data from the MAJIC trial.Progression-free on ruxolitinib to Progressed disease was based on ruxolitinib PFS data from the MAJIC trial. Progression-free on BAT to Progressed disease was based on the BAT PFS data from the MAJIC trial combined with ratio of AML/MDS to MF ratio of 0.39 from Alvarez-Larrán et al. (2022) Progression-free on ruxolitinib and Progression-free on BAT to Dead were both based on pre-progression death rate from the MAJIC trial. Progressed disease (AML) to Dead from Tang et al. (2017). Progressed disease (Low/Intermediate-1 MF) to Dead from Tefferi et al. (2019). Progressed disease (Intermediate-2/High MF) to Dead from Ruxolitinib for MF PBAC submission July 2014 economic model. |
| Extrapolation method | For progression events, the proportion of patients that progressed in the MAJIC trial was used in combination with time to event data from the literature to establish a KM plot that could be used to inform a parametric extrapolation. A Weibull curve was selected to establish the proportion of patients in PFS from 0 to 20 years based on the proportion of events in the MAJIC trial and the time to event data from Szuber et al. (2019). The resubmission reported that the selection of the curve was based on statistical goodness of fit (AIC/BIC), visual fit and clinical plausibility criteria. Due to the small number of events on which the curve was based, the AIC and BIC were not able to strongly differentiate goodness of fit. Furthermore, the resubmission did not provide the clinical plausibility criteria on which the selection was based. OS data from pre progression, and progressed health states were extrapolated using individual Weibull curves, as the risk of death was different depending on the progression events. The resubmission did not justify the selection of the Weibull curve for the extrapolation of these events.72% of incremental QALY gains occurred between years 5 and 20 of the economic model.  |
| Health related quality of life | Pre-progression treatment specific utilities were applied based on EQ-5D-5L data collected in the RESPONSE-2 trial, ruxolitinib 0.821, BAT 0.743, based on the mean utility of patients in the trial while on treatment. For patients who develop AML/MDS a health state utility of 0.63 was applied based on Mamalo et al. (2019). Utility for patients with low/intermediate-1 risk MF was 0.71 derived from Mesa et al. (2021). For patients who develop intermediate-2/high risk MF, a one-off QALY gain of 3.163 was applied upon entering the health state based on the July 2014 ruxolitinib submission. This approach was inconsistent with the approach applied for other health states, and may not have been appropriate as it was based on the outputs of an economic evaluation for ruxolitinib for patients with MF and included patients who did not previously have PV. |

Source: Compiled during the evaluation based on information provided in Sections 3.3, 3.4, 3.5 and 3.6 of the resubmission

Abbreviations: AIC, Akaike information criterion; AML, acute myeloid leukemia; BAT, best available treatment; BIC Bayesian information criterion; EQ-5D-5L, EuroQol-5 Dimension-5 levels; MBS, Medicare Benefits Schedule; MDS myelodysplastic syndrome; MF myelofibrosis; OS, overall survival; PFS, progression-free survival; PV, polycythaemia vera; QALY, quality-adjusted life year; TTD, time to treatment discontinuation.

* 1. The PBAC previously considered that the economic model in the November 2019 submission relied on responder health states that do not correlate to clinically relevant outcomes and therefore do not adequately capture benefits, if any, of treatment (para 7.13, ruxolitinib, PSD, November 2019 PBAC meeting). The updated economic model presented by the resubmission was based on progression events rather than responder status of patients. This forewent the need for the resubmission to establish a clinical link between response status and OS. The evaluation considered the updated economic model structure was reasonable. However, the ESC and the evaluation noted that the economic model relied on selected outcomes that were not statistically significant different and that the therapeutic claims of improvements in PFS, and OS on which the economic model is based were not adequately supported.
	2. The economic model had four health states. Patients entered the model in one of two states: Progression-free on ruxolitinib or Progression-free on BAT. Patients who did not respond to treatment on ruxolitinib could progress to Progression-free on BAT, otherwise patients remained in the Progression-free health states until they developed AML/MDS, MF or died. Patients in the progressed disease states could remain in that state or die. Progression events in the model were defined as the development of MF, AML/MDS or death. In clinical practice MF and AML events are not mutually exclusive, a standard assumption of a Markov model. Patients who develop MF, can later transition into AML. For example, in Szuber et al. (2019) of 1,282 patients with primary myelofibrosis treated at the Mayo clinic 9% transitioned to AML (median follow up 3.2 years).
	3. In the economic model patients who were Progression free on ruxolitinib could move to being Progression free on BAT if treatment was discontinued but patients remained progression free. The resubmission estimated the ratio of patients who progressed to the patients who discontinued treatment (HR: 1.055; 95% CI: 0.59, 1.90), based on pseudo-individual patient data KM plots for treatment discontinuation, rather than individual patient data as these were not available from the MAJIC trial. This ratio was used to preserve the relationship between PFS and time to discontinuation (TTD) beyond the 5 years of the MAJIC trial. The ESC agreed with theevaluation that it wasnot reasonable to assume the association between PFS and TTD will remain constant over time, as this was not supported with empirical data.
	4. The Progressed disease health state in the economic model included three substates AML/MDS, low/intermediate-1 risk MF, and intermediate-2/high risk MF. Transformation into MF and AML/MDS, PFS was modelled under a competing risk framework, where each competing event (progression due to death, progression due to MF and progression due to AML/MDS) was modelled separately. The decision to model progression events separately in the economic model added uncertainty. When considered together the progression events that were applied in the economic model (MF, AML/MDS, and death) showed a point estimate improvement for ruxolitinib compared to BAT (HR 0.64 95%CI: 0.35, 1.14), however the CIs were wide, and the estimate was not statistically significant (p=0.13). When considering the progression events individually the number of events on which each transition probability is based decrease substantially. There were 5 MF events in the ruxolitinib arm and 10 in the BAT arm, 4 AML/MDS events in the ruxolitinib arm and 1 in the BAT arm, and 10 deaths in the ruxolitinib arm and 17 in the BAT arm. This is important as the primary driver of the economic model was the difference in the probability of progression events, and this difference was not well supported by empirical evidence. Furthermore, patients who developed AML, low/intermediate-1 MF, and intermediate-2/high MF were assumed to have different clinical trajectories and therefore, different extrapolation functions were applied, this meant that initial differences in outcomes associated with progression led to differences in OS that were maintained throughout the time horizon.
	5. The resubmission claimed that the number of AML/MDS events reported in the BAT arm of the MAJIC trial was low compared with other literature and was likely driven by the small sample size and length of follow up. Consequently, the resubmission calculated the 5-year probability of AML/MDS using the ratio of AML/MDS to MF events (0.39 AML/MDS for every MF) reported in Alvarez-Larrán et al. (2022). This meant that the leukemia free survival (LFS) in the BAT arm applied in the economic model was based on a 5-year AML/MDS probability of 5.69% rather than 1.15% (based on 1 event in 87 patients). This adjustment does not appear to be reasonable based on the availability of the MAJIC trial that did not observe those event rates. This was identified to be an important driver of the model; when the AML/MDS events from the MAJIC trial were applied in the economic model the ICER increased from $55,000 to < $75,000 per QALY gained to $55,000 to < $75,000 (+| |%). The PSCR argued that Alvarez-Larrán was the best available evidence to inform the rate of transformations into AML and MDS for the economic model.
	6. To account for time-varying incidence of transformation into MF, AML/MDS, and PFS, time to event data were derived from the literature, as time to event data were not available in the MAJIC trial. Data on transformation of disease were extracted from Szuber et al. (2019). The inclusion of an additional source to establish the change in hazard rate over time added an additional layer of uncertainty. The population in the Szuber et al. (2019) article included patients newly diagnosed with PV, not exclusively those who were resistant or intolerant to HC/HU. To manage this, the resubmission used the change in hazard rate starting at 91 months (the median time from diagnosis in the MAJIC trial), however this did not address the underlying difference in the populations. Patients who developed PV 91 months prior, that were not necessarily resistant or intolerant to HC/HU, were likely to demonstrate different rates of progression. Furthermore, these time to event estimates were used to establish the KM plot on which the parametric extrapolation function was based, so initial uncertainties in time to event data may have considerable impact on the applied parametric extrapolation functions and subsequently to the economic model.
	7. OS in the economic model was based on both pre progression mortality, from the MAJIC trial and mortality from progressed disease, based on literature. In November 2019, the PBAC noted that the evidence from the MAJIC trial did not clearly support a benefit in terms of OS (para 7.1, ruxolitinib, PSD, November 2019 PBAC meeting). The ESC agreed with the evaluation that the longer follow up data presented from the MAJIC trial still did not support an OS benefit. Although the point estimate for OS favoured ruxolitinib (HR 0.73 95%CI 0.36 – 1.50), the confidence intervals were wide and the results were not statistically significant different.
	8. OS in patients who had progressed was modelled separately. OS following transformation into AML/MDS was taken from Tang et al. (2017) in patients with PV in the accelerated/blast phase (median OS of 9 months). OS following transformation into low/intermediate-1 risk MF was derived from Tefferi et al. (2012). OS following transformation into intermediate-2/high risk MF was based on the ruxolitinib MF model considered by PBAC in July 2014 and subsequently in March 2015. Including outputs from a different economic model as inputs in this economic model is unlikely to be reasonable as the limitations of underlying structure, inputs and uncertainties of the model would also need to be considered. Post-PV MF is a subset of MF. The population considered in the March 2015 PBAC consideration of ruxolitinib for first-line or second-line management of MF and Tefferi et al. (2012) also included primary MF as well as post-essential thrombocythemia MF. The ESC agreed with the evaluation that it is plausible that the post-PV subset may experience differences in prognosis[[9]](#footnote-10) adding further uncertainty to the approach taken.
	9. The resubmission used parametric extrapolation (base case Weibull) to model the progression of disease stating this was based on visual fit, statistical fit and clinical plausibility. The range of extrapolation functions considered had minimal impact on the ICER (Table 16). Establishing the clinical plausibility of the curves is difficult as there are limited long-term PFS data against which the curves could be validated, particularly in the ruxolitinib arm.
	10. The OS extrapolation function for patients in the pre-progression, AML/MDS, or MF health states were not described by the resubmission. The resubmission stated that a Weibull function was applied but did not provide evidence on how the curves were selected, nor any validation data. The ESC noted theOS in the economic model at 20 years was 5.2% in the BAT arm (Figure 7), which was higher than the 1% OS reported by Alvarez-Larrán et al. (2012) in a real-world sample of patients with PV who were resistant to or intolerant of HU/HC.
	11. The time horizon applied in the economic model was 20 years, compared to 5 years follow up in the MAJIC trial. The evaluation considered the length of the time horizon was reasonable given the long-term survival in these patients, but noted most of the incremental health outcomes occurred after 5-years. The ESC noted that assumptions in the model regarding differences in PFS and OS, which were not supported by the clinical evidence, combined with extrapolation meant that initial differences were maintained throughout the time horizon of the model. At 20 years 17% of patients remain progression free in the ruxolitinib arm compared to 5% in the BAT arm (Figure 7). The model was not specified to force the PFS and OS curves to converge.

**Figure 7: KM and predicted PFS and OS from economic model**

****

Source: Economic model ‘Base Case Results’

Abbreviations: BAT, best available treatment; KM Kaplan Meier; PFS, progression-free survival; OS, overall survival; Rux, ruxolitinib.

* 1. The resubmission maintained a difference in pre-progression utility that was treatment specific and favourable to ruxolitinib. The resubmission supported this assumption with data from both the RESPONSE and RESPONSE-2 trials. Regarding the previous submission, ESC had considered it to be unclear why ruxolitinib responders would have an improvement in QoL over BAT responders and had considered the application of this assumption in the model to be poorly justified (para 6.54, ruxolitinib, PSD, November 2019 PBAC meeting). The resubmission included additional information of mean utility values from both the RESPONSE and RESPONSE-2 trials that showed little difference between responders and non-responders, but did appear to demonstrate a small difference between ruxolitinib and BAT. In the RESPONSE trial the mean utilities in the ruxolitinib arm and the BAT arm were 0.80 and 0.69 respectively. In the RESPONSE-2 trial the respective mean utility values (applied in the base case) were 0.82 and 0.74. The evaluation considered the justification provided by the resubmission appeared reasonable; however, uncertainty remained due to placebo effects and performance bias as the RESPONSE trials were unblinded and QoL was self-reported. Furthermore, the resubmission did not present standard deviations for mean utilities. The ESC agreed with the evaluator that the assumption of a difference in pre-progression utility remained uncertain due to the limitations in the evidence base.The ESC noted themodel was highly sensitive to these utility values, when the mean utility value for ruxolitinib was applied in both arms the ICER increased from $55,000 to < $75,000 per QALY gained to $75,000 to < $95,000 (+| |%).
	2. The economic model applied a per cycle AE cost for BAT ($189) that is more than <500 times larger than for ruxolitinib ($| |). The per cycle disutility applied while on BAT was 7 times larger than while on ruxolitinib (disutility values of -0.000105 and -0.000015 respectively). The resubmission did not provide a clear justification to support this difference. Management of AEs was the largest cost offset apart from treatment costs. It is unclear what contributed to the large cost of managing AEs in the BAT arm compared to ruxolitinib. Concerns in the approach to costing AEs were also evident (some AE costs, such as those reported for fatigue, appeared overestimated) and the evaluation considered the large offset observed did not align with the clinical evidence which reported similar proportions of Grade ≥3 and serious AEs across treatment arms (Table 11). When AEs were turned off in the model (i.e. incidence = 0%) the ICER increased from $55,000 to < $75,000 per QALY gained to $55,000 to < $75,000 (+| |%).
	3. Key drivers of the model are presented in Table 14.

| **Description** | **Method/Value** | **Impact****Base case: ||||1/QALY gained.** |
| --- | --- | --- |
| Progression-free survival | Difference in PFS was based on the rate of progression events in the MAJIC trial. Time to event data from Szuber et al. (2019) was used to establish KM data for the 5 year period of the trial. An extrapolation function was applied to these KM estimates to estimate the progression events between years 5 and 20.  This assumption was highly uncertain and not adequately supported by the clinical data. The MAJIC trial showed point estimate improvement for ruxolitinib compared to BAT however the confidence intervals were wide and crossed 1 (HR 0.64; 95%CI 0.35, 1.14). Furthermore, the resubmission claimed that the number of AML/MDS events (n=1) in the BAT arm of the MAJIC trial was artificially low, and therefore applied an adjustment based on the ratio of AML/MDS to MF events in the literature of 0.39. The adjustment was favourable to the intervention.  | Very high, favours ruxolitinib. Removal of difference in PFS increased the ICER to $|||| 2 (+||||%) |
| Pre progression OS | Difference in pre-progression OS was based on OS data from the MAJIC trial. Although the point estimate for OS favoured ruxolitinib (HR 0.73 95% CI 0.36 – 1.50), the results were uncertain as the confidence intervals were wide and crossed 1. It is unclear how the resubmission established the proportion of deaths that occurred in the pre progression health state. Without patient level data there is the potential that the difference in the proportion of death events may be partially attributable to the difference in MF and AML/MDS progression events. | High, favours ruxolitinib.  |
| Pre progression utility | The resubmission maintained treatment specific utilities for pre- progression HRQoL that favoured ruxolitinib. The resubmission supported this assumption with data from both the RESPONSE and RESPONSE-2 trials. The resubmission included additional information of mean utility values from both the RESPONSE and RESPONSE-2 trials that showed little difference between responders and non-responders, but did appear to demonstrate a small difference between ruxolitinib and BAT.  | High, difference favours ruxolitinib. When the mean utility value for ruxolitinib (0.821) was applied in both arms the ICER increased from ||||**1** per QALY gained to ||||3 (+||||%). When the BAT value (0.743) was used it increased to |||| 3 (+||||%) |

**Table 14: Key drivers of the model**

Source: Compiled during evaluation for information provided in Section 3 of the resubmission.

Abbreviations: AML, acute myeloid leukemia; BAT, best available therapy; CI, confidence interval; HR, hazard ratio; HRQoL, health related quality of life; ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; MDS, myelodysplastic syndrome; MF, myelofibrosis; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; PFS, progression-free survival; QALY, quality-adjusted life year; QoL, quality of life;

*The redacted values correspond to the following ranges:*

*1 $55,000 to < $75,000*

*2 $155,000 to < $255,000*

*3 $75,000 to < $95,000*

* 1. The results of the stepped economic evaluation are presented in Table 15.

**Table 15: Results of the stepped economic evaluation**

| **Step and component** | **Ruxolitinib** | **BAT** | **Increment** |
| --- | --- | --- | --- |
| **Step 1: Quasi trial-based costs and outcomes (5 year time horizon)** |
| Costs | $| | $51,824 | $| |
| LY | 4.26 | 4.118 | 0.15 |
| Incremental cost/LY gained | |1 |
| **Step 2: 20 year time horizon**  |
| Costs | $| | $97,255 | $| |
| LY | 9.056 | 7.805 | 1.25 |
| Incremental cost/LY gained | |2 |
| **Step 3: 20 year time horizon including utilities** |
| Costs | $| | $97,255 | $| |
| QALY | 7.252 | 5.637 | 1.62 |
| Incremental cost/QALY gained | |3 |

Source: Table 3-31, p190 of the resubmission

Abbreviations: Abbreviations: BAT, Best Available Therapy; LY, life years; QALYs, Quality-Adjusted Life Years

*The redacted values correspond to the following ranges:*

*1 $255,000 to < $355,000*

*2 $75,000 to < $95,000*

*3 $55,000 to < $75,000*

* 1. In Step 1, the quasi trial-based analysis showed that at the end of 5 years, there was an incremental gain of 0.15 life years (LYs). The ICER reduced by | |% between years 5 and 20 in Step 2, the incremental cost more than doubled, and there is a greater than an 8-fold increase in the incremental LYs gained. Step 3 highlighted that the differences in pre-progression utility, combined with lower utility weights in progressed health states resulted in the incremental QALYs gained exceeding incremental LYs gained.
	2. Figure 8 shows the cumulative QALYs gained throughout the time horizon of the model.

**Figure 8: Cumulative QALYs (undiscounted)**

**

Source: Compiled during the evaluation from information in tabs ‘Trace\_Rux\_pfs’ and ‘Trace\_BAT\_pfs’ of the economic model

Abbreviations: BAT, best available treatment; Cum, cumulative; QALY, quality-adjusted life year; Rux, ruxolitinib

* 1. The ESC noted the (undiscounted) cumulative QALYs do not diverge substantially until approximately 4 years and considered that initial differences in PFS and OS that were assumed by the economic model, led to differences in QALY gains that were maintained throughout the time horizon (20 years) and beyond. The ESC noted thatin the economic model 72% of the incremental QALY gains occurred between years 5 and 20.
	2. The results of key univariate sensitivity analyses conducted by the resubmission and during the evaluation are summarised in Table 16.

**Table 16: Sensitivity analyses**

| **Analyses** | **Incremental cost ($)** | **Incremental QALY** | **ICER****($/QALY gained)** | **Change to ICER** |
| --- | --- | --- | --- | --- |
| **Base case** | **|** | **1.62** | **|1** | **-** |
| **Discount rate (base case ||||%)** |  |  |  |  |
|  ||||% | | | 2.57 | |2 | -|% |
|  ||||% | | | 1.84 | |**1** | -|% |
| **Time horizon (base case 20 years)** |  |  |  |  |
|  15 years | | | 1.34 | |**1** | +　|　% |
|  25 years | | | 1.74 | |**1** | -|% |
| **HR for PFS (base case 0.64)** |  |  |  |  |
|  HR=1 | | | 0.32 | |3 | +　|　% |
| **PFS extrapolation method (base case Weibull)** |
|  Log Logistic | | | 1.51 | |**1** | +　|　% |
|  Log Normal | | | 1.53 | |**1** | +　|　% |
|  Exponential | | | 1.56 | |**1** | +　|　% |
|  Gompertz | | | 1.68 | |**1** | -|% |
| **Progression to AML** |
|  Rate from MAJIC trial | | | 1.35 | |**1** | +　|　% |
| **Pre progression utility (base case ruxolitinib 0.821, BAT 0.743)** |
|  Utility equal (0.821)  | | | 1.13 | |4 | +　|　% |
|  Utility equal (0.743) | | | 1.00 | |4 | +　|　% |
|  Utilities from Response | | | 1.86 | |2 | -|% |
| **Mortality rate** |
|  Intermediate between MAJIC and general population | | | 1.07 | |4 | +　|　% |
| **Adverse events** |
|  No disutility applied | | | 1.61 | |**1** | +　|　% |
|  All AEs removed | | | 1.61 | |**1** | +　|　% |
| **Per cycle cost ruxolitinib (base case $|||| based on relative dose intensity from RESPONSE-2 trial)** |
|  Weighted average dose  from RESPONSE and RESPONSE-2 trials ($||||) | | | 1.62 | |**1** | +　|　% |
|  RESPONSE dosage ($||||) | | | 1.62 | |**1** | +　|　% |
| **BAT costs (base case $340.99 per cycle)** |
|  Combination therapy valued at  cost of most expensive drug | | | 1.62 | |**1** | +　|　% |
|  Combination therapy values at cost of least expensive drug | | | 1.62 | |**1** | +　|　% |
|  Ratio of peginterferon α-2a to  HC/HU (16/84) | | | 1.62 | |**1** | +　|　% |
|  Ratio of peginterferon α-2a to  HC/HU (21/79) | | | 1.62 | |**1** | +　|　% |
| **Treatment effectiveness against key events** |
|  TE (IRR=1) | | | 1.60 | |**1** | +　|　% |
|  Bleeding/haemorrhage (IRR=1) | | | 1.60 | |**1** | +　|　% |
|  Key events removed | | | 1.59 | |**1** | +　|　% |

Source: Table 3-36, p193 of the resubmission, and compiled during evaluation using Attachment 3 Economic model

Abbreviations: AE, adverse event; AML, acute myeloid leukemia; BAT, best available treatment; G1, Grade 1; G2, Grade 2; G3, Grade3; G4, Grade 4; ICER, incremental cost-effectiveness ratio; IRR, incident rate ratio; LFT, liver function test; MDS, myelodysplastic syndrome; MF, myelofibrosis; NMSC, non-melanoma skin cancer; PFS, progression-free survival; QALY, quality-adjusted life year; TE, thromboembolic event

*The redacted values correspond to the following ranges:*

*1 $55,000 to < $75,000*

*2 $45,000 to < $55,000*

*3 $155,000 to < $255,000*

*4 $75,000 to < $95,000*

* 1. The results of the sensitivity analysis showed that the economic model was most sensitive to the baseline difference in PFS, the difference in pre-progression utility, pre-progression OS, and the adjustment used to alter the rate of progression to AML.
	2. Sensitivity analysis conducted by the resubmission also demonstrated that the model was sensitive to the ratio of peginterferon to HC/HU. The resubmission did not present a base case ratio, and it was unclear how these analyses were conducted. The model was not designed to easily explore changing the ratio of peginterferon to HC/HU, and the model appears to be moderately sensitive to this assumption. The PBAC previously noted the range of 16-39% peginterferon use from the clinical trials to be reasonable (para 7.13, ruxolitinib, PSD, November 2019 PBAC meeting), however noting this may have changed since 2019 (para 5.3).
	3. The PSCR argued that the 5-year follow up data from MAJIC demonstrated a trend towards a substantial benefit in PFS (HR 0.64, 95% CI: 0.35, 1.14; p=0.13) and OS
	(HR 0.72, 95% CI: 0.35, 1.48; p=0.38) in favour of ruxolitinib. In addition, the PSCR argued that significant improvements in clinically relevant endpoints including complete haematological response (p=0.02), duration of response (p<0.01), EFS (p=0.04) and a reduction in the risk of thromboembolic events (p=0.05) all favoured ruxolitinib. As such, the PSCR stated that the totality of the evidence presented supported the therapeutic claim of improvement in PFS and OS in patients with PV treated with ruxolitinib.
	4. The ESC considered that it is likely patients do benefit from ruxolitinib treatment (para 6.54), however the economic model was based on endpoints where statistical significance was not demonstrated. The ESC considered that extrapolation based on initial differences in PFS and OS at 5 years, that were not statistically significant, led to differences in health outcomes that were compounded over time and drove the economic model results (Figure 7 and Table 14). The ESC noted the removal of differences in PFS increased the ICER from $55,000 to < $75,000 to $155,000 to < $255,000 per QALY gained. The ESC noted that the model was also driven by an assumed difference in pre-progression utilities that was uncertain and favoured ruxolitinib (para 6.72). The ESC noted that when the mean utility value for ruxolitinib (0.821) was applied in both arms the ICER increased from $55,000 to < $75,000 per QALY gained to $75,000 to < $95,000 (+| |%). Overall, the ESC considered the modelled benefits to be highly uncertain due to the lack of clinical data to support the claimed benefits the model was based upon. The ESC considered that it would be informative for the PBAC for the benefits observed in the trial to be compared with the modelled benefits (i.e. the model outputs). The ESC noted this could potentially be supported by comparing the trial based cost-per-responder (noting that this was the primary outcome of the trials) with the result from the economic model.
	5. The pre-PBAC response proposed a revised base case that:
* Assumed pre-progression survival for ruxolitinib is between that modelled from MAJIC and an assumption of no pre-progression survival benefits for ruxolitinib;
* Changed the rate of AML to be between that of MAJIC and Alvarez-Larrán et al. (2022); and
* Reduced the EMP from $| | to $| | for across all strengths.

The pre-PBAC response stated that these changes resulted in a revised ICER of $55,000 to < $75,000 per QALY gained.

* 1. The pre-PBAC response also provided a cost-per-responder analysis (Table 17) based on patients remaining in response at 5 years.

Table 17: Economic evaluation: cost-per-responder analysis - pre-PBAC response

|  |  |  |  |
| --- | --- | --- | --- |
|  | Cost | Response | ICER |
| Ruxolitinib | BAT | Incr. | Ruxolitinib | BAT | Incr.  |
| Overall response (CR or PR) at 5 years a | $|| | $52,251 | $|| | 88% | 41% | 47% | $||||1/overall response |

Source: Table 3 of the pre-PBAC response

a Assumes a 5-year time horizon, including all costs with discounting, rate of AML set to MAJIC (i.e. trial based)

*The redacted values correspond to the following ranges:*

*1 $45,000 to < $55,000*

* 1. The PBAC noted previous recommendations it had made using an incremental cost-per-responder analysis, as outlined in Table 18.

Table 18: Examples of cost-per-responder analyses previously considered by the PBAC

|  |  |
| --- | --- |
| Drug & condition (PBAC meeting) | Cost-per-responder |
| Ravulizumab for neuromyelitis optica spectrum disorders (NMOSD) (November 2024) | The cost-per-relapse avoided was around $115,000 to < $135,000 per 26 weeks. The PBAC noted this was very high a |
| Osilodrostat for Cushing’s Syndrome (September 2024) | The cost-per-responder of [redacted as per PSD] over a period of 26 weeks |
| Bevacizumab for relapsed or refractory glioblastoma (May 2019) | The cost-per-responder (ORR) was [redacted as per PSD] |
| Brentuximab vedotin for refractory or relapsed CD30 positive cutaneous T-cell lymphomas (CTCL) (Nov 2018) | The cost-per-responder (ORR) was $45,000 - $75,000 and the cost per additional year without progression was $15,000 - $45,000 |
| Vorinostat for refractory or relapsed cutaneous T-cell lymphoma (CTCL) March 2017 | Cost-per-responder was [redacted as per PSD] |
| Clostridium botulinum type A toxin haemagglutinin complex (Dysport®) for focal spasticity of the upper limb following a stroke, to also include spasticity following acute events other than stroke (March 2019) | Cost-per-responder: less than $15,000 |
| Denosumab giant cell tumour of bone (November 2013) | Incremental cost-per-responder of less than $15,000 |
| Etanercept severe chronic plaque psoriasis in patients >1 8 years (March 2012) | Incremental cost-per-PASI 75 response: less than $15,000 |
| Tiotropium severe asthma in children and adolescents aged 6-17 years who have not achieved adequate asthma control (November 2018)  | Incremental cost-per-symptomatic exacerbation avoided: less than $15,000 |

Source: Constructed from PSDs

a The PBAC noted the cost-per-response was very high in the context of previous recommendations, but considered it was adequately supported given the substantial and potentially irreversible impact of NMOSD relapses on patient quality of life, and the impact on families and carers (paragraph 7.10, ravulizumab PSD, November 2024 PBAC Meeting).

* 1. The PBAC noted that the pre-PBAC response cost-per-responder analysis was based on the proportion of patients who maintained a CR or PR at 5 years and that the result was informed by a small number of patients. The PBAC considered that the use of duration of response data at 3 years would be more reliable due to the larger sample size (para 6.20). In addition, the PBAC considered that the cost should be restricted to drug costs. The PBAC noted that the cost-per-responder at 3 years was estimated to be $75,000 to < $95,000 (Table 19). The PBAC noted that many of the previous cost-per-responder analyses had been for time-limited therapies, with response assessed at 26 weeks or one year. For comparison with previous PBAC decisions, this is equivalent to approximately $| | per overall response over 26 weeks if it is assumed that the costs are accrued uniformly.

Table 19: Revised economic evaluation: cost-per-responder analysis

|  |  |  |  |
| --- | --- | --- | --- |
|  | Cost | Response | ICER |
| Ruxolitinib | BAT | Incr. | Ruxolitinib | BAT | Incr.  |
| Overall response (CR or PR) at 3 years a | $||| b | $13,344 c | $|| | 91% | 55% | 36% | $||||1/overall response |

Source: Compiled for the PBAC Meeting

a Based on duration of response data at 3 years from the MAJIC trial.

b Cost/patient/year in the ruxolitinib model (Table 20) $| | \*3

c Cost/patient/year in the BAT model (Table 20) $4,448\*3

*The redacted values correspond to the following ranges:*

*1 $75,000 to < $95,000*

***Ruxolitinib cost/patient/year***

* 1. The per patient cost of ruxolitinib alone as used in the RESPONSE-2 trial, economic model and financial estimates are presented in Table 20. The pre-PBAC response offered a reduced EMP of $| | for PV across all strengths.

**Table 20: 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** |
| --- | --- | --- | --- | --- | --- | --- |
| Mean daily dose  | 10 mg BD a | 22.6 mg d | NR | NR | IFN-alfa 6.42 mgHC/HU 2,328 mgBulsulfan 1 mg h | NR |
| Mean duration | NR | 11.35 years e | NR g | NR | 10.58 years e | NR |
| Cost/patient/month | $| | $　|　f | $　|　b | NR | $371i | $184j |
| Cost/patient/year  | $|c,l | $　|　 | $||c, l | NR | $4,448 | $2,213k |
| Cost/patient/month pre-PBAC response | $|m | $　|　n | $||m | NR | $371i | $184j |
| Cost/patient/year pre-PBAC response | $|o | $　|　p | $　|　o | NR | $4,448 | $2,213k |

Source: Compiled during the evaluation using MAJIC trial data from Harrison et al, 2023; Attachment 3 Economic model, Table 4.17, p206 of the resubmission; Table 4.9, p201 of the resubmission; Section 4 workbook provided by sponsor.

Abbreviations: AUC, area under the curve; BAT, best available therapy; BD, twice daily; DPMQ, dispensed price for maximum quantity, HC/HU, hydroxycarbamide/hydroxyurea; IFN, interferon; mg, milligram; NR, not reported; TTD, time-to treatment discontinuation

a. As reported in the MAJIC trial

b Calculated based on ruxolitinib DMPQ ($| |) and number of scripts per year (13.04) divided by 12

c. Calculated based on footnote ‘b’ multiplied by 12

d Mean dose from RESPONSE-2

e Calculated using AUC method for Time and TTD on ruxolitinib

f. Cost per 28-day cycle applied in the economic model of $| | multiplied by number of cycles per year (13.0446) then divided by 12

g The resubmission indicated a variable persistence rate ranging from 100% in Year 1 to 93.60% in Year 6; however, it was unclear how this was applied in the model

h reflects doses given for each medication if prescribed, does not account for proportion of each that were prescribed in MAJIC

i. Cost per 28-day cycle applied in the economic model of $| | multiplied by number of cycles per year (13.0446) then divided by 12

j. Calculated based on footnote “k” divided by 12

k Calculated based on the weighted average of the DMPQ and estimated scripts per as provided in the resubmission for HC/HU (63%), peginterferon α-2a (30%), and busulfan (7%)

l/ Minor discrepancies may be due to rounding

m Calculated based on the pre-PBAC response ruxolitinib DMPQ ($| |) and number of scripts per year (13.04) divided by 12

n Cost per 28-day cycle applied in the economic model based on pre-PBAC price ($| |) multiplied by number of cycles per year (13.0446) then divided by 12

o Calculated based on footnote ‘m’ multiplied by 12

p Calculated based on footnote 'n’ multiplied by 12

* 1. While the per patient costs of ruxolitinib were similar across the trial, model and financial estimates, the costs of BAT varied between the model and the financial estimates. This is likely due to the approach used in the submission to estimate script offsets for BAT, which replied on outputs from the economic model (para 6.94).

***Estimated PBS usage & financial implications***

* 1. This resubmission was not considered by DUSC.
	2. The resubmission used a mixed prevalence-incidence approach to estimate the financial implications associated with the proposed listing of ruxolitinib. The financial model estimated the number of patients with PV that are resistant or intolerant to HC/HU likely to receive ruxolitinib based on the data from the AIHW Cancer Database, proportion likely to be resistant or intolerant to HC/HU and uptake rates. The approach applied in the resubmission modelled incident and prevalent patients together, applying the same assumptions (e.g. uptake rate, response to treatment) to both populations, which may not be reasonable.
	3. Although the source of the prevalence data was updated using the AIHW cancer data in the resubmission in response to PBAC’s concerns relating to applicability to the Australian population (para 6.77, ruxolitinib, PSD, November 2019 PBAC meeting), this data differed from that extracted during the evaluation which reported lower rates The ESC considered the resubmissions inputs were overestimated (see Table 21).
	4. The resubmission adjusted the uptake rate for prevalent patients in year 1 in response to DUSC’s advice that it was too low (20%) in the previous submission (para 6.82, ruxolitinib, PSD, November 2019 PBAC meeting). The resubmission applied uptake rates to patients not yet commenced, rather than cumulative uptake rates as per the previous submission.
	5. A summary of the key inputs in the financial analysis is presented in Table 21.

**Table 21: Key inputs for financial estimates**

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Value applied and source** | **Comment** |
| Incidence rate of PV | 1.33/100,000: calculated using AIHW cancer data 2020 | This source was reasonable, however the method described in the resubmission did not match the numbers presented by the resubmission. Evaluator-extracted AIHW data based on the age-standardised rate of the 2001 Australian Standard Population reported an average incidence rate of 1.19 per 100,000 and an average prevalence rate of 8.2 per 100,000. The ESC noted the corrected evaluator-extracted incidence and prevalence rates and advised that the resubmission inputs for these parameters were overestimated.  |
| Prevalence rate of PV | 10.2/100,000: calculated using AIHW cancer data 2020 |
| Proportion of patients R/I to HC/HU | 22.5%: Resubmission’s assumptions based on estimated number of grandfathered patients | This was higher than rates available from the literature which reported 10 to 20% (Barosi et al, 2015; Pastor-Galán et al, 2020; Parasuraman et al, 2016, MAJIC trial). However, this was within the range (20-30%) estimated by the Australian PV Advisory Board (based on three Australian consultant haematologists). The ESC recalled that in November 2019 the DUSC had considered the proportion of patients intolerant or resistant to HC/HU (24%) was overestimated. Noting the rates available from the literature the ESC considered the proportion remained overestimated. |
| Uptake rate | ||||% in Year 1, ||||% in Year 2 and ||||% from Year 3 onwards | This was uncertain. The uptake rate in year 1 was increased from the previous submission in line with DUSC’s advice. In subsequent years the resubmission applied uptake rates to patients not yet commenced, rather than cumulative uptake rates as per the previous submission. The uptake rate was similarly applied to both the prevalent and incident patients based on the approach applied by the resubmission.  |
| Variable persistence rate | Ranging from 100% in Year 1 to 93.60% in Year 6 sourced from the economic model | The resubmission described that this rate was applied to account for the proportion of patients who do not achieve a response within the first 12 months of treatment and the number of patients who lose their response while receiving continuing treatment over time.  |
| Proportion of patients electing treatment  | ||||%  | There was no justification for the application of this rate in the resubmission. The ESC noted an uptake rate is already included in the methodology described above and advised this parameter should be justified by the sponsor or removed.  |
| Number of BAT treatment cycles (scripts) that would be offset | 9.70 scripts per year: Based on incremental treatment difference and cost of BAT (from patient distribution in MAJIC trial) estimated from the economic model | This approach relied on the outputs of the economic model which increased uncertainty. The estimates produced relied on the BAT distribution in MAJIC trial which may not be fully reflective of the split in clinical practice. |
| Number of venesections offset and cost | 1.01 per patient per year: Based on outputs of economic model and $83.10 (100% benefit): MBS item 13757 | The approach relied on output from the economic model. However, the estimate was likely reasonable as those in the ruxolitinib arm of the MAJIC and RESPONSE trials reported lower number of venesections compared to those treated with BAT. |

Source: Compiled during the evaluation based on information sources for Section 4.1, 4.2 and 4.3 of the resubmission, and from the Section 4 workbook provided by the sponsor.

Abbreviations: AIHW, Australian Institute of Health and Welfare; BAT, best available therapy; DUSC, Drug Utilisation Sub Committee; HC/HU, hydroxycarbamide/hydroxyurea; R/I, resistant to or intolerant of; PBS, Pharmaceutical Benefits Scheme; MBS, Medicare Benefits Schedule.

* 1. Table 22 summarises the estimated net cost of ruxolitinib to the Australian health budget.

**Table 22: Estimated use and financial implications**

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| --- | --- | --- | --- | --- | --- | --- |
| **Estimated extent of use** |
| Number of initiating patients treated | 　|　1 | 　|　1 | 　|　1 | 　|　1 | 　|　1 | 　|　1 |
| Number of scripts dispensed a | 　|　2 | 　|　3 | 　|　3 | 　|　 | 　|　3 | 　|　3 |
| **Estimated financial implications of ruxolitinib** |
| Cost to PBS/RPBS less copayments | 　|　4 | 　|　4 | 　|　4 | 　|　5 | 　|　5 | 　|　5 |
| **Estimated financial implications for BAT** |
| Cost to PBS/RPBS less copayments | 　|　6 | 　|　6 | 　|　6 | 　|　6 | 　|　6 | 　|　6 |
| **Net financial implications** |
| Net cost to PBS/RPBS | 　|　4 | 　|　4 | 　|　4 | 　|　4 | 　|　5 | 　|　5 |
| Net cost to MBS | 　|　6 | 　|　6 | 　|　6 | 　|　6 | 　|　6 | 　|　6 |
| Net cost to health budget | **|**4 | **|**4 | **|**4 | **|**4 | **|**5 | **|**5 |
| **Previous submission November 2019** |
| Total commencing patients | 　|　2 | 　|　1 | 　|　1 | 　|　1 | 　|　1 | 　|　1 |
| Total ruxolitinib (PV) scripts | 　|　3 | 　|　3 | 　|　7 | 　|　7 | 　|　7 | 　|　7 |
| Net cost to PBS/RPBS | 　|　4 | 　|　4 | 　|　4 | 　|　4 | 　|　4 | 　|　4 |

Source: Table 4.2 and 4.7, pp196 and 199 of the submission, March 2025 Section 4 workbook and Table 4.2.of the November 2019 evaluation

Abbreviations: MBS, Medicare Benefits Schedule; PBS, Pharmaceutical benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

a The script numbers presented in Table 4.14, p204 of the submission do not align with the script numbers calculated in the Section 4 of the workbook. For example, <500 scripts were estimated in Year 1 for 5mg (initiating) in the resubmission; however, according to the workbook, <500 scripts were estimated. The figures presented in Table 19 are based on the Section 4 workbook.

*The redacted values correspond to the following ranges:*

*1 < 500*

*2 500 to < 5,000*

*3 5,000 to < 10,000*

*4 $0 to < $10 million*

*5 $10 million to < $20 million*

*6 net cost saving*

*7 10,000 to < 20,000*

* 1. The total cost to the PBS/Repatriation Pharmaceutical Benefits Scheme (RPBS) of listing ruxolitinib was estimated to be $10 million to < $20 million in Year 6, and a total of $50 million to < $60 million in the first 6 years of listing.
	2. The estimated use and financial estimates presented in the resubmission were considered uncertain for the following reasons:
* The resubmission’s approach of modelling both incident and prevalent populations together was inappropriate. It had structural implications for the model that impacted the prescription numbers and the resulting financial estimates. Further, the application of the same assumptions (e.g. uptake rate, response to treatment) to both populations may not be reasonable. The PSCR acknowledged that the incident and prevalent populations should be modelled separately.
* The incidence and prevalence rates used were based on outdated data, likely leading to overestimation. They also appear to be higher than rates reported by Baade et al., 2019[[10]](#footnote-11) which reported a lower incidence rate (0.9 per 100,000) using the same data source. The ESC considered the resubmissions inputs for incidence and prevalence rates were overestimated (see Table 21).
* The ESC recalled that in November 2019 the DUSC had considered the proportion of patients intolerant or resistant to HC/HU (24%) was overestimated (para 6.82, ruxolitinib, PSD, November 2019 PBAC meeting). Noting the rates available from the literature outlined in Table 21 (10% to 20%) the ESC considered that the proportion remained overestimated.
* The rationale for the inclusion of a parameter titled ‘the proportion of patients electing treatment (| |%)’ in addition to the application of an uptake rate was unclear. The ESC advised that this parameter should be justified or removed by the sponsor.
	1. The financial estimates were most sensitive to the assumptions on the proportion of patients resistant or intolerant to HC/HU and prevalence and incidence rates. The impact on the financial estimates for PBS/RPBS were:
* Proportion of patients resistant or intolerant to HC/HU was 22.5% in the base case: Decreasing this proportion to 10% reduces the financial estimates to the PBS/RPBS across the 6 years of listing from $50 million to < $60 million to $20 million to < $30 million (-52%).
* Incidence and prevalence rates were 1.33 and 10.2 per 100,000 in the base case: Using the incidence and prevalence rates of 1.19 and 8.2 per 100,000 from AIHW [2024] data extracted during the evaluation reduces the financial estimates to $40 million to < $50 million (-17%).
	1. The pre-PBAC response provided revised financial estimates which:
* Amended the estimates for the incidence and prevalence rates of PV to be consistent with the evaluator extracted rates of 1.19 and 8.2 per 100,000 respectively;
* Reduced the proportion of patients who are resistant or intolerant to HC/HU from 22.5% to 20%;
* Removed the parameter titled ‘the proportion of patients electing treatment (| |%)’;
* Modelled incident and prevalent patients separately;
* Increased the rate of uptake in the incident population to 100% (previously ranged from | |% to | |%). The rate of uptake in the prevalent population remained at the original range of | |% to | |% presented in the resubmission; and
* Included the price reduction proposed in the pre-PBAC response (see paragraph 3.2).

The pre-PBAC response noted that the resulting net cost to the PBS/RPBS of listing ruxolitinib was estimated to be $40 million to < $50 million over 6 years.

***Quality Use of Medicines***

* 1. At the November 2019 meeting for the previous submission, the PBAC had noted that provision for ruxolitinib dosing to be tapered down in the event of treatment discontinuation had not been provided in the requested restriction (para 6.83, ruxolitinib, PSD, November 2019 PBAC meeting). The resubmission acknowledged that treatment with ruxolitinib involves a dose titration period where patients’ dose is increased in 5 mg BD increments to reach a maximum dose. During this period patients are required to be closely monitored by the treating physician. The sponsor has proposed to work collaboratively with healthcare practitioners to ensure that ruxolitinib is used appropriately. Additionally, advice received from the Australian PV Advisory Board indicated that there was agreement amongst the clinical experts there was no need for the proposed restriction to mandate dose tapering when patients discontinue treatment (Australian PV Advisory Board Minutes; Attachment 5).

***Financial Management – Risk Sharing Arrangements***

* 1. No risk-sharing arrangements were proposed in the resubmission.

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

1. **PBAC Outcome**
	1. The PBAC recommended the listing of listing for ruxolitinib for the treatment of adult patients with polycythaemia vera (PV) who are resistant to or intolerant of hydroxycarbamide (hydroxyurea) (HC/HU). The PBAC noted the resubmission provided updated data which reported significant improvements in major event-free survival (EFS), reductions in venesections and improvements in duration of response that were clinically relevant. As such, the PBAC is satisfied that ruxolitinib provides, for some patients, a significant improvement in efficacy over best available therapy (BAT). The PBAC noted that while no statistically significant differences in progression-free survival (PFS) or overall survival (OS) were reported in the clinical trial evidence, differences in these outcomes were assumed in the economic model and maintained throughout the 20 year time horizon. Despite revisions to the economic model inputs in the pre-PBAC response the PBAC considered the resulting incremental cost-effectiveness ratio (ICER) remained uncertain. The PBAC noted a cost-per-overall response was determined and advised that, together with the economic model, it adequately supported the cost-effectiveness of ruxolitinib at the price proposed in the pre-PBAC response.
	2. The PBAC noted the input from individuals, health care professionals and organisations that which described the burden of frequent hospital visits, along with how the symptoms and complications of PV significantly affect patients’ quality of life (QoL). The PBAC noted the input described the benefits of patients responding to ruxolitinib in terms of reducing complication rates and improving symptom burden. The PBAC noted the input also outlined the issues associated with the treatment options currently available (including supply concerns with peginterferon α-2a) and acknowledged the need for alternative therapies.
	3. The PBAC noted the clinician in the sponsor hearing raised the possibility of ruxolitinib being used second line for patients treated with peginterferon α-2a as first-line therapy (para 6.1). The PBAC noted that use as second-line therapy for patients commenced on peginterferon α-2a first-line was not consistent with the clinical trial evidence or the TGA indication. As such, the PBAC considered that the clinical place for ruxolitinib should be restricted to patients who were resistant to or intolerant of HC/HU.
	4. With regard to the requested listing and restriction, the PBAC advised that:
* A General Schedule Authority Required (Written/HPOS upload) listing with 5 repeats was appropriate for the initial treatment restriction. A General Schedule Authority Required (Telephone/Online PBS Authorities system) listing with 5 repeats was appropriate for the balance of initial treatment – up to 48 weeks, first continuing and subsequent continuing treatment restrictions.
* The inclusion of a population criteria stating a patient must be at least 18 years of age was appropriate.
* The resubmission’s proposed amendment limiting the number of times a patient may access ruxolitinib under the initial treatment restriction, in order to prevent patients from re-trialling treatment, was appropriate.
* Consistent with the MAJIC trial, demonstration of response to treatment within 12 months was appropriate. As such, a balance of initial treatment restriction was appropriate to provide the remaining 6 months of initial treatment. The PBAC advised the continuing treatment restriction should be separated into a first continuing treatment restriction and a subsequent continuing treatment restriction to allow response to treatment to be assessed in the first continuing treatment restriction.
* A prescribing instruction in the first continuing treatment restriction defining the response to treatment was appropriate. The PBAC considered a response to treatment should include as least one of the following: haematocrit (HCT) < 45% without venesection for 3 months; platelet count ≤ 400 x 10^9/L; or absence of palpable splenomegaly.
* Inclusion of grandfathering patients was appropriate. However, a separate grandfathering restriction was not required as the initial treatment restriction would not exclude these patients from receiving subsidised therapy if they are resistant, intolerant or have a contraindication to HC/HU.
	1. The PBAC considered the nominated comparator of BAT was appropriate.
	2. The PBAC recalled that in November 2019 it had considered that the evidence from the key trial (MAJIC) did not clearly support a benefit in terms of clinically relevant outcomes or overall survival (paragraph 7.1, ruxolitinib, PSD, November 2019 PBAC meeting). The PBAC noted that since the November 2019 consideration the results of the MAJIC trial are now published and a clinical study report (CSR) was available (para 6.7). In addition, the resubmission presented updated data with a longer follow-up period of up to five years for the MAJIC trial and the supporting RESPONSE and RESPONSE-2 trials.
	3. The PBAC noted that a statistically significant higher proportion of patients treated with ruxolitinib achieved a complete response (CR) at 12 months compared to BAT (43% vs 26%; OR 2.10; 95% CI: 1.12, 3.94) in the MAJIC trial. The PBAC noted that while almost all patients achieved either a CR or partial response (PR) across 5 years (proportion achieving an overall response [CR+PR]: 97% vs 98% for ruxolitinib and BAT arms respectively), there was a trend towards a higher proportion of patients achieving a CR in the ruxolitinib arm (OR 1.48; 95% CI 0.81, 2.73). In addition, the PBAC noted that patients treated with ruxolitinib in MAJIC achieved a significantly more durable CR or PR compared to those who had received BAT (HR 0.14, 95% CI: 0.07, 0.30). The PBAC also noted the incidence of thromboembolic and haemorrhagic events were numerically higher in patients treated with BAT across trials, with MAJIC showing an improvement in favour of ruxolitinib in thromboembolic event-free survival (TEFS) (HR 0.57, 95% CI: 0.32, 0.99; p=0.05) and a significant difference in major EFS (HR 0.60, 95% CI: 0.37, 0.97; p=0.04). Furthermore, the PBAC noted that the MAJIC trial reported a reduction in the number of venesections in the ruxolitinib arm compared to those receiving BAT (30 vs 49) with similar results reported in the RESPONSE and RESPONSE-2 trials.
	4. The PBAC noted that while PFS rates at 3- and 5-years were numerically higher in the ruxolitinib arm compared to BAT (84% vs 75% and 76% vs 64% respectively), median PFS was not reached and no significant differences were observed between treatment arms based on the results across all three trials. The PBAC also noted that no statistically significant OS benefit was reported (HR 0.73, 95% CI: 0.36, 1.50). The PBAC acknowledged the limitations of the clinical evidence and considered that, although uncertain, the claim of superior effectiveness was supported by the significant improvements in major EFS, the reductions in venesections and the improvements in duration of response reported for ruxolitinib compared to BAT.
	5. The PBAC noted that there were no significant differences in Grade ≥3 AEs, SAEs and deaths reported by the 5-year follow up in the MAJIC trial. However, differences in AE profiles were evident between ruxolitinib and BAT in the MAJIC, RESPONSE and RESPONSE-2 trials. Overall, the PBAC advised that ruxolitinib has a different safety profile compared to BAT, and considered that this is likely to be manageable.
	6. The resubmission presented an updated economic model that was based on progression in acute myeloid leukaemia (AML)/myelodysplastic syndrome (MDS), myelofibrosis (MF) or death. The PBAC agreed with the ESC that the updated model structure appeared reasonable, however the extrapolation of PFS and OS in the economic model was highly uncertain. The PBAC noted that each progression event in the economic model (i.e. AML/MDS, MF and death) was modelled separately with an assumption of treatment benefit favouring ruxolitinib despite the MAJIC trial reporting no significant difference in PFS between treatment arms. The PBAC noted that when the difference in PFS was removed the ICER increased from $55,000 to
	< $75,000 per quality adjusted life year (QALY) gained to $155,000 to < $255,000 per QALY gained. The economic model also maintained a difference in pre-progression OS despite no statistically significant benefit reported in the MAJIC trial. The PBAC considered that initial differences in PFS and OS that were assumed by the economic model, led to differences in QALY gains that were highly uncertain and were maintained throughout the 20 year time horizon. In addition, the PBAC noted the model was also driven by an assumed difference in pre-progression utilities that it considered were uncertain and favoured ruxolitinib (para 6.72). Overall, the PBAC agreed with the ESC that the modelled benefits were highly uncertain due to the lack of clinical data to support the claimed benefits of PFS and OS that the model was based on.
	7. The PBAC noted that the pre-PBAC response provided a revised base case that made amendments to pre-progression survival for ruxolitinib and the rate of AML (para 6.84). The PBAC also noted that the revised base case incorporated the price reduction proposed in the pre-PBAC response (para 3.2). The pre-PBAC response stated that these changes returned an ICER of $55,000 to < $75,000 per QALY gained. The PBAC considered that as the model remained based on endpoints where statistical significance has not been demonstrated the revised base case ICER remained uncertain. The PBAC considered that the uncertainty in the ICER was unlikely to be adequately resolved with further revisions to the model inputs. The PBAC acknowledged the unmet need for alternative treatments, the impact of PV on patients quality of life and the importance of improvements in duration of response in this condition. In this overall context, the PBAC considered that a cost-per-responder analysis would provide additional support for the assessment of cost-effectiveness in this instance.
	8. The PBAC noted the pre-PBAC response provided a cost-per-responder analysis which returned a cost-per-overall response of $| | over 5 years. The PBAC noted the analysis was based on the proportion of patients who maintained a CR or PR at 5 years from the MAJIC trial. The pre-PBAC response stated that all modelled costs were included and discounted at 5% per annum. The PBAC noted that data at year 5 was informed by a small number of patients and advised that use of duration of response data at 3 years would be more robust (para 6.20). In addition, the PBAC considered that the cost should be restricted to drug costs. The PBAC noted that the incremental cost-per-overall responder over 3 years was estimated to be $75,000 to < $95,00. The PBAC noted that many of the previous cost-per-responder analyses had been for time-limited therapies, with response assessed at 26 weeks or one year. For comparisons with previous PBAC decisions, the Committee noted that this was equivalent to approximately $| | per overall response over 26 weeks if it is assumed that the costs are accrued uniformly. The PBAC considered that this was within the range of the cost-per-responder analyses previously accepted by the Committee. The PBAC considered that ruxolitinib was cost-effective at the price proposed in the pre-PBAC response based on: (i) the expected benefits associated with treatment as outlined in paragraph 7.7; (ii) comparison with previously accepted cost-per-responder analyses (Table 18); and (iii) the results of the economic model, noting the uncertainties outlined in paragraph 7.11.
	9. The PBAC noted that the pre-PBAC response provided revised financial estimates which amended the incident and prevalent rates to be consistent with the evaluator extracted rates, reduced the proportion of patients resistant or intolerant to HC/HU from 22.5% to 20% and removed the parameter titled ‘the proportion of patients electing treatment.’ The PBAC considered these amendments were appropriate. The PBAC noted the revised estimates modelled incident and prevalent patients separately. Uptake in prevalent patients was unchanged from the resubmission, and estimated to be 100% in incident patients. The PBAC advised that uptake was more likely to be 80% in the incident patient population and recommended it be revised accordingly. The PBAC advised that, with the revision of the uptake rate in the incident patient population, the financial estimates provided in the pre-PBAC response were appropriate.
	10. The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for ruxolitinib:
	11. The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over BAT, as while statistically significant benefits were reported for other clinically relevant outcomes, they were not reported for PFS or OS.
	12. The treatment is not expected to address a high and urgent unmet clinical need, as while alternative treatments are required, treatment options are currently available for PV.
	13. It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
	14. The PBAC advised that this submission would not meet the criteria for an Independent Review as it received a positive PBAC recommendation.

**Outcome:**

Recommended

1. **Recommended listing**
	1. Add new item:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of****Rpts** | **Available brands** |
| RUXOLITINIB |
| ruxolitinib 5mg tablet, 56 | NEW | 1 | 56 | 5 | JAKAVI |
| ruxolitinib 10 mg tablet, 56 | NEW | 1 | 56 | 5 | JAKAVI |
| ruxolitinib 15mg tablet, 56 | NEW | 1 | 56 | 5 | JAKAVI |
| ruxolitinib 20mg tablet, 56 | NEW | 1 | 56 | 5 | JAKAVI |
|  |
| **Restriction Summary [new1] / Treatment of Concept: [new1A]** |
| **Concept ID** (for internal Dept. use) | **Category / Program:** [x]  GENERAL - General Schedule (Code GE)  |
| **Prescriber type:** [x] Medical Practitioners  |
| **Restriction type:** [x] Authority Required (in writing only via post/HPOS upload)  |
| Prescribing rule level |  | **Administrative Advice:**No increase in the maximum quantity or number of units may be authorised. |
|  | **Administrative Advice:**No increase in the maximum number of repeats may be authorised. |
|  | **Administrative Advice:**Special Pricing Arrangements apply. |
|  | **Condition:** Polycythemia vera |
|  | **Indication:** Polycythemia vera |
|  | **Treatment Phase:** Initial treatment |
|  | **Clinical criteria:**  |
|  | Patient must be resistant to hydroxycarbamide (hydroxyurea); |
|  | **OR** |
|  | Patient must have an intolerance to hydroxycarbamide (hydroxyurea) of a severity necessitating permanent treatment withdrawal; |
|  | **OR** |
|  | Patient must have developed a clinically important adverse event/contraindication to hydroxycarbamide (hydroxyurea) as defined in the TGA-approved Product Information necessitating permanent treatment withdrawal; |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must not have previously received PBS-subsidised treatment with this drug for this condition. |
|  | **AND** |
|  | **Population criteria:** |
|  | Patient must be at least 18 years of age. |
|  | **Prescribing Instructions:** Hydroxycarbamide (hydroxyurea) resistance is defined as a minimum of 12 consecutive weeks treatment at a dose of at least 1.5 grams/day or at the maximum tolerated that still results in one of the following: (i) the need to reduce haematocrit levels to below 45% through phlebotomy; or(ii) a platelet count greater than 400 x 10^9/L and a white blood cell count greater than 10 x 10^9/L  |
|  | **Prescribing Instructions:** If applicable, details of prior systemic treatment with hydroxycarbamide (hydroxyurea) that caused either (i) an intolerance (ii) an adverse event as listed in the TGA approved Product Information or (iii) a contraindication as listed in the TGA approved Product Information necessitating permanent treatment withdrawal should be documented in the patient’s medical records. |
|  | **Prescribing Instructions:** If the application is submitted through HPOS form upload or mail, it must include:(i) details of the proposed prescription; and(ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
|  | **Administrative advice:**Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.auApplications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hposOr mailed to:Services AustraliaComplex DrugsReply Paid 9826HOBART TAS 7001 |
|  |
| **Restriction Summary [new2] / Treatment of Concept: [new2A]** |
| **Concept ID** (for internal Dept. use) | **Category / Program:** [x]  GENERAL - General Schedule (Code GE)  |
| **Prescriber type:** [x] Medical Practitioners  |
| **Restriction type:** [x]  Authority Required (telephone/online PBS Authorities system) |
| **Condition:** Polycythemia vera |
|  | **Indication:** Polycythemia vera |
|  | **Treatment Phase:** Balance of Initial treatment – up to 48 weeks |
|  | **Clinical criteria:**  |
|  | Patient must have received this drug as their most recent course of PBS-subsidised treatment for this condition. |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must not receive more than 24 weeks of treatment under this restriction |
|  | **AND** |
|  | **Population criteria:** |
|  | Patient must be at least 18 years of age. |
|  | **Prescribing Instruction:**If a patient fails to demonstrate a response to treatment with this drug under this restriction they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. |
|  | **Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see [www.servicesaustralia.gov.au/HPOS](http://www.servicesaustralia.gov.au/HPOS)) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).  |
|  |
| **Restriction Summary [new3] / Treatment of Concept: [new3A]** |
| **Concept ID** (for internal Dept. use) | **Category / Program:** [x]  GENERAL - General Schedule (Code GE)  |
| **Prescriber type:** [x] Medical Practitioners  |
| **Restriction type:** [x]  Authority Required (telephone/online PBS Authorities system) |
| **Condition:** Polycythemia vera |
|  | **Indication:** Polycythemia vera |
|  | **Treatment Phase:** First continuing treatment |
|  | **Clinical criteria:**  |
|  | Patient must have received this drug as their most recent course of PBS-subsidised treatment for this condition. |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have achieved and maintained a response to treatment with this drug for this condition  |
|  | **Prescribing Instructions:** A response to treatment is defined as:* Maintaining a haematocrit level of less than 45% without relying on phlebotomy and which was measured at least 12 weeks after the most recent phlebotomy procedure (if performed to reduce red blood cell levels); or
* Ability to demonstrate or maintain a normal platelet count of less than or equal to 400 x 10^9/L; or
* The absence of palpable splenomegaly
 |
|  | **Population criteria:** |
|  | Patient must be at least 18 years of age. |
|  | **Prescribing Instructions:** Details (dates, unique identifying number/code, or provider number) of the pathology report confirming the patient has achieved and maintained a response within 48 weeks of treatment initiation; or(b) confirmation that the patient does not have palpable splenomegaly must be documented in the patient’s medical records. |
|  | **Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see [www.servicesaustralia.gov.au/HPOS](http://www.servicesaustralia.gov.au/HPOS)) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).  |
|  |  |
| **Restriction Summary [new4] / Treatment of Concept: [new4A]** |
| **Concept ID** (for internal Dept. use) | **Category / Program:** [x]  GENERAL - General Schedule (Code GE)  |
| **Prescriber type:** [x] Medical Practitioners  |
| **Restriction type:** [x]  Authority Required (telephone/online PBS Authorities system) |
| **Condition:** Polycythemia vera |
|  | **Indication:** Polycythemia vera |
|  | **Treatment Phase:** Subsequent continuing treatment |
|  | **Clinical criteria:**  |
|  | Patient must have previously received PBS-subsidised treatment with this drug for this condition under the First continuing treatment restriction |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have achieved and maintained a response to treatment with this drug for this condition  |
|  | **Population criteria:** |
|  | Patient must be at least 18 years of age. |
|  | **Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see [www.servicesaustralia.gov.au/HPOS](http://www.servicesaustralia.gov.au/HPOS)) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).  |

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

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 welcomes the PBAC’s decision to recommend ruxolitinib for adults with PV who are resistant to or intolerant of HC/HU. Novartis would like to take this opportunity to thank the PV community and healthcare professionals who supported the resubmission. Novartis looks forward to working with the Department of Health to secure a PBS listing for ruxolitinib in adults with PV who are resistant to or intolerant of HC/HU at the earliest opportunity.

1. Complete response defined as meeting all i) HCT <45% without venesection for 3 months, ii) platelet count ≤400 x 109/L, iii) white blood cell (WBC) count ≤10 × 109/L and iv) normal spleen size on imaging [↑](#footnote-ref-2)
2. High risk patients: those who have experienced thromboses or who are aged over 60 years. [↑](#footnote-ref-3)
3. Abu-Zeinah G, Krichevsky S, Cruz T, Hoberman G, Jaber D, Savage N, Sosner C, Ritchie EK, Scandura JM and Silver RT, 2021. Interferon-alpha for treating polycythemia vera yields improved myelofibrosis-free and overall survival. *Leukemia*, *35*(9), pp.2592-2601.

Kiladjian JJ, Klade C, Georgiev P, Krochmalczyk D, Gercheva-Kyuchukova L, Egyed M, Dulicek P, Illes A, Pylypenko H, Sivcheva L and Mayer J, 2022. Long-term outcomes of polycythemia vera patients treated with ropeginterferon Alfa-2b. *Leukemia*, 36(5), pp.1408-1411.

Gisslinger H, Klade C, Georgiev P, Krochmalczyk D, Gercheva-Kyuchukova L, Egyed M, Dulicek P, Illes A, Pylypenko H, Sivcheva L and Mayer J, 2023. Event-free survival in patients with polycythemia vera treated with ropeginterferon alfa-2b versus best available treatment. *Leukemia*, *37*(10), pp.2129-2132. [↑](#footnote-ref-4)
4. Harrison CN, Nangalia J, Boucher R, Jackson A, Yap C, O'Sullivan J, Fox S, Ailts I, Dueck AC, Geyer HL, Mesa RA, Dunn WG, Nadezhdin E, Curto-Garcia N, Green A, Wilkins B, Coppell J, Laurie J, Garg M, Ewing J, Knapper S, Crowe J, Chen F, Koutsavlis I, Godfrey A, Arami S, Drummond M, Byrne J, Clark F, Mead-Harvey C, Baxter EJ, McMullin MF and Mead AJ, 2023. Ruxolitinib Versus Best Available Therapy for Polycythemia Vera Intolerant or Resistant to Hydroxycarbamide in a Randomized Trial. J Clin Oncol, *41*(19), pp.3534-3544. [↑](#footnote-ref-5)
5. HCT <45% without phlebotomy (at least 3 months since last phlebotomy); OR platelet count ≤400 x 109/L OR absence of palpable splenomegaly. [↑](#footnote-ref-6)
6. Rocca Mora et al. (2024) ‘Efficacy and safety of ruxolitinib vs best available therapy for polycythemia vera: An updated systematic review and meta-analysis’. APMIS. 132: 775-786. <https://doi.org/10.1111/apm.13472> [↑](#footnote-ref-7)
7. Rocca Mora et al. (2024) ‘Efficacy and safety of ruxolitinib vs best available therapy for polycythemia vera: An updated systematic review and meta-analysis’. APMIS. 132: 775-786. <https://doi.org/10.1111/apm.13472> [↑](#footnote-ref-8)
8. Rocca Mora et al., (2024) ‘Efficacy and safety of ruxolitinib vs best available therapy for polycythemia vera: An updated systematic review and meta-analysis’. APMIS. 132: 775-786. <https://doi.org/10.1111/apm.13472> [↑](#footnote-ref-9)
9. Wang et al., (2023), *Differences in post-polycythaemia vera and post-essential thrombocythemia myelofibrosis vs primary myelofibrosis in the fibrotic stage: a retrospective, real-world study conducted in China.* [*10.1097/01.HS9.0000975592.83600.cf*](https://doi.org/10.1097/01.HS9.0000975592.83600.cf) [↑](#footnote-ref-10)
10. Baade et al., (2019), 'Changing incidence of myeloproliferative neoplasms in Australia, 2003-2014', Am J Hematol, 94, 4. [↑](#footnote-ref-11)