5.15 MOMELOTINIB, Tablet 100 mg (as dihydrochloride monohydrate), Tablet 150 mg (as dihydrochloride monohydrate), Tablet 200 mg (as dihydrochloride monohydrate), Omjjara®, GLAXOSMITHKLINE AUSTRALIA PTY LTD.

1 Purpose of submission

1.1 The Category 1 submission requested a General Schedule, Authority Required (Telephone/Online) listing for initial treatment and an Authority Required (STREAMLINED) listing for continuing treatment with momelotinib for intermediate or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis in patients with moderate to severe anaemia and who are Janus kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.

1.2 Listing was requested on the basis of a cost-minimisation approach versus ruxolitinib.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Patients with intermediate or high-risk myelofibrosis (primary, post-polycythaemia vera or post-essential thrombocythaemia), who have moderate to severe anaemia and who are naïve to JAK inhibitor treatments or have been treated with ruxolitinib.
Intervention	Momelotinib 200 mg once daily
Comparator	JAK inhibitor naïve: ruxolitinib twice daily [a] JAK inhibitor experienced: best available therapy, represented by ruxolitinib twice daily [a]
Outcomes	Spleen volume, total symptom score, transfusion independence [b], transfusion dependence [c], rate of red blood cell transfusions, safety
Clinical claim	JAK inhibitor naïve: Momelotinib is non-inferior in terms of efficacy and overall safety compared to ruxolitinib in JAK inhibitor naïve patients with moderate to severe anaemia; providing clinically meaningful improvements in anaemia-related outcomes. JAK inhibitor experienced: Momelotinib has an overall positive benefit/risk balance for the treatment of myelofibrosis in JAK inhibitor experienced patients with moderate to severe anaemia.

Source: Table 1, p22 of the submission.
Abbreviations: JAK, Janus kinase
[a] The recommended starting dose of ruxolitinib (from TGA Product Information) is based on platelet count: 5 mg twice daily ($50x10^9$/L to less than $100x10^9$/L), 15 mg twice daily ($100x10^9$/L to $200x10^9$/L), 20 mg twice daily (more than $200x10^9$/L). The dose is then titrated based on efficacy and safety, up to a maximum of 25 mg twice daily.
[b] Transfusion independence defined in the SIMPLIFY trials as the proportion of patients with no RBC transfusion and no haemoglobin level < 80 g/L in the 12 weeks prior to Week 24.
[c] Transfusion dependence defined in the SIMPLIFY trials as the proportion of patients with at least 4 units of RBC transfusion or haemoglobin < 80 g/L in the prior 8 weeks ending with Week 24.

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. During the evaluation, the sponsor provided the outcome of TGA's first round evaluation (consolidated section 31 request for information). The clinical evaluation report attachment was not included, however the S.31 request stated there were no clinical questions for Module 5 of the dossier.

2.2 An application for marketing authorisation was accepted by the TGA in May 2024, to be reviewed under the Comparable Overseas Regulator Approach A Pathway, based on the EMA-approved indication of:

> The treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.

2.3 A preliminary Delegate's decision was provided on [redacted]. The Delegate proposed to approve registration of momelotinib for the following indication:

> OMJJARA is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.

2.4 Momelotinib is currently approved for use in the UK, US, Japan and all European Economic Area countries. The US FDA approved momelotinib in September 2023 for the treatment of intermediate or high-risk myelofibrosis, including primary myelofibrosis or secondary myelofibrosis, in adults with anaemia. The EMA and the UK Medicines and Healthcare products Regulatory Agency (MHRA) approved momelotinib in January 2024, for the same indication as proposed for the current submission (see above). The approved indication in Japan (June 2024) is for the treatment of myelofibrosis in both newly diagnosed and previously treated patients.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
MOMELOTINIB					
Initial treatment					
Momelotinib 200 mg tablet, 30	$[redacted] published price $TBD effective price	1	30	0	Omjjara
Momelotinib 150 mg tablet, 30		1	30	0	Omjjara
Momelotinib 100 mg tablet, 30		1	30	0	Omjjara
Continuing treatment					
Momelotinib 200 mg tablet, 30	$[redacted] published price $TBD effective price	1	30	5	Omjjara
Momelotinib 150 mg tablet, 30		1	30	5	Omjjara

Momelotinib 100 mg tablet, 30		1	30	5	Omjjara
Category / Program: General Schedule					
Prescriber type: Medical Practitioners					
Restriction type: Authority Required (telephone/online PBS Authorities system)					
INITIAL TREATMENT: HIGH AND INTERMEDIATE-2 RISK MYELOFIBROSIS					
Severity: High risk and intermediate-2 risk					
Condition: Myelofibrosis					
Indication: High risk and intermediate-2 risk myelofibrosis					
Treatment Phase: Initial					
Clinical criteria:					
The condition must be either: (i) primary myelofibrosis, (ii) post-polycythaemia vera myelofibrosis, (iii) post-essential thrombocythaemia myelofibrosis, confirmed through a bone marrow biopsy report.					
AND					
Clinical criteria:					
Patient must have a haemoglobin level of less than 100 g per L prior to commencing treatment with this drug for this condition.					
AND					
Clinical criteria:					
The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition.					
INITIAL TREATMENT: INTERMEDIATE-1 RISK MYELOFIBROSIS					
Severity: Intermediate-1 risk					
Condition: Myelofibrosis					
Indication: Intermediate-1 risk myelofibrosis					
Treatment Phase: Initial					
Clinical criteria:					
The condition must be either: (i) primary myelofibrosis, (ii) post-polycythaemia vera myelofibrosis, (iii) post-essential thrombocythaemia myelofibrosis, confirmed through a bone marrow biopsy report.					
AND					
Clinical criteria:					
Patient must have severe disease-related symptoms that are resistant, refractory or intolerant to available therapy prior to commencing treatment with this drug for this condition.					
AND					
Clinical criteria:					
Patient must have a haemoglobin level of less than 100 g per L prior to commencing treatment with this drug for this condition.					
AND					
Clinical criteria:					
The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition.					
Prescribing Instructions: Details of: (a) the bone marrow biopsy report confirming diagnosis of myelofibrosis (date, unique identifying number/code or provider number); and (b) a classification of risk of myelofibrosis according to either the IPSS, DIPSS, or the Age-Adjusted DIPSS, must be documented in the patient's medical records.					
Administrative Advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) or the Age-Adjusted DIPSS (aaDIPSS). Special Pricing Arrangements apply.					
Category / Program: General Schedule					
Prescriber type: Medical Practitioners					
Restriction type: Authority Required (STREAMLINED)					

CONTINUING TREATMENT: HIGH AND INTERMEDIATE-2 RISK MYELOFIBROSIS
Severity: High risk and intermediate-2 risk
Condition: Myelofibrosis
Indication: High risk and intermediate-2 risk myelofibrosis
Treatment Phase: Continuing
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition.
CONTINUING TREATMENT: INTERMEDIATE-1 RISK MYELOFIBROSIS
Severity: Intermediate-1 risk
Condition: Myelofibrosis
Indication: Intermediate-1 risk myelofibrosis
Treatment Phase: Continuing
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition.
Administrative Advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) or the Age-Adjusted DIPSS (aaDIPSS). Special Pricing Arrangements apply.

TBD, to be determined

3.1 The submission noted that ruxolitinib is subject to a special pricing arrangement and that the effective price of ruxolitinib is unknown. Prices included in the submission were based on the cost-minimised price of momelotinib to the published prices of ruxolitinib. A special pricing arrangement was requested for momelotinib.

3.2 The submission claimed that the proposed anaemia clinical criterion (Hgb < 100 g/L) is in line with the proposed TGA indication, Common Terminology Criteria for Adverse Events grading scale, clinical prognostic criteria in myelofibrosis, Australian guidelines, and prior PBAC considerations. While the proposed TGA indication specifies moderate to severe anaemia, it does not nominate a haemoglobin threshold.

3.3 The proposed restriction is also narrower than the proposed TGA indication, with the restriction additionally specifying the patient's disease risk classification (intermediate-1, intermediate-2 or high).

3.4 The proposed restriction is generally consistent with the restriction for ruxolitinib, except for the following:

- Inclusion of a clinical criterion specifying haemoglobin level < 100 g/L prior to commencing treatment with momelotinib.

- Inclusion of the criterion 'The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition'. The ESC considered this criterion needs to be flowed onto the listing of ruxolitinib.
- The restriction level for initial treatment was amended from Authority Required (Written) to Authority Required (Telephone/Online); and for continuing treatment amended from Authority Required (Telephone/Online) to Authority Required (Streamlined). The ESC considered this was reasonable.

3.5 The submission stated that the amendments to the authority levels compared to current ruxolitinib restrictions were made as the market has matured and stabilised since ruxolitinib's PBS listing, and clinicians are now familiar with JAK inhibitor prescribing. The changes were not expected to influence the frequency of prescribing as documentation will still be required to demonstrate patient eligibility for initial prescribing. The submission assumed that, if recommended, these amendments would also apply to ruxolitinib. The ESC considered these flow-on changes to the ruxolitinib PBS listing were appropriate.

3.6 Consistent with the current ruxolitinib restriction, the proposed restriction for intermediate-1 risk myelofibrosis includes the clinical criterion that patients must have severe disease-related symptoms that are resistant, refractory or intolerant to available therapy prior to commencing treatment with this drug for this condition. It is unclear how existing ruxolitinib-treated patients would be assessed against this criterion, as disease-related symptoms may be controlled with ruxolitinib treatment despite dose reductions or interruptions, although concomitant RBC transfusions may be required to manage treatment-or disease-related anaemia. The ESC considered the restriction for JAK inhibitor experienced patients should include an option to switch treatment without needing to satisfy the disease-related symptoms requirement, as the reason for switching may be to avoid adverse events, or to reduce transfusion dependence. This allowance for treatment switching without experiencing disease-related symptoms should flow on to ruxolitinib. Wording proposed in the Pre-Sub-Committee Response (PSCR) and pre-PBAC response was as follows: "Patient must have, either: (i) severe disease-related symptoms that are resistant, refractory or intolerant to available therapy, (ii) intolerance to prior treatment with a JAK inhibitor for this condition".

3.7 The submission claimed that no tests or examinations beyond those already administered in routine clinical practice are required to determine patient eligibility or continuing eligibility for momelotinib.

3.8 The submission stated that a patient access program for momelotinib is anticipated to commence at the [redacted], following TGA approval. A separate grandfather restriction was not proposed, as the initial treatment restriction would allow patients who fulfilled the PBS eligibility criteria before commencing non-PBS subsidised treatment to transition to PBS-subsidised treatment. The submission did not specify the anticipated number of patients to be treated under this program.

3.9 The submission noted that should the PBAC consider that further clinical evidence is required to support reimbursement in the JAK inhibitor experienced population, an alternative PBS listing in JAK inhibitor naïve patients only was proposed. On balance, the ESC considered the available evidence supported sequential use of momelotinib in JAK inhibitor experienced patients.

3.10 The ESC considered treatment with ruxolitinib and momelotinib should be limited to once in a lifetime for each medicine for this disease to prevent multiple or repeated switching, which is not supported by the available evidence.

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

4 Population and disease

4.1 Myelofibrosis is a rare bone marrow malignancy that primarily affects older adults (median age 67 years). Signs and symptoms of myelofibrosis may include: fatigue, shortness of breath, pain caused by splenomegaly (enlarged spleen), easy bruising or bleeding, night sweats, fever, and bone pain. Patients with myelofibrosis have an increased mortality risk compared to the general population due to increased infection risk, thrombohaemorrhagic events, cardiac or pulmonary failure and leukaemic transformation.

4.2 Myelofibrosis may arise spontaneously as primary myelofibrosis, or secondary to polycythaemia vera (PV) or essential thrombocythaemia (ET), however the histopathology, clinical manifestations and treatment are similar regardless of the origin. Patients are stratified into low, intermediate-1, intermediate-2, and high risk based on patient characteristics and clinical features, including constitutional symptoms (weight loss, fever, drenching night sweats), haemoglobin levels, leukocytes and circulating blasts.

4.3 Anaemia is a key feature of myelofibrosis, with approximately 40% of patients having haemoglobin (Hgb) levels < 100 g/L, and nearly a quarter dependent on red blood cell (RBC) transfusions at diagnosis (Tefferi, 2012). Disease-related anaemia may also be exacerbated by treatment with existing JAK inhibitors (ruxolitinib; Naymagon, 2017). The proportion of patients with anaemia increases with disease progression, with even mild anaemia significantly affecting survival. In addition to predicting poor survival, anaemia and transfusion dependence are inversely associated with quality of life (Naymagon, 2017).

4.4 Momelotinib is a selective JAK1 and JAK2 inhibitor that also inhibits ACVR1. Inhibition of JAK1 and JAK2 signalling reduces constitutional symptoms and splenomegaly through decreased inflammatory cytokine signalling, haematopoietic stem cell proliferation and red blood cell sequestration. Inhibition of ACVR1 results in decreased hepcidin expression, the regulator of iron metabolism that is elevated in patients with myelofibrosis, which restores iron homeostasis and increased serum iron availability for erythropoiesis. As a result, haemoglobin levels may improve and the need for RBC transfusions may be reduced.

4.5 The submission positioned momelotinib as an alternative treatment option to existing treatments (allogeneic stem cell transplant (if eligible), ruxolitinib, busulfan, hydroxyurea and peginterferon alfa-2a) for JAK inhibitor naive patients with Hgb < 100 g/L with either: intermediate-1 risk myelofibrosis who have severe disease-related symptoms that are resistant, refractory or intolerant to available therapy; or intermediate-2 or high risk myelofibrosis (regardless of symptoms). Concomitant treatment includes anaemia supportive measures (RBC transfusions with or without iron chelation therapy) as required.

4.6 Momelotinib was positioned as an alternative to ruxolitinib (or sub-optimal dosing of ruxolitinib) for patients who have been previously treated with a JAK inhibitor, with Hgb < 100 g/L. Co-administered therapies for these patients may include palliative care, hydroxyurea, peginterferon alfa-2A, busulfan, other chemotherapies, radiation therapy, or splenectomy, with or without anaemia supportive measures as required (RBC transfusions with or without iron chelation therapy).

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

5 Comparator

5.1 The submission nominated ruxolitinib as the main comparator for JAK inhibitor naïve patients; and best available therapy, represented by ruxolitinib, for JAK inhibitor experienced patients. The main arguments provided in support of this nomination were: ruxolitinib is a selective JAK1 and JAK2 inhibitor, and is the current standard of care for intermediate-2 and high-risk myelofibrosis patients, and intermediate-1 risk patients who have severe disease-related symptoms that are resistant, refractory, or intolerant to available therapy. The evaluation and the ESC considered ruxolitinib was an appropriate comparator for both populations.

5.2 The submission noted that overseas clinical guidelines for myelofibrosis-associated anaemia recommend a number of therapies to treat anaemia, such as erythropoietin stimulating agents, danazol, and immunomodulatory drugs (e.g. thalidomide, lenalidomide), but these agents are not TGA-approved nor PBS listed for this indication in Australia. In addition, the European Medicines Agency (EMA) assessment report for momelotinib (November 2023) noted that the efficacy, durability and tolerability of these therapies are limited. In Australia, patients who develop anaemia while being treated with ruxolitinib would remain on treatment with either dose modification and/or concomitant red blood cell transfusions. In the majority of patients who develop anaemia or thrombocytopenia, dose-adjusted ruxolitinib remains the preferred standard of care therapy because of rapid symptom rebound on dose interruption or treatment discontinuation of ruxolitinib (Ho, 2017).

5.3 Other JAK inhibitor therapies available overseas include pacritinib (FDA approved in 2022 for patients with myelofibrosis and severe thrombocytopenia) and fedratinib (FDA and EMA approved for intermediate-2 or high risk primary or secondary myelofibrosis for both JAK inhibitor naïve patients and those previously treated with

ruxolitinib). Fedratinib is currently under TGA consideration (submitted February 2024) for treatment of disease-related splenomegaly. The submission argued that fedratinib was not a near-market comparator as, like ruxolitinib, it does not address myelofibrosis-associated anaemia and has been shown to exacerbate anaemia in the pivotal clinical trials and is not expected to be used in patients with moderate to severe anaemia. Fedratinib is a similar therapy to the nominated comparator ruxolitinib and was therefore a potential near market comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician described how anaemia impacts the quality of life of patients with myelofibrosis and how patients on ruxolitinib often develop worsening anaemia eventually leading to red blood cell transfusions. Momelotinib was considered to have equivalent symptom control and better anaemia outcomes than ruxolitinib providing a valuable alternative for patients with severe anaemia due to myelofibrosis or who develop severe anaemia whilst on ruxolitinib. This was considered an important additional treatment option to improve quality of life for patients with anaemia and avoid long-term complications from red blood cell transfusions such as iron overload. The PBAC considered that the hearing was informative as it provided a succinct and clear clinical perspective on the importance of an alternative treatment option for treating this disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (16), health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described the impact of anaemia on quality of life and the impacts this has on family, work and social life, with exhaustion and fatigue limiting patient's ability to function. Momelotinib would provide an alternative treatment to ruxolitinib with less anaemia, leading to improved outcomes for patients, increasing energy levels and the period of tolerance to a JAK inhibitor. In addition to these benefits, consumer organisations highlighted the potential for reduced transfusion requirements, and providing an effective option for patients who become refractory to ruxolitinib.

Clinical trials

6.3 The submission was based on one head-to-head randomised trial comparing momelotinib to ruxolitinib in JAK inhibitor naïve patients (SIMPLIFY-1) and one head-to-head randomised trial comparing momelotinib to best available therapy (including ruxolitinib) in JAK inhibitor experienced patients (SIMPLIFY-2). In line with the proposed PBS listing, the submission presented subgroup analyses of efficacy and

safety data from the SIMPLIFY-1 and SIMPLIFY-2 trials for patients with baseline Hgb < 100 g/L, along with the complementary subgroup.

6.4 A randomised trial comparing momelotinib to danazol in JAK inhibitor experienced patients was included as supplementary evidence (MOMENTUM). Danazol is not TGA-indicated nor PBS-listed for myelofibrosis in Australia and was not identified as a comparator in the submission.

6.5 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
SIMPLIFY-1	A phase 3, randomized, double-blind active-controlled study evaluating momelotinib versus ruxolitinib in subjects with primary myelofibrosis or post-polycythemia vera or post-essential thrombocythemia myelofibrosis.	Clinical Study Report March 2021
	Mesa RA, Kiladjian J-J, Catalano JV, et al. Simplify-1: A phase III randomized trial of momelotinib versus ruxolitinib in Janus kinase inhibitor–naïve patients with myelofibrosis.	Journal of Clinical Oncology 2017; 35(34): 3844–3850
	Gupta V, Oh S, Devos T, et al. (2024). Momelotinib vs. ruxolitinib in myelofibrosis patient subgroups by baseline hemoglobin levels in the SIMPLIFY-1 trial.	Leukemia and Lymphoma 2024; 65(7): 965-977
	Oh ST, Verstovsek S, Gupta V, et al. (2024). Changes in bone marrow fibrosis during momelotinib or ruxolitinib therapy do not correlate with efficacy outcomes in patients with myelofibrosis.	E J Haem 2024; 5(1): 105–116.
	Mesa R, Oh S, Gerds A, et al. (2022). Momelotinib reduces transfusion requirements in patients with myelofibrosis.	Leukemia & Lymphoma 2022; 63(7),1718-1722
SIMPLIFY-2	A phase 3, randomized study to evaluate the efficacy of momelotinib versus best available therapy in anemic or thrombocytopenic subjects with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis who were treated with ruxolitinib.	Clinical Study Report January 2021
	Harrison CN, Vannucchi AM, Platzbecker U, et al. Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY 2): A randomised, open-label, phase 3 trial.	The Lancet Haematology 2018; 5(2): e73–e81.
MOMENTUM	A randomized, double-blind, phase 3 study to evaluate the activity of momelotinib versus danazol in symptomatic, anemic subjects with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis who were previously treated with JAK inhibitor therapy.	Clinical Study Report. 15 August 2022

Source: Table 17, pp50-55 of the submission.
Note: Abstract-only publications were excluded from this list if full-text trial publications available.

6.6 The key features of the key randomised trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes
Momelotinib versus ruxolitinib in JAK inhibitor naïve patients					
SIMPLIFY-1	432	Multicentre, randomised, double-blind, active controlled non-inferiority trial; 24 week duration with open-label extension[a]	Low	Adults with primary, post-PV or post-ET myelofibrosis with high or intermediate-2 risk, or intermediate-1 risk with symptomatic splenomegaly, hepatomegaly, anaemia (Hgb <100 g/L) and/or unresponsiveness to available therapy, not previously treated with a JAK inhibitor	Splenic response rate; TSS response rate; RBC transfusion independence/ dependence; RBC transfusion rate; change in haemoglobin and platelets; quality of life; overall survival; safety
Momelotinib versus best available therapy (including ruxolitinib) in JAK inhibitor experienced patients					
SIMPLIFY-2	156	Multi-centre, randomised, open label, active-controlled, superiority trial; 24 week duration with open-label extension[a]	High	Adults with primary, post-PV or post-ET myelofibrosis with high, intermediate-2 or intermediate-1 risk with symptomatic splenomegaly or hepatomegaly who had a suboptimal response[b] or haematological toxicity[c] after receiving ruxolitinib	Splenic response rate; TSS response rate; RBC transfusion independence/ dependence; RBC transfusion rate; change in haemoglobin and platelets; quality of life; overall survival; safety

Source: Table 18, p56 of the submission.

Abbreviations: ET, essential thrombocythaemia; Hgb, haemoglobin; JAK, Janus kinase; PV, polycythaemia vera; RBC, red blood cell; TSS, total symptom score

[a] The clinical study reports for SIMPLIFY-1 and SIMPLIFY-2 state that the sponsor terminated the extension study prior to subjects completing the 5 years of follow-up.

[b] Requirement for red blood cell transfusion while on ruxolitinib treatment

[c] Required a dose reduction of ruxolitinib to <20 mg twice daily and also had grade ≥3 anaemia, thrombocytopenia or haematoma) after receiving ruxolitinib

6.7 The SIMPLIFY-1 trial had an overall low risk of bias.

6.8 In the SIMPLIFY-1 trial, more patients in the momelotinib arm (12.6%) compared to the ruxolitinib arm (4.1%) discontinued the trial during the double-blind phase, primarily due to adverse events (4.7% vs 1.8%).

6.9 Less than half the patients in the SIMPLIFY-1 ITT population had moderate to severe anaemia at baseline (Hgb < 100 g/L; 40% momelotinib; 43% ruxolitinib arm). These patients were slightly older and a greater proportion were at high risk (approximately 70%) compared to the overall ITT population (approximately 45%).

6.10 There were differences between momelotinib and ruxolitinib treatment arms in the SIMPLIFY-1 post hoc subgroup with Hgb < 100 g/L at baseline: with more patients with transfusion dependence (57% versus 46%, respectively) and fewer patients with transfusion independence (29% versus 44%); and fewer patients with high risk disease (67% versus 75%) in the momelotinib treatment arm. The submission argued that the difference between treatments for baseline transfusion dependence/independence rates was expected to favour the ruxolitinib treatment arm. This was reasonable. Despite these baseline differences, at week 24 there were fewer momelotinib-treated patients classed as transfusion dependent, and more patients as transfusion independent, compared to ruxolitinib treated patients.

6.11 The SIMPLIFY-2 trial had an overall high risk of bias. The open-label trial design has the potential to introduce bias as knowledge of treatment assignment may affect disease management decisions, and assessment of outcomes (e.g. self-reported total symptom score, adverse events).

6.12 SIMPLIFY-2 was designed without consideration for the use of ruxolitinib in the best available therapy arm, based on the treatment effect of the best available therapy arm of the COMFORT ruxolitinib phase III trial, which excluded the use of JAK inhibitors from the comparator arm. At the time of SIMPLIFY-2 protocol development, comparator treatments were anticipated to comprise hydroxyurea, steroids or erythropoietin stimulating agents. Subsequently, however, ruxolitinib became standard of care and 88.5% of patients in the best available therapy arm received ruxolitinib. While this resulted in a comparator arm that may better reflect current Australian clinical practice, it had a significant impact on the results of the trial.

6.13 In addition, the SIMPLIFY-2 trial had no washout period between prior ruxolitinib use and the start of the randomised phase of the trial, which confounded the primary endpoint analysis. Patients entering the study had either suboptimal responses or haematological toxicity with ruxolitinib treatment but were not necessarily ruxolitinib-refractory (lack or loss of splenic response). Patients receiving ruxolitinib at the start of the study were required to maintain their existing dose throughout the screening period up until baseline, therefore maintaining therapeutic ruxolitinib doses or switching immediately to momelotinib at baseline.

6.14 More than half the patients in the SIMPLIFY-2 ITT population had moderate to severe anaemia at baseline (Hgb < 100 g/L; 63.5% momelotinib; 75.0% best available therapy). These patients were generally similar to the ITT patients, but larger proportions of patients were at intermediate-2 and high risk, and a greater proportion were transfusion dependent at baseline (73% in the Hgb < 100 g/L subgroup versus 54% in the ITT population).

6.15 There were differences between momelotinib and best supportive care treatment arms in the SIMPLIFY-2 Hgb < 100 g/L subgroup for proportion of males (79% versus 46% respectively), and rates of transfusion dependence (78.8% versus 64.1%). Similar to the SIMPLIFY-1 trial, the submission argued that the difference in transfusion dependence and independence rates favoured the comparator arm. This was reasonable. Despite these baseline differences, at week 24 there were fewer momelotinib-treated patients classed as transfusion dependent, and more patients as transfusion independent, compared to patients treated with best available therapy.

Comparative effectiveness

SIMPLIFY-1: JAK-inhibitor naïve patients

6.16 Table 4 below summarises the results for the primary and key secondary endpoint of SIMPLIFY-1, splenic response rate and total symptom score (TSS) at Week 24 for the ITT population and post hoc Hgb < 100 g/L and Hgb ≥ 100 g/L subgroups.

Table 4: SIMPLIFY-1: Splenic response rate and TSS response rate at Week 24 (ITT population and post hoc Hgb < 100 g/L and Hgb ≥ 100 g/L subgroups)

Outcome	ITT population		Hgb <100 g/L		Hgb ≥100 g/L	
	Momelotinib N=215	Ruxolitinib N=217	Momelotinib N=86	Ruxolitinib N=94	Momelotinib N=129	Ruxolitinib N=122
Primary outcome - splenic response rate at Week 24						
Responder, n (%)	57 (26.5)	64 (29.5)	27 (31.4)	31 (33.0)	30 (23.3)	33 (27.0)
Non-inferior difference (95% CI), p-value [a]	**0.09 (0.02, 0.16), p = 0.014**		**0.13 (0.01, 0.24), p = 0.029**		0.06 (-0.03, 0.15), p = 0.18	
Superior difference (95% CI), p-value	-0.03 (-0.12, 0.05), p = 0.45		0.00 (-0.14, 0.14), p = 0.98		-0.05 (-0.16, 0.06), p = 0.38	
Secondary outcome - total symptom score response rate at Week 24						
Responder, n (%)	60 (28.4)	89 (42.2)	21 (25.0)	33 (35.5)	39 (30.7)	55 (47.0)
Non-inferior difference (95% CI), p-value [b]	0.0 (-0.08, 0.08), p = 0.98		-0.12 (-0.26, 0.02), p = 0.11		-0.02 (-0.12, 0.08), p = 0.70	

Source: Table 33, p81; Table 34, p83 of the submission

Abbreviations: CI, confidence interval; Hgb, haemoglobin; ITT, intent to treat; TSS, total symptom score

Note: Splenic response rate was defined as the proportion of patients who achieved spleen volume reduction of ≥ 35% from baseline at the Week 24 assessment as measured by MRI or CT scans. TSS response rate was defined as the proportion of patients who achieved a ≥ 50% reduction in TSS at Week 24 versus baseline as measured by the modified MPN-SAF TSS v2.0 diary.

Bold indicates statistically significant difference

[a] Non-inferiority for splenic response was calculated as momelotinib response rate – 0.6 × ruxolitinib response rate. If the lower bound of the 2-sided confidence 95% interval (calculated based on stratum-adjusted Cochran-Mantel-Haenszel proportion) was greater than 0, the momelotinib group would be non-inferior to the ruxolitinib group for this outcome.

[b] Non-inferiority for TSS was calculated as momelotinib response rate – 0.67 × ruxolitinib response rate. If the lower bound of the 2-sided confidence 95% interval (calculated based on stratum-adjusted Cochran-Mantel-Haenszel proportion) was greater than 0, the momelotinib group would be non-inferior to the ruxolitinib group for this outcome.

6.17 For the primary outcome, similar proportions of patients in the ITT population achieved splenic response at Week 24 in the momelotinib and ruxolitinib treatment groups. Momelotinib met the primary endpoint of non-inferior splenic response rate over ruxolitinib (the lower bound of the 95% confidence interval was greater than 0, where the non-inferiority difference was calculated as the momelotinib splenic response rate – 0.6 × the ruxolitinib splenic response rate). The EMA assessment report for momelotinib (November 2023) noted that the selected non-inferiority margins seemed to be arbitrarily chosen, without clinical judgement on the importance of loss of efficacy of momelotinib compared to the reference of ruxolitinib. However, the EMA noted that the margins correspond to the lower bound of the 95% confidence intervals, and the chance of the true difference being worse than that suggested by this bound is generally considered acceptably small. A test for superiority did not demonstrate statistically significant differences between treatments.

6.18 Results for the post hoc subgroup with Hgb < 100 g/L were generally consistent with results for the ITT population, with nominally statistically significant non-inferiority achieved for momelotinib compared to ruxolitinib in splenic response rate at Week 24. In the post hoc Hgb ≥ 100 g/L subgroup fewer momelotinib-treated patients (23.3%) achieved splenic response compared to ruxolitinib-treated patients (27.0%), which did not meet the requirements for nominal non-inferiority.

6.19 In the ITT population, fewer patients in the momelotinib arm (28.4%) had a TSS reduction of ≥ 50% from baseline, compared to the ruxolitinib group (42.2%). Because

the lower bound of the 2-sided 95% CI was not greater than 0, non-inferiority of the momelotinib group to the ruxolitinib group was not met. Results for the post hoc Hgb subgroups were consistent with results in the ITT population, failing to demonstrate non-inferiority of momelotinib to ruxolitinib.

6.20 The submission noted a number of factors related to the study design that were considered to have influenced this result. The pre-specified non-inferiority margin of 0.67 was not rigorously derived from the COMFORT-I ruxolitinib trial, and failed to consider that the COMFORT-I study used a 6-item scale that did not include the fatigue/tiredness item included in the TSS measure in SIMPLIFY-1 (typically the most severe and prevalent item). In addition, patients with missing data at Week 24, or who discontinued prior to the end of the double-blind period, were counted as non-responders. Differential discontinuation rates from the treatment arms (14.7% in the momelotinib arm versus 5.7% in the ruxolitinib arm) meant that more momelotinib-treated patients were counted as non-responders. Patient enrolment was not stratified by TSS and more patients in the momelotinib arm (5.7%) had baseline TSS scores > 45 compared to the ruxolitinib arm (1.4%), which would require a large absolute improvement in order to achieve the prespecified ≥ 50% reduction in TSS scores. Subsequently, a post hoc longitudinal mixed-effects model (MMRM) was conducted to provide a method to estimate the TSS treatment effect as a continuous variable and incorporate longitudinal data for each 4-week period leading up to each study visit (rather than only the final 4 weeks to Week 24). Results of the post hoc analysis are summarised in Table 5.

Table 5: SIMPLIFY-1: Model based TSS change from baseline (ITT population, post hoc Hgb <100 g/L subgroup)

ITT population	ITT population		Hgb <100 g/L population	
	Momelotinib N=215	Ruxolitinib N=217	Momelotinib N=86	Ruxolitinib N=94
LS Mean overall change from baseline to Week 12 (SE)	-5.40 (0.9)	-6.28 (0.9)	-4.62 (7.9)	-5.75 (7.6)
LS Mean difference from ruxolitinib to Week 12 (95% CI)	0.88 (-0.51, 2.27)		1.03 (-1.14, 3.20)	
LS Mean overall change from baseline to Week 24 (SE)	-5.87 (0.9)	-7.11 (0.9)	-4.73 (8.8)	-6.55 (8.1)
LS Mean difference from ruxolitinib to Week 24 (95% CI)	1.24 (-0.40, 2.88)		2.05 (-0.36, 4.47)	

Source: Table 35, p85 of the submission

Abbreviations: CI, confidence intervals; ITT, intent-to-treat, LS, least squares; SE, standard error; TSS, total symptom scores.

Note that the post-hoc model based TSS change from baseline was provided for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.21 The submission noted that while greater reductions in TSS scores from baseline were observed at Week 12 and Week 24 for the ruxolitinib treatment group compared to the momelotinib group, the differences (0.88 and 1.24 points, respectively) were considered small for a 70 point scale. Results of the post hoc MMRM analysis for the Hgb < 100 g/L subgroup were consistent with the ITT population, with similar mean differences between treatment arms (1.03 and 2.05 points, respectively).

6.22 The submission additionally presented results of a post hoc analysis comparing median changes from baseline to Week 24 in the individual symptom scores, which

showed similar levels of improvement for all symptoms regardless of treatment assignment.

6.23 Results for the key secondary transfusion-related efficacy endpoints for SIMPLIFY-1, for the ITT population and for the post hoc Hgb < 100 g/L and Hgb ≥ 100 g/L subgroups are summarised in Table 6.

Table 6: SIMPLIFY-1: Secondary transfusion related endpoints (ITT population and post hoc Hgb < 100 g/L and Hgb ≥ 100 g/L subgroups)

Population	Momelotinib	Ruxolitinib	Difference
ITT population	**N = 215**	**N = 217**	
Transfusion independent, n (%) [a]	143 (66.5)	107 (49.3)	0.18 (0.09, 0.26)
Transfusion dependent, n (%) [b]	65 (30.2)	87 (40.1)	-0.10 (-0.19, -0.02)
RBC transfusions, mean units/patient month (95% CI) [c]	0.4 (0.3, 0.6)	1.5 (1.1, 2.2)	0.28 (0.19, 0.43)
Hgb <100 g/L subgroup	**N = 86**	**N = 94**	
Transfusion independent, n (%) [a]	40 (46.5)	25 (26.6)	0.23 (0.09, 0.37)
Transfusion dependent, n (%) [b]	41 (47.7)	58 (61.7)	-0.16 (-0.31, -0.02)
RBC transfusions, mean units/patient month (95% CI) [c]	0.8 (0.6, 1.2)	1.8 (1.3, 2.5)	0.46 (0.30, 0.70)
Hgb ≥100 g/L subgroup	**N = 129**	**N = 122**	
Transfusion independent, n (%) [a]	103 (79.8)	81 (66.4)	0.11 (-0.00, 0.22)
Transfusion dependent, n (%) [b]	24 (18.6)	29 (23.8)	-0.03 (-0.14, 0.07)
RBC transfusions, mean units/patient month (95% CI) [c]	0.1 (0.0, 0.3)	0.7 (0.2, 2.0)	0.15 (0.07, 0.36)

Source: Table 36, p88; Table 37, p89; Table 38, p90 of the submission

Abbreviations: CI, confidence interval; ITT, intent to treat; RBC, red blood cell; TSS, total symptom score

[a] Transfusion independence defined as the proportion of patients with no RBC transfusion and no haemoglobin level < 80 g/L in the 12 weeks prior to Week 24; difference between treatment arms is superior proportion difference.

[b] Transfusion dependence defined as the proportion of patients with at least 4 units of RBC transfusion or haemoglobin < 80 g/L in the prior 8 weeks ending with Week 24; difference between treatment arms is superior proportion difference.

[c] Rate of RBC transfusions defined as the average number of RBC units transfused per patient-month during the double-blind phase; difference between treatment arms is rate ratio of RBC transfusions (95% CI, negative binomial model adjusted for strata).

6.24 In the ITT population, a nominally statistically significantly greater proportion of patients in the momelotinib group was transfusion independent at Week 24 compared with the ruxolitinib group. Similarly, momelotinib was associated with a nominally statistically significantly higher transfusion independence rate in patients with Hgb < 100 g/L compared to ruxolitinib (momelotinib 46.5%, ruxolitinib 26.6%), despite a lower proportion of patients in the momelotinib treatment arm being transfusion independent at baseline (29.1% in the momelotinib group versus 43.6% in the ruxolitinib group). As expected, patients in the Hgb ≥ 100 g/L subgroup were more likely to be transfusion independent at both baseline and week 24 compared to the ITT population and Hgb <100 g/L subgroup. A greater proportion of patients in the Hgb ≥ 100 g/L momelotinib group (79.8%) was transfusion independent at Week 24 compared with the ruxolitinib group (66.4%), however the difference between treatment arms was not nominally statistically significant. The submission noted that following crossover to momelotinib at Week 24, the rate of transfusion independence in patients originally randomised to ruxolitinib (n=92) increased from 9.8% at Week 4 after crossover, to 45.7% at Week 12 after crossover.

6.25 A smaller proportion of patients in the momelotinib group of the ITT population was transfusion dependent at Week 24 (30.2%), compared to the ruxolitinib group (40.1%), with the difference nominally statistically significant. Results for the Hgb

< 100 g/L subgroup were consistent with the ITT population, while there was no nominally statistically significant difference noted between treatments for patients in the Hgb ≥ 100 g/L subgroup.

6.26 For the ITT population, the rate of RBC transfusion was nominally statistically significantly lower in the momelotinib group with a transfusion rate ratio of 0.28 (95% CI 0.19, 0.43). The median rate of RBC transfusion was lower in the momelotinib group (0.0, range 0.0 to 9.1 units/month) compared with the ruxolitinib group (0.4, range 0.0 to 8.2 units/month) through Week 24. Results for the Hgb < 100 g/L subgroup were consistent with the ITT population, although the rates of RBC transfusions for both treatment arms were higher in this subgroup than the ITT population (median rate for momelotinib arm 0.4 (range 0.0 to 9.1) units/month; ruxolitinib arm 1.2 (range 0.0 to 8.2) units/month). As expected, rates of RBC transfusion were lower in the Hgb ≥ 100 g/L subgroup, with similar transfusion rates between treatment groups.

6.27 SIMPLIFY-1 included a range of patient-reported outcomes as exploratory endpoints (in the ITT population only), including change from baseline in Short Form 36 (SF-36) scores, EQ-5D Visual Analog Scale, and the Patient Global Impression of Change (a single question to assess the patient's impression of change in myelofibrosis symptoms, with the option of 7 responses ranging from 'very much improved' to 'very much worse'). There were improvements noted in both treatment groups for all measures, with no nominally statistically significant differences noted between groups for most measures. The exception was the Patient Global Impression of Change, with a greater number of ruxolitinib patients indicating an improvement in symptoms at Week 24 (76.5%) compared to momelotinib patients (65.1%).

6.28 Overall survival was estimated in SIMPLIFY-1 based on the safety analysis set for the ITT population. By Week 24, 14 patients (6.5%) in the momelotinib arm and 19 (8.8%) in the ruxolitinib arm had died, with the Kaplan-Meier median survival estimate not reached in either arm. At the final analysis, 61 (28.5%) of patients originally randomised to momelotinib and 66 (30.6%) originally randomised to ruxolitinib had died. Median survival was not reached in the momelotinib arm, with the ruxolitinib arm median survival at 53.1 months (95% CI 48.7 months, not estimated). However, the submission noted that fewer than 7 patients remained at risk when the median was estimated for the ruxolitinib group, thus results should be interpreted with caution. Rank preserving structural failure time models, performed to adjust for treatment switching in the overall survival analysis in the ITT population, did not note any differences between treatment arms in overall survival. Overall survival analyses adjusted for treatment switching were not performed for the Hgb < 100 g/L and Hgb ≥ 100 g/L subgroups, due to the reduced statistical power in these subgroups.

6.29 One-, 2- and 3- year survival rates in the momelotinib group were approximately 93%, 82%, and 71%, respectively (estimated in the submission from a Kaplan-Meier plot of overall survival by treatment in the ITT population from SIMPLIFY-1). The submission noted comparable overall survival rates for ruxolitinib (91%, 80% and 70%) were reported in the pivotal ruxolitinib trials (COMFORT-I and COMFORT-II).

SIMPLIFY-2: JAK-inhibitor experienced patients

6.30 Table 7 below summarises the results for the primary and key secondary endpoint of SIMPLIFY-2, splenic response rate and total symptom score (TSS) at Week 24 for the ITT population and post hoc Hgb < 100 g/L and Hgb ≥ 100 g/L subgroups.

Table 7: SIMPLIFY-2: Splenic response rate and TSS response rate at Week 24 (ITT population and post hoc Hgb < 100 g/L and Hgb ≥ 100 g/L subgroups)

Outcome	ITT population		Hgb <100 g/L		Hgb ≥100 g/L	
	Momelotinib N=104	BAT N=52	Momelotinib N=66	BAT N=39	Momelotinib N=38	BAT N=13
Primary outcome - splenic response rate at Week 24						
Responder, n (%)	7 (6.7)	3 (5.8)	6 (9.1)	2 (5.1)	1 (2.6)	1 (7.7)
Superior difference (95% CI), p-value	0.01 (-0.09, 0.10), p = 0.90		0.03 (-0.09, 0.16), p = 0.59		-0.04 (-0.34, 0.25), p = 0.77	
Secondary outcome - total symptom score response rate at Week 24						
Responder, n (%)	27 (26.2)	3 (5.9)	21 (32.3)	1 (2.6)	6 (15.8)	2 (15.4)
Superior difference (95% CI), p-value	0.20 (0.09, 0.32), p < 0.001		0.30 (0.15, 0.44), p < 0.001		-0.01 (-0.35, 0.34), p = 0.97	

Source: Table 63, p130; Table 64, p133 of the submission

Abbreviations: BAT, best available therapy; CI, confidence interval; Hgb, haemoglobin; ITT, intent to treat; TSS, total symptom score

Note: Splenic response rate was defined as the proportion of patients who achieved spleen volume reduction of ≥ 35% from baseline at the Week 24 assessment as measured by MRI or CT scans. TSS response rate was defined as the proportion of patients who achieved a ≥ 50% reduction in TSS at Week 24 versus baseline as measured by the modified MPN-SAF TSS v2.0 diary.

6.31 For the primary outcome, similar low proportions of patients in the ITT population achieved splenic response at Week 24 in the momelotinib (6.7%) and best available therapy (BAT, 5.8%) treatment groups. The difference in response rates was not statistically significant, thus the primary endpoint of the trial was not met. Results for the post hoc subgroup analysis of splenic response rate at Week 24 for the Hgb < 100 g/L and Hgb ≥ 100 g/L subgroups were consistent with results in the ITT population, with low rates of splenic response observed in either treatment arm, and no statistically significant differences between treatments.

6.32 The submission noted that the design of the SIMPLIFY-2 study may have influenced the outcome for this endpoint in patients in both treatment groups, due to the continuation of active therapy prior to randomisation with no washout period. In the absence of restored splenic volume post-washout, the achievement of an additional 35% splenic volume reduction to meet the response definition, in addition to that already achieved during continuous ruxolitinib therapy, was considered unrealistic. At the time the protocol for this study was written, it was anticipated that most patients in the BAT group would be on other therapeutic agents such as hydroxyurea, immunomodulatory drugs, erythropoiesis-stimulating agents, steroids, or on a subtherapeutic dose of ruxolitinib. Although all patients enrolled in SIMPLIFY-2 had ruxolitinib-related toxicities, changes to dosing guidelines, increased familiarity and clinical experience with ruxolitinib dosing meant most patients in the BAT group (approximately 88%) were maintained on ruxolitinib as the BAT of choice. Thus, while the intent of the study was to demonstrate the superiority of momelotinib to BAT other than ruxolitinib, BAT was ruxolitinib for the majority of patients in that

treatment group. As superiority was not achieved in the primary endpoint of spleen response rate, only nominal significance was reported for subsequent endpoints in the statistical hierarchy.

6.33 For the secondary outcome of TSS response at Week 24 in the ITT population, 26.2% of the momelotinib group had a TSS reduction of 50% or more from baseline compared to 5.9% of the BAT group, a nominally statistically significant difference. Results in the Hgb < 100 g/L subgroup were consistent with the ITT population, demonstrating nominal superiority of momelotinib over BAT. The submission noted that that TSS response rate was at least as high as the overall population in the Hgb < 100 g/L subgroup, whereas a smaller proportion of patients in the BAT arm of this subgroup were responders compared to the ITT population. In the Hgb ≥ 100 g/L subgroup there were no differences in TSS response between treatment arms.

6.34 Results for the key secondary transfusion-related efficacy endpoints for SIMPLIFY-2, for the ITT population and for the post hoc Hgb < 100 g/L and Hgb ≥ 100 g/L subgroups are summarised in Table 8.

Table 8: SIMPLIFY-2: Secondary transfusion related endpoints (ITT population and post hoc Hgb < 100 g/L and Hgb ≥ 100 g/L subgroups)

Population	Momelotinib	BAT	Difference
ITT population	**N = 104**	**N = 52**	
Transfusion independent, n (%) [a]	45 (43.3)	11 (21.2)	0.23 (0.09, 0.37)
Transfusion dependent, n (%) [b]	52 (50.0)	33 (63.5)	-0.13 (-0.29, 0.03)
RBC transfusions, mean units/patient month (95% CI) [c]	1.2 (0.9, 1.6)	1.4 (1.0, 2.1)	0.80 (0.49, 1.31)
Hgb <100 g/L subgroup	**N = 66**	**N = 39**	
Transfusion independent, n (%) [a]	22 (33.3)	5 (12.8)	0.21 (0.05, 0.36)
Transfusion dependent, n (%) [b]	39 (59.1)	28 (71.8)	-0.11 (-0.30, 0.08)
RBC transfusions, mean units/patient month (95% CI) [c]	1.6 (1.2, 2.2)	1.4 (1.0, 2.1)	1.10 (0.71, 1.70)
Hgb ≥100 g/L subgroup	**N = 38**	**N = 13**	
Transfusion independent, n (%) [a]	23 (60.5)	6 (46.2)	0.17 (-0.24, 0.58)
Transfusion dependent, n (%) [b]	13 (34.2)	5 (38.5)	-0.06 (-0.47, 0.35)
RBC transfusions, mean units/patient month (95% CI) [c]	0.6 (0.2, 2.3)	2.0 (0.3, 12.7)	0.32 (0.04, 2.40)

Source: Table 65, pp134-135; Table 66, pp135-136; Table 67, pp136-137 of the submission

Abbreviations: BAT, best available therapy; CI, confidence interval; ITT, intent to treat; RBC, red blood cell; TSS, total symptom score

[a] Transfusion independence defined as the proportion of patients with no RBC transfusion and no haemoglobin level < 80 g/L in the 12 weeks prior to Week 24; difference between treatment arms is superior proportion difference.

[b] Transfusion dependence defined as the proportion of patients with at least 4 units of RBC transfusion or haemoglobin < 80 g/L in the prior 8 weeks ending with Week 24; difference between treatment arms is superior proportion difference.

[c] Rate of RBC transfusions defined as the average number of RBC units transfused per patient-month during the double-blind phase; difference between treatment arms is rate ratio of RBC transfusions (95% CI, negative binomial model adjusted for strata).

6.35 The ESC noted the nominal significance means that the confidence intervals in Table 8 are all 95% confidence intervals, with no sequential testing or alpha spending in place, which increases the risk of Type I error across the large number of statistical tests conducted.

6.36 A nominally greater proportion of patients in the momelotinib group (43.3%) was transfusion independent at Week 24 in the ITT population compared with the BAT group (21.2%). Overall, the proportion of patients with transfusion independence status increased by 12.5% (from 30.8%) in the momelotinib group and decreased by

15.3% (from 36.5%) in the BAT group at Week 24 compared to baseline. Results in the post hoc Hgb < 100 g/L subgroup were consistent with the ITT population. While the same pattern of results was observed in the Hgb ≥ 100 g/L subgroup, the difference between treatment arms was not nominally statistically significant.

6.37 Transfusion dependence rates were higher in the BAT arm than the momelotinib arm for the ITT population and both Hgb subgroups, however the difference was not nominally statistically significant in any case. For both the ITT population and the Hgb < 100 g/L subgroup, transfusion dependence rates decreased from baseline in the momelotinib arm and increased in the BAT arm, while in the Hgb ≥ 100 g/L subgroup, transfusion dependence rates increased by similar proportions in both treatment arms.

6.38 For the ITT population, the median rate of RBC transfusion was lower in the momelotinib group (0.5, range 0.0 to 8.7 units/month) compared with the BAT group (1.2, range 0.0 to 7.6 units/month). The rate of RBC transfusions in the Hgb < 100 g/L subgroup was higher in the momelotinib group (median 1.6 units/month, range 0.0 to 8.2) than the BAT group (median 1.4 units/month, range 0.0 to 7.6), potentially due to two patients in the momelotinib group who received more than 8 units/month. The rate of RBC transfusion in the Hgb ≥ 100 g/L subgroup was numerically lower in the momelotinib group, though the difference was not nominally statistically significant.

6.39 SIMPLIFY-2 included the same patient-reported outcomes as in SIMPLIFY-1 as exploratory endpoints - change from baseline in Short Form 36 (SF-36) scores, EQ-5D Visual Analog Scale (VAS), and the Patient Global Impression of Change. While there was a positive median percentage improvement in SF-36 physical component scores in the momelotinib arm, there was no change in mental component scores. BAT-treated patients showed no change in physical component scores, and decreased scores from baseline for the SF-36 mental component. The differences between treatment arms for both components were nominally statistically significant in favour of momelotinib. There were no differences noted between groups for EQ-5D VAS change from baseline, with both groups showing little change in scores. Improvement in symptoms at Week 24, measured by the Patient Global Impression of Change item, was reported by 50.0% of patients in the momelotinib group compared with 25.0% in the BAT group, a nominally statistically significant difference. Worsening of symptoms at Week 24 was reported by 4.8% of momelotinib treated patients and 19.2% of BAT treated patients, which was also nominally statistically significant.

6.40 By Week 24 of SIMPLIFY-2, 14 patients (13.5%) in the momelotinib arm and 11 (21.2%) in the BAT arm had died (median OS not reached in the momelotinib group; 15.8 months, 95% CI 15.8, 16.4 in the BAT group). The submission noted a trend towards improved survival in the initial randomised phase (HR = 0.62, 95% CI 0.28, 1.38) however the difference was not nominally statistically significant. At the final analysis, 46 (44.2%) patients originally randomised to momelotinib and 23 (44.2%) originally randomised to best available therapy had died. The median Kaplan-Meier estimate of OS was 34.3 months for the momelotinib group and 37.5 months for the

BAT group, with the difference not reaching nominal significance. Rank preserving structural failure time models, performed to adjust for treatment switching in the overall survival analysis in the ITT population, did not note any differences between treatment arms in overall survival.

Supplementary evidence: MOMENTUM trial

6.41 The MOMENTUM trial was included in the submission as supportive evidence for the JAK inhibitor experienced population. MOMENTUM was a multicentre, randomised, double-blind trial investigating the efficacy and safety of momelotinib 200 mg once daily compared to danazol 300 mg twice daily in symptomatic and anaemic (Hgb < 100 g/L) adults with primary myelofibrosis, or post-PV or post-ET myelofibrosis (N=195), who were previously treated with a JAK inhibitor. The active comparator used in the trial, danazol, is not TGA-indicated nor PBS-listed for myelofibrosis in Australia.

6.42 The MOMENTUM trial met the prespecified dual primary endpoints (statistically significant superiority of momelotinib over danazol for total symptom score response, and statistically significant non-inferiority for transfusion independence rate). All key secondary efficacy endpoints were statistically significant in favour of momelotinib, and the safety profile of momelotinib was consistent with the SIMPLIFY trials. JAK inhibitor experienced patients treated with momelotinib in the MOMENTUM trial demonstrated a similar rate of splenic response over 24 weeks, after a 2-week washout of prior JAK-inhibitor treatment (22.3%), to JAK inhibitor naïve patients treated with momelotinib in SIMPLIFY-1 (26.5%).

Comparative harms

SIMPLIFY-1: JAK-inhibitor naïve patients

6.43 Adverse events reported during the double-blind treatment phase, the first 24 weeks of the open-label treatment phase and in patients exposed to momelotinib at any time during the SIMPLIFY-1 trial are summarised in Table 9.

Table 9: Summary of adverse events in the SIMPLIFY-1 trial

	Double-blind Phase		Open Label phase (Weeks 24-48)		Overall exposed to momelotinib
	MMB (N=214)	RUX (N=216)	MMB to MMB (N=171)	RUX to MMB (N=197)	Total (N=411)
Treatment emergent adverse events, n (%) patients					
Any	198 (92.5)	206 (95.4)	134 (78.4)	177 (89.8)	397 (96.6)
Treatment-related	139 (65.0)	143 (66.2)	67 (39.2)	111 (56.3)	289 (70.3)
Any Grade ≥ 3	77 (36.0)	94 (43.5)	47 (27.5)	76 (38.6)	262 (63.7)
Treatment-related Grade ≥ 3	45 (21.0)	62 (28.7)	21 (12.3)	40 (20.3)	127 (30.9)
Serious	49 (22.9)	39 (18.1)	27 (15.8)	46 (23.4)	186 (45.3)
Treatment-related serious	15 (7.0)	13 (6.0)	12 (7.0)	13 (6.6)	53 (12.9)
Leading to premature discontinuation of study drug	27 (12.6)	12 (5.6)	15 (8.8)	29 (14.7)	120 (29.2)
Leading to study drug dose reduction/ temporary interruption of study drug	39 (18.2)	79 (36.6)	18 (10.5)	35 (17.8)	129 (31.4)
Deaths	7 (3.3)	7 (3.2)	1 (0.6)	7 (3.6)	42 (10.2)

Source: Table 43, pp100-101 of the submission
Abbreviations: MMB, momelotinib; RUX, ruxolitinib

6.44 In the randomised treatment phase of SIMPLIFY-1, adverse events were generally similar between treatment arms, with the exception of Grade ≥ 3 adverse events that occurred in more patients treated with ruxolitinib than momelotinib, particularly treatment related Grade ≥ 3 anaemia adverse events (3.3% momelotinib versus 18.5% ruxolitinib). Adverse events leading to study drug discontinuation were higher in the momelotinib group (12.6%) compared to the ruxolitinib group (5.6%), while adverse events leading to dose reduction or temporary interruption were higher in the ruxolitinib group (36.6%) than the momelotinib group (18.2%). The higher reported incidence of anaemia in the ruxolitinib group (30.1% versus 8.4%) was assessed as directly related to ruxolitinib given its known myelosuppressive properties. Thrombocytopenia (25.5% versus 15.9%), and to a lesser extent neutropenia (5.6% versus 3.7%), were reported to be related to ruxolitinib at a higher percentage than the momelotinib group. In the momelotinib group headache, dizziness, nausea, peripheral sensory neuropathy, fatigue, hypotension, flushing, and paraesthesia were considered treatment related in a slightly higher proportion of patients than the ruxolitinib group.

6.45 Serious adverse events were reported in a similar proportion between treatment groups (22.9% momelotinib, 18.1% ruxolitinib). Serious adverse events reported in patients exposed to momelotinib during either phase of the trial were consistent with events that occur in patients with myelofibrosis and in the age cohort, with infections and infestation and cardiac disorders the most frequently reported events.

6.46 The safety profile observed in the Hgb < 100 g/L and Hgb ≥ 100 g/L subgroups was generally consistent with that of the overall safety population.

SIMPLIFY-2: JAK-inhibitor experienced patients

6.47 Adverse events reported during the randomised treatment phase, the first 24 weeks of the open-label treatment phase and in patients exposed to momelotinib at any time during the SIMPLIFY-2 study are summarised in Table 10.

Table 10: Summary of adverse events in the SIMPLIFY-2 trial

	Randomised Phase		Open Label phase (Weeks 24-48)		Overall exposed to momelotinib
	MMB (N=104)	BAT (N=52)	MMB to MMB (N=64)	BAT to MMB (N=40)	Total (N=144)
Treatment emergent adverse events, n (%) patients					
Any	101 (97.1)	46 (88.5)	60 (93.8)	40 (100.0)	142 (98.6)
Treatment-related	77 (74.0)	20 (38.5)	19 (29.7)	27 (67.5)	113 (78.5)
Any Grade ≥ 3	60 (57.7)	22 (42.3)	18 (28.1)	22 (55.0)	109 (75.7)
Treatment-related Grade ≥ 3	32 (30.8)	9 (17.3)	6 (9.4)	12 (30.0)	58 (40.3)
Serious	37 (35.6)	12 (23.1)	13 (20.3)	11 (27.5)	77 (53.5)
Treatment-related serious	12 (11.5)	2 (3.8)	2 (3.1)	3 (7.5)	23 (16.0)
Leading to premature discontinuation of study drug	22 (21.2)	1 (1.9) [a]	5 (7.8)	15 (37.5)	57 (39.6)
Lading to study drug dose reduction/ temporary interruption of study drug	17 (16.3)	10 (19.2)	9 (14.1)	11 (27.5)	47 (32.6)
Deaths	6 (5.8)	4 (7.7)	3 (4.7)	1 (2.5)	23 (16.0)

Source: Table 72, pp146-147 of the submission
Abbreviations: BAT, best available therapy; MMB, momelotinib

6.48 In the randomised treatment phase, reported adverse events were generally higher in the momelotinib arm than the best available therapy arm, particularly for events considered related to the study drug. The submission noted that SIMPLIFY-2 was an open label study and the relationship to the study drug could be confounded by the investigator's awareness of treatment assignment. Differences in study drug discontinuation (21.2% for momelotinib, 1.9% for best available therapy) could be an artefact of the study design and execution. Because changes in therapy and no-therapy were both permitted in the best available treatment group, discontinuations in this group may have been inconsistently reported or recorded. Dose interruptions or reductions during the randomised phase were higher in the best available therapy arm (19.2%) than in the momelotinib arm (16.3%), primarily due to cytopenia. Overall, in patients exposed to momelotinib at any time during the study, the primary reasons for dose interruption, reduction or treatment discontinuation were cytopenias and infections, consistent with events experienced by patients with advanced myelofibrosis.

6.49 Adverse events considered to be treatment related during the randomised phase were reported at a higher frequency in the momelotinib group (74.0%) than the best available therapy group (38.5%). For patients who received momelotinib at any time during the study, 78.5% had at least one treatment-related adverse event, with the most commonly reported being diarrhoea (18.8%), thrombocytopenia (18.1%), peripheral sensory neuropathy (12.5%), nausea (11.8%), and anaemia (10.4%). During the randomised treatment phase, treatment-related Grade 3 or 4 adverse events

occurred in more momelotinib treated patients (30.8%) than best available therapy treated patients (17.3%), primarily due to thrombocytopenia (7.7% versus 3.8%), asthenia (1.9% versus 0%) and neutropenia (3.8% versus 0%). The incidence of Grade 3 or 4 anaemia was similar in both randomised groups (6.7% momelotinib, 7.7% best available therapy).

6.50 During the randomised phase, serious adverse events were reported more frequently for momelotinib treated patients (35.6%) than best available therapy (23.1%), with no single event driving the difference between the two arms. Serious adverse events reported in patients exposed to momelotinib during either phase of the trial were consistent with events that occur in patients with advanced myelofibrosis, with infections and infestation, cardiac disorders, and respiratory disorders the most frequently reported events.

Benefits/harms

6.51 A benefits/harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

6.52 The submission described momelotinib as non-inferior in terms of effectiveness and overall safety compared with ruxolitinib in JAK inhibitor naïve patients with myelofibrosis and moderate to severe anaemia. Further, the submission claimed that momelotinib provides a clinically meaningful improvement in anaemia-related outcomes and has a safety advantage in lowering the risk of anaemia adverse events compared to ruxolitinib. The evaluation and ESC considered this claim was reasonable, however the following should be considered:

- Momelotinib demonstrated a statistically significant non-inferior splenic response to ruxolitinib, meeting the primary endpoint of the SIMPLIFY-1 trial. The EMA assessment report for momelotinib (November 2023) noted that the selected non-inferiority margin seemed to be arbitrarily chosen, without clinical judgement on the importance of loss of efficacy of momelotinib compared to the reference of ruxolitinib. However, the margin corresponds to the lower bound of the 95% confidence interval, and the chance of the true difference being worse than that suggested by this bound is generally considered acceptably small.
- Momelotinib failed to demonstrate non-inferiority to ruxolitinib for the secondary outcome of total symptom score response rate at Week 24 in either the ITT population or post hoc Hgb < 100 g/L subgroup, with a number of trial design features (such as lack of stratification for baseline symptom scores, differential treatment discontinuation between treatment arms, with patients with missing data or who discontinued treatment counted as non-responders) potentially impacting the result. However alternate post hoc analyses of total symptom scores as a continuous variable, and comparison of scores by specific symptoms, suggested little difference between treatment arms over time.

- Rates of transfusion independence, transfusion dependence and RBC transfusions during the double-blind phase of the SIMPLIFY-1 trial were all nominally statistically significantly in favour of momelotinib over ruxolitinib, in both the ITT population and the Hgb < 100 g/L subgroup.
- Adverse events reported in the SIMPLIFY-1 trial were broadly comparable between treatments. While a greater proportion of patients discontinued treatment due to adverse events in the momelotinib group compared to the ruxolitinib group, there were more ruxolitinib-treated patients who reported dose adjustments or interruptions compared to those treated with momelotinib.

6.53 The submission described momelotinib as having an overall positive benefit/risk balance for the treatment of myelofibrosis in JAK inhibitor experienced patients with moderate to severe anaemia. The evaluation considered this claim may be reasonable, however the following should be considered:

- There was limited comparative evidence of efficacy of momelotinib compared to ruxolitinib in JAK inhibitor experienced patients.
- Momelotinib failed to demonstrate superiority over best available therapy (BAT) for the primary outcome of splenic response rate in the SIMPLIFY-2 trial. The submission noted that the design of the trial may have influenced the outcome for the endpoint in patients in both treatment groups, due to the continuation of active therapy prior to randomisation with no washout period. In addition, at the time the protocol for this study was written, it was anticipated that most patients in the BAT group would be on therapeutic agents other than ruxolitinib. Although all patients enrolled in SIMPLIFY-2 had experienced ruxolitinib-related toxicities prior to the trial, changes to dosing guidelines, increased familiarity and clinical experience with ruxolitinib dosing meant approximately 88% of patients in the BAT arm were maintained on ruxolitinib.
- Despite the lack of treatment washout, a nominally statistically significantly greater rate of total symptom score response and transfusion independence rate were observed for momelotinib-treated patients compared to those treated with best available therapy, with results in the Hgb < 100 g/L subgroup consistent with the ITT population.
- Although higher rates of adverse events were observed in the momelotinib group compared to the best available therapy group, the open-label trial design, and permissibility of changes to therapy and the option of no therapy in the BAT arm, may have confounded the reporting of relationship to study drug and premature treatment discontinuation. The overall safety profile of momelotinib was broadly consistent across the Phase III clinical studies.
- JAK inhibitor experienced patients treated with momelotinib in the supportive MOMENTUM trial demonstrated a similar rate of splenic response over 24 weeks,

after a 2-week washout of prior JAK-inhibitor treatment (22.3%), to JAK inhibitor naïve patients treated with momelotinib in SIMPLIFY-1 (26.5%).

6.54 The PSCR acknowledged there were limitations associated with SIMPLIFY-2 that complicate interpretation of the evidence, however argued it represented the best available evidence for JAK inhibitor experienced patients from which an overall positive risk/benefit balance can be concluded. The PSCR also noted international regulators have approved momelotinib in both JAK inhibitor naive and experienced patients.

6.55 The ESC considered there were limitations with the SIMPLIFY-2 trial, particularly given the level at which ruxolitinib ultimately formed part of the BAT arm of the study, and the plausible confounding effects of no washout period for the momelotinib arm prior to commencing study drug. However the ESC considered, on balance, that the evidence was supportive of a conclusion that momelotinib is effective in JAK inhibitor experienced patients and the claim of a positive benefit/risk profile was reasonable. Further to this conclusion however, the ESC considered the evidence should be interpreted with caution because (in addition to the issues raised in the evaluation):

- The effects of ruxolitinib treatment within the BAT arm are difficult to disentangle, and the submission did not explore analyses within the group who did not receive ruxolitinib as part of BAT; but the ESC acknowledged analyses in this group may be too small to be informative or meaningful; and
- The reliance on nominal statistical significance for secondary outcomes (when the primary outcome was not met) was concerning, and such a reliance to support therapeutic conclusions in the JAK inhibitor experienced population should be interpreted with significant caution as corrections were in place to the 95% CIs for these secondary outcomes.

6.56 The ESC noted the MOMENTUM study was also supportive of the submission claim.

6.57 For a comparative efficacy claim versus ruxolitinib in JAK experienced patients, the ESC considered the clinical evidence overall appears supportive of non-inferiority to ruxolitinib.

6.58 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.59 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.60 The submission presented a cost-minimisation of momelotinib versus ruxolitinib in patients with myelofibrosis and moderate to severe anaemia, based on the JAK inhibitor naïve population in the SIMPLIFY-1 trial only, given the limitations associated with the clinical evidence for JAK inhibitor experienced patients (primary endpoint for superiority versus best available therapy not met in SIMPLIFY-2, danazol comparator

in MOMENTUM trial not TGA registered/PBS listed in Australia). The ESC considered the use of SIMPLIFY-1 was appropriate as evidence in SIMPLIFY-2 was less reliable and dosing would be similar in practice across naive and treatment experienced patients.

6.61 The key components of the cost minimisation approach are summarised in Table 11.

Table 11: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented, effectiveness is claimed to be non-inferior to ruxolitinib.
Therapeutic claim: safety	Based on evidence presented, safety is claimed to be non-inferior to ruxolitinib
Evidence base	Direct comparison of momelotinib and ruxolitinib in the SIMPLIFY-1 trial (Hgb <100 g/L subgroup)
Equi-effective doses	Momelotinib at a fixed daily cost for 20.4 weeks* (200 mg, 150 mg, 100 mg once daily; 98.18% adherence) is equivalent to ruxolitinib for 23.1 weeks (23.6% 5 mg, 17.4% 10 mg, 19.3% 15 mg, 35.5% 20 mg, 3.4% 25 mg twice daily; 99.24% adherence)
Direct medicine costs	Momelotinib = $[redacted]; ruxolitinib = $24,447.04
Other costs or cost offsets	Red blood cell transfusion costs: momelotinib $2,490.63; ruxolitinib $4,464.34 Adverse event costs (thrombocytopenia): momelotinib $339.68; ruxolitinib $266.38

Source: Table 101, p190 of the submission.
Abbreviations: Hgb, haemoglobin
** Note that the duration of treatment is provided for the purposes of informing the PBAC consideration. Interpretation of the duration of treatment and its application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.62 The submission's estimation of equi-effective doses was based on the average distribution of dose strengths and the mean duration of exposure for momelotinib and ruxolitinib in the Hgb < 100 g/L subgroup across the 24 week randomised phase of the SIMPLIFY-1 trial.

6.63 The proposed equi-effective doses for momelotinib and ruxolitinib were:

> momelotinib at any dose (200 mg, 150 mg or 100 mg once daily, with fixed daily cost) for 20.4 weeks at 98.18% adherence is equivalent to
>
> ruxolitinib for 23.1 weeks based on a weighted average dose (23.6% 5 mg, 17.4% 10 mg, 19.3% 15 mg, 35.5% 20 mg, 3.4% 25 mg; twice daily) at 99.24% adherence.

6.64 The ESC noted the equi-effective doses presented in the submission represented how the costs might be calculated. The ESC advised PBAC consider the following equi-effective doses, using mean daily doses from SIMPLIFY-1:

> momelotinib mean daily dose of 186.2 mg is equivalent to
>
> ruxolitinib mean daily dose of 26.2 mg.

6.65 The submission noted that ruxolitinib is subject to a special pricing arrangement. Published ruxolitinib prices were applied as a proxy to illustrate the operation of the cost minimisation approach.

6.66 Table 12 presents the results of the cost-minimisation of momelotinib versus ruxolitinib, using published prices.

Table 12: Results of the cost-minimisation approach

Component	Value	Source/calculation
Ruxolitinib		
Total drug costs	$24,447.04	Based on the published AEMPs for ruxolitinib ($2,375.00 for 56 × 5 mg tablets; $4,750.00 for 56 × 10 mg, 15 mg and 20 mg tablets), and the dose distribution (5 mg 23.6%; 10 mg 17.43%; 15 mg 19.32%; 20 mg 35.51%; 25 mg 3.38%) and treatment duration (23.1 weeks) from the double blind treatment period of the SIMPLIFY-1 Hgb <100 g/L post hoc subgroup.
RBC transfusion costs	$4,464.34	Based on the cost per unit of RBC: $375.03 (National Blood Authority); and the cost of transfusion administration $94.90 (MBS item 13706). Costs applied to the mean number of RBC units: 9.5 (SIMPLIFY-1 Hgb <100 g/L subgroup).
Thrombocytopenia	$266.38	Cost of $4,173.27, based on weighted average cost of AR-DRG Q61A-C (RBC disorders: major, intermediate and minor complexity), weighted by number of separations. Costs applied to the incidence of Grade ≥3 thrombocytopenia: 6.4% (SIMPLIFY-1 Hgb <100 g/L subgroup).
Total costs	$29,177.76	Sum of total drug costs, RBC infusion costs and costs of thrombocytopenia.
Momelotinib		
Total costs	$29,177.76	Total costs of ruxolitinib.
RBC transfusion costs	$2,490.63	Based on the cost per unit of RBC: $375.03 (National Blood Authority); and the cost of transfusion administration $94.90 (MBS item 13706). Costs applied to the mean number of RBC units: 5.3 (SIMPLIFY-1 Hgb <100 g/L subgroup).
Thrombocytopenia	$339.68	Cost of $4,173.27, based on weighted average cost of AR-DRG Q61A-C (RBC disorders: major, intermediate and minor complexity), weighted by number of separations. Costs applied to the incidence of Grade ≥3 thrombocytopenia: 8.1% (SIMPLIFY-1 Hgb <100 g/L subgroup).
Total drug costs	$[redacted]	Total costs minus the costs of RBC transfusion costs and costs of thrombocytopenia.
Mean duration of treatment	20.4 weeks*	Average treatment duration from the double-blind treatment period of the SIMPLIFY-1 Hgb <100 g/L post hoc subgroup.
Dose compliance	98.18%	Proportion of patients receiving non-zero momelotinib doses from the double-blind treatment period of the SIMPLIFY-1 Hgb <100 g/L subgroup.
Cost per day	$[redacted]	Total drug costs divided by mean treatment duration (in days, ×7), divided by dose compliance.
AEMP per pack of 30 tablets	$[redacted]	Cost per day multiplied by 30 tablets.

Source: Table 112, p200 of the submission

Abbreviations: AEMP, approved ex-manufacturer price; AR-DRG, Australian Refined Diagnosis Related Group; Hgb, haemoglobin; RBC, red blood cell

** Note that the duration of treatment is provided for the purposes of informing the PBAC consideration. Interpretation of the duration of treatment and its application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.67 The submission's cost-minimisation approach using ruxolitinib published prices resulted in a calculated ex-manufacturer price of $[redacted] per pack of momelotinib, based on the proposed flat pricing structure. The approach resulted in a higher total drug cost for momelotinib over the treatment duration due to the reduced cost of RBC transfusions and shortened mean treatment duration associated with momelotinib treatment compared to ruxolitinib, based on data from the SIMPLIFY-1 trial. Adverse event costs for thrombocytopenia were estimated to be higher for momelotinib

treated patients compared to ruxolitinib but contributed minimally to the overall costs for each treatment.

6.68 The submission argued that the cost-minimisation approach was likely to be conservative given the actual cost of blood transfusions is greater than the cost of the blood products, and the approach does not take into account other patient relevant benefits of avoiding transfusions such as fewer hospital visits. The submission explored the impact of including increased blood transfusion costs ($700) and costs of anaemia-related adverse events ($2,727.36) in a sensitivity analysis, which resulted in a calculated AEMP of $ for momelotinib. The submission also argued that treatment with momelotinib may result in less wastage given more patients are able to maintain the recommended dose strength, with minimal dose adjustments, compared to ruxolitinib. The ESC considered that while the cost offsets for the estimated differences in RBC transfusions may have been conservatively calculated, it was uncertain whether the difference in the number of transfusions would be as pronounced outside the clinical trial setting; with changes to dosing guidelines and increased clinical experience with ruxolitinib dosing, patients with severe anaemia symptoms would potentially be managed through dose modification more often. Therefore, the ESC considered the likely difference in RBC transfusion events (and therefore associated costs) may be smaller in practice than that estimated based on data from SIMPLIFY-1 (which informed the costs in the CMA).

6.69 The pre-PBAC response argued the number of transfusions observed in the clinical trial setting can be considered applicable to current clinical practice, noting eviQ, 2020 guidelines described how during the ruxolitinib COMFORT-II trial, anaemia and thrombocytopenia were managed by dose modification and/or red cell transfusion rather than treatment discontinuation. After 3 years follow-up, the rate of haematological adverse events (ie anaemia and thrombocytopenia) and other adverse events of special interest (bleeding and infection) were greatest in the first 6 months of therapy and reduced over time.[1] The pre-PBAC response also referenced Ho et al, 2015, which states “For anaemia because of ruxolitinib treatment, blood transfusions can be considered rather than dose reduction if good symptom control has been achieved, because lower doses of ruxolitinib are less effective in controlling symptoms and splenomegaly”. [2]

[1] https://www.eviq.org.au/haematology-and-bmt/leukaemias/myelodysplastic-disorders/1509-primary-myelofibrosis-ruxolitinib#evidence

[2] Ho, P. J., Marlton, P., Tam, C., Stevenson, W., Ritchie, D., Bird, R., Dunlop, L. C., Durrant, S., & Ross, D. M. (2015). Practical management of myelofibrosis with ruxolitinib. *Internal Medicine Journal*. https://doi.org/10.1111/imj.12921

Drug cost/patient/year

6.70 Drug costs per patient in the submission's cost-minimisation approach (based on the JAK inhibitor naïve population only) were based on the mean duration of exposure to the study drugs (20.4 weeks for momelotinib, 23.1 weeks for ruxolitinib) and the distribution of doses (including non-zero doses only) in the 24 week double-blind treatment phase of the SIMPLIFY-1 trial (Hgb < 100 g/L subgroup). Based on published AEMPs ($ proposed for momelotinib; $2,375.00 for ruxolitinib 5 mg and $4,750.00 for ruxolitinib 10 mg, 15 mg and 20 mg), the total cost over 24 weeks was $ for momelotinib and $24,447.04 for ruxolitinib. Converting costs to one year (cost × 52/24) results in a cost per patient per year of $ for momelotinib and $52,968.59 for ruxolitinib.

6.71 Based on assumptions used in the submission's financial estimates, the cost per JAK inhibitor naïve patient per year for ruxolitinib is $53,056.08 (based on the published DPMQ of $4,912.60, and 10.8 × 28-day scripts per patient per year, sourced from the 2018 ruxolitinib 24 month DUSC review), and $ for momelotinib (based on the proposed DPMQ of $, and 10.08 [=10.8×28-day scripts/30-day scripts] × 30-day scripts per patient per year).

Estimated PBS usage & financial implications

6.72 This item was considered by DUSC.

6.73 The submission used a market share approach to estimate utilisation of momelotinib. For JAK inhibitor naïve patients with moderate to severe anaemia, momelotinib was expected to replace ruxolitinib; and for patients who experienced moderate to severe anaemia while being treated with ruxolitinib (JAK inhibitor experienced), patients were expected to switch from ruxolitinib to momelotinib.

6.74 Table 13 presents the key data sources and parameter values applied in the utilisation and financial estimates.

Table 13: Key inputs for financial estimates

Data	Value	Source	Commentary on Submission	DUSC Comments
Treatment utilisation				
Projected number of ruxolitinib prescriptions for myelofibrosis	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][2]	Average growth rate (9.1%) based on historical Services Australia data for ruxolitinib (2019-2023). Applied to both initiating and continuing scripts.	The Services Australia data included in the submission showed a 12.5% average growth rate in ruxolitinib initiating scripts from 2019 to 2023, with a 35.6% increase in scripts from 2022 to 2023; while continuing script numbers were more stable with 6-8% growth in 2021-2023 (average 9.0% increase from 2019 to 2023).	DUSC considered this to be an underestimate.

Data	Value			Source	Commentary on Submission	DUSC Comments
% with Hgb <100 g/L	41.7% of initiating scripts 60.0% of continuing scripts			SIMPLIFY-1 trial; % patients with Hgb <100 g/L at baseline (JAKi naïve) and % patients with a Grade ≥2 anaemia adverse event (Hgb <100 g/L) in ruxolitinib arm (JAKi experienced)*	It is unclear whether the proportions of patients with Hgb <100 g/L in the trial are representative of the Australian patient population.	DUSC considered this to likely be an underestimate.
Ruxolitinib dose distribution (% scripts)	**Dose**	**Init**	**Cont**	Services Australia (2023) – ruxolitinib scripts, adjusted to reflect dose distribution observed in SIMPLIFY-1 trial (Hgb <100 g/L subgroup); Week 1 dose for initiating; Week 2-24 average dose for continuing (3.5% use of 25 mg dose strength added to each of the 5 mg and 20 mg scripts). Population-based proportion of 5 mg use from the trial was halved when converted to a script-based proportion, as this dose strength is provided in twice the quantity of others.	There was a greater proportion of patients in the SIMPLIFY-1 Hgb <100 g/L subgroup initiating ruxolitinib at higher dose strengths compared to the PBS population (78.8% initiating on 15 mg or 20 mg dose in SIMPLIFY-1 trial versus 65.4% for PBS data), while the distribution of continuing dose strengths was more consistent between the two sources. Use of ruxolitinib dose distribution from Services Australia data without adjustment to match SIMPLIFY-1 distribution was tested in the submission's sensitivity analyses.	DUSC considered this to be uncertain.
	5 mg	14.9%	27.5%			
	10 mg	6.4%	17.9%			
	15 mg	30.9%	18.8%			
	20 mg	47.9%	38.5%			
Adjusting continuing ruxolitinib scripts for JAK inhibitor naïve patients	One initial ruxolitinib script = one patient. Mean 10.8 continuation scripts/patient/year for JAKi naïve patients (9.8 in Year 1 to account for initiating script; 5 mg dose strength = 5.4 and 4.4 scripts/patient year for Year 1 and subsequent years, respectively)			Ruxolitinib DUSC report (2018) used to estimate average scripts/year (adjusting 5 mg scripts to account for differences in dispensing frequency). Dose distribution recalculated based on Week 2-24 of SIMPLIFY-1 (as described above).	After accounting for continuing scripts for JAKi naïve patients, the remaining scripts were considered to represent utilisation in JAKi experienced patients.	DUSC considered this to likely be an underestimate.
	80% of patients progress to subsequent years of treatment).			PBS 10% sample data used to estimate continuation rate in subsequent years	Documentation of the PBS 10% sample analysis was limited and the estimate could not be verified.	DUSC considered this to be an underestimate.
Uptake rates for momelotinib	Init Cont Yr 1: [redacted]% [redacted]% Yr 2: [redacted]% [redacted]% Yr 3: [redacted]% [redacted]% Yr 4: [redacted]% [redacted]% Yr 5: [redacted]% [redacted]% Yr 6: [redacted]% [redacted]%			Assumption based on consultation with Australian clinicians. Initial script uptake represents JAKi naïve patients and Continuing script uptake represents JAKi experienced patients (after adjustment for continuing	The submission assumed higher uptake rates in JAKi naïve patients with pre-existing moderate to severe anaemia, with JAKi experienced patients more likely to remain on ruxolitinib (with dose adjustments and concomitant RBC	DUSC considered this to be an underestimate.

Data	Value	Source	Commentary on Submission	DUSC Comments
		scripts attributable to JAKi naïve patients)	transfusions) due to product familiarity. The uptake rates were assumptions and may over- or underestimate uptake in the Australian population. No details were provided on the consultations with Australian clinicians.	
Script equivalence	6.52 ruxolitinib 5 mg scripts = 10.64 momelotinib scripts (x 87.19%, adjustment to avoid double counting for 25 mg dose strength) 13.04 ruxolitinib 10 mg, 15 mg or 20 mg scripts = 10.64 momelotinib scripts.	Incorporates differences in mean duration and dose compliance (non-zero dose) in Hgb <100 g/L subgroup of SIMPLIFY-1 trial. Assumption that ruxolitinib continuing scripts will be substituted by momelotinib continuing scripts for JAK inhibitor experienced patients, for simplicity (omitting initiating scripts). Momelotinib dose distribution not included due to flat pricing across doses.	The submission acknowledged that JAK inhibitor experienced patients on continuing scripts would first switch to momelotinib initiating scripts before transitioning to continuing scripts, but argued that the financial estimates Excel workbook does not provide the functionality to effectively model this transition. It is unclear whether the relative dose duration and non-zero dose strengths observed in the trial are representative of use in the Australian patient population.	DUSC considered this to uncertain and possibly an underestimate.
Costs				
Momelotinib	All doses (flat pricing): $[redacted] (Published)	Requested price	-	
Ruxolitinib	Published price: 5 mg: $4,912.61 10 mg, 15 mg, 20 mg: $4912.60	Based on PBS item numbers: 10614P, 10616R, 10913J, 10927D, 10619X, 10615Q, 10618W, 10617T	Ruxolitinib 5 mg has a maximum quantity of 112 units, compared to 56 units for all other dose strengths.	
Patient copayment	$12.99 (PBS) $4.42 (RPBS)	Ruxolitinib utilisation by beneficiary type for 2023	This was reasonable	
NBA costs	$375.03	National Blood Authority cost per RBC unit for transfusion	-	DUSC considered this to be an underestimate.
MBS costs (transfusions)	$94.90	MBS item 13706 (transfusion administration; 80% of fee)		DUSC considered this to be an underestimate.

Source: Table 118, p209; Table 119, p211; Table 120, p211; Table 121, p214; Table 122, p215; Table 124, p217 of the submission.
Abbreviations: Hgb, haemoglobin; JAK, Janus kinase; JAKi, JAK inhibitor; MBS, Medicare Benefits Schedule; RBC, red blood cell
* *Note that the percentage of patients with a Grade ≥2 anaemia adverse event (Hgb <100 g/L) in ruxolitinib arm of the SIMPLIFY-1 trial is provided for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis of the PBAC outcome and should not be used for any other purpose.*
The redacted values correspond to the following ranges:
[1] 20,000 to < 30,000
[2] 30,000 to < 40,000

6.75 The estimated utilisation and financial implications of listing momelotinib (based on published prices) are presented in Table 14. Estimates based on the effective price for

ruxolitinib and derived effective price for momelotinib are presented in the CIC section of the commentary.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications of momelotinib						
Cost to PBS/RPBS less copayments	$[redacted][4]	$[redacted][5]	$[redacted][6]	$[redacted][7]	$[redacted][8]	$[redacted][9]
Estimated financial implications for ruxolitinib						
Cost to PBS/RPBS less copayments	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]
Net financial implications to the PBS/RPBS/MBS/NBA						
Net cost to PBS/RPBS	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]
Net cost to the MBS [a]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]
Net cost to the NBA [a]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]
Net cost to the PBS/RPBS/ MBS/NBA	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]

Source: Table 135, p224; Table 136, p225 of the submission

Abbreviations: MBS, Medicare Benefits Schedule; NBA, National Blood Authority; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme

[a] MBS item 13706 - transfusion administration; National Blood Authority – cost of blood products for transfusion

The redacted values correspond to the following ranges:

[1] 500 to < 5,000
[2] 5,000 to < 10,000
[3] 10,000 to < 20,000
[4] $20 million to < $30 million
[5] $40 million to < $50 million
[6] $60 million to < $70 million
[7] $70 million to < $80 million
[8] $80 million to < $90 million
[9] $90 million to < $100 million
[10] net cost saving
[11] $0 to < $10 million

6.76 The net cost to the PBS/RPBS of listing momelotinib (published price) was estimated at $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, a total net cost to PBS/RPBS of $20 million to < $30 million over the first 6 years of listing.

6.77 Despite the cost-minimisation approach, the submission estimated a cost to government (PBS/RPBS/MBS/National Blood Authority) of $0 to < $10 million over the first 6 years of listing. The submission claimed that the net cost to government was likely due to the full MBS Schedule fee for transfusion administration ($94.90) being included in the cost-minimised price while lower cost offsets at 80% of the MBS benefit ($75.92) were included in the financial estimates. However, when MBS benefits were set to 100% in the submission's financial model, there remained a net cost to Government of $0 to < $10 million over 6 years that was not accounted for.

6.78 The PSCR presented a revised base case incorporating higher uptake rates for JAK inhibitor (JAKi) experienced patients. The adjusted uptake rates for the JAKi experienced population were increased by [redacted]% each year, representing the midpoint between the JAKi naïve and JAKi experienced uptake rates presented in the July 2024

submission. Revised base case financial estimates based on adjusted JAKi experienced uptake rates and correction to ruxolitinib continuation rate were taken from the PSCR and are presented in the table below.

Table 15: Revised financial estimates

	2025	2026	2027	2028	2029	2030
Net financial impact on PBS/RPBS						
Net change in scripts	- [1]	- [1]	- [1]	- [1]	- [1]	- [1]
Net cost of momelotinib on PBS/RPBS	$ [2]	$ [3]	$ [4]	$ [5]	$ [6]	$ [7]
Net cost of ruxolitinib on PBS/RPBS	-$ [8]	-$ [8]	-$ [8]	-$ [8]	-$ [8]	-$ [8]
Overall net cost on PBS/RPBS	$ [9]	$ [9]	$ [9]	$ [9]	$ [9]	$ [9]
Net changes to the MBS/NBA						
Net change in transfusion services	- [10]	- [11]	- [12]	- [12]	- [12]	- [12]
Net cost to MBS/NBA	-$ [8]	-$ [8]	-$ [8]	-$ [8]	-$ [8]	-$ [8]
Net cost to Government health budget						
Net cost to Govt (PSCR)	$ [9]	$ [9]	$ [9]	$ [9]	$ [9]	$ [9]
Net cost to Govt (submission)	$ [9]	$ [9]	$ [9]	$ [9]	$ [9]	$ [9]

Source: Table 1, p3 of the PSCR.

Abbreviations: MBS = Medicare Benefits Schedule; NBA = National Blood Authority; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Note changes from the November 2024 submission include: (i) uptake rates + [redacted]% each year for the JAKi experienced population, (ii) continuation rate corrected from 80.5% to 80.3%

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*
[2] *$30 million to < $40 million*
[3] *$50 million to < $60 million*
[4] *$60 million to < $70 million*
[5] *$70 million to < $80 million*
[6] *$90 million to < $100 million*
[7] *$100 million to < $200 million*
[8] *net cost saving*
[9] *$0 to < $10 million*
[10] *5,000 to < 10,000*
[11] *10,000 to < 20,000*
[12] *20,000 to < 30,000*

6.79 DUSC considered the estimates presented in the submission to be underestimated for the following reasons:

- the risk for both overall market growth in the myelofibrosis (MF) market and increased market share for momelotinib.
- DUSC considered that the uptake rate is underestimated due to improvements in anaemia with momelotinib, potential increased substitution in patients currently being treated with ruxolitinib, as well as by uptake by populations currently not on ruxolitinib due to side effects of ruxolitinib including anaemia.

6.80 DUSC also considered that the data in the 2018 DUSC review of ruxolitinib to be too old and the use of more up to date data would be beneficial (DUSC has provided some up-to-date data from a 100% PBS sample).

6.81 DUSC considered that the costs associated with RBC transfusions to be an underestimate. DUSC noted that the cost distribution for RBC is complex and that there was a possibility of less transfusion requirements with momelotinib leading to greater uptake of momelotinib than expected. DUSC also noted the benefits of reduced RBC transfusions impact patients' quality of life and hospital admissions and this could lead to greater uptake of momelotinib.

6.82 The pre-PBAC response stated that majority of patients who develop anaemia while being treated with ruxolitinib are expected to remain on treatment to maintain control over splenomegaly and constitutional symptoms, with the anaemia being frequently managed through concomitant RBC transfusions (eviQ, 2020; Ho et al., 2015). It was further argued, 'watch and wait' was only considered appropriate for asymptomatic individuals. It was thus argued the availability of momelotinib on the PBS was not expected to grow the market and the market share approach was appropriate with momelotinib expected to replace ruxolitinib in patients with moderate to severe anaemia. Acknowledging the high clinical utility of momelotinib may result in a greater uptake amongst anaemic JAKi experienced patients, the pre-PBAC response included sensitivity analysis using the same uptake rate as JAKi naïve patients (% in Year 1, increasing to % in Years 3+) (see Table 16 below).

6.83 The pre-PBAC response also provided sensitivity analyses using the updated data provided by DUSC (9.1 scripts/patient/year, 8.6 scripts/patient/year), resulting in a 0.7-0.9% increase in the overall net cost to the health budget over 6 years compared to the PSCR base case (see Table 16).

Table 16: Net cost to overall health budget across different scenarios

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case (Sep 24 PSCR)	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]
SA.1: Uptake rate for JAKi experienced the same as JAKi naive	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]
SA.2: 8.6 scripts/patient (09/23–08/24: Table 4, 5.15.DUSC ADV.13)	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]
SA.3: 9.1 scripts/patient (09/22–08/23: Table 4, 5.15.DUSC ADV.13)	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]	$ [redacted] [1]

Source: Table 1, p3 of the pre-PBAC response.
The redacted values correspond to the following ranges:
[1] $0 to < $10 million

Quality Use of Medicines

6.84 DUSC noted the increased risk of cardiovascular disease and cancer with the use of the Janus kinase inhibitors baricitinib, tofacitinib and upadacitinib for chronic inflammatory conditions. DUSC noted that the MOMENTUM clinical trial excluded patients on current statin therapy thereby having a better cardiovascular risk profile

than non-trial MF patients[3]. DUSC noted that there were no increases in cardiovascular disease nor cancer with the use of momelotinib.

6.85 DUSC noted that 14.8% of momelotinib treated patients had peripheral neuropathy[4]. DUSC additionally noted that patients with the presence of peripheral neuropathy ≥ Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 were excluded from the listed clinical trials.

Financial Management – Risk Sharing Arrangements

6.86 A risk sharing arrangement was not proposed in the submission.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of momelotinib, on the basis that it should be available as a General Schedule, Authority Required (Telephone/Online) listing for initial treatment and an Authority Required (STREAMLINED) listing for continuing treatment for intermediate or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis in patients with moderate to severe anaemia and who are Janus kinase (JAK) inhibitor naïve or have been treated with ruxolitinib. The PBAC's recommendation for listing was based on its assessment that the cost-effectiveness of momelotinib would be acceptable if it were cost-minimised against ruxolitinib.

7.2 The PBAC considered there was a moderate need for a new JAK inhibitor in this disease area and momelotinib would provide patients with an alternative to ruxolitinib, with potentially lower incidence of anaemia (see paragraph 6.48) and fewer red blood cell transfusions (see paragraph 6.28).

7.3 The PBAC noted the sponsor hearing supported the sequential use of the JAK inhibitors and highlighted the potential advantages of less anaemia and fewer red blood cell transfusions with momelotinib treatment (see paragraph 6.1). The PBAC noted the consumer support for an alternative treatment option, with potential to

[3] *The sponsor noted during the preparation of the Public Summary Document (PSD) that the MOMENTUM trial excluded patients on simvastatin, atorvastatin, lovastatin or rosuvastatin due to a known drug interaction with danazol. The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with these statins which are metabolised significantly by CYP3A4.*

[4] *The sponsor noted during the preparation of the PSD that this is based on an integrated safety analysis of momelotinib from the MOMENTUM, SIMPLIFY-1 and SIMPLIFY-2 trials (Verstovsek et al., 2023). The authors concluded that* "Peripheral neuropathy, mostly characterized by grade 1 or 2 numbness and paresthesia, occurred at low rates in the pooled analysis, with only 2 events considered serious. Therefore, this AE does not seem to be a reaction of significant concern in the treated population."

improve and maintain quality of life for longer, and considered this was an important consideration in its recommendation for a new JAK inhibitor for both treatment naïve and treatment experienced patients.

7.4 The PBAC agreed with the ESC that, on balance, the evidence supported sequential use of momelotinib following ruxolitinib (paragraph 3.9). The PBAC noted the ESC's concern regarding unlimited sequential use of treatments, for which there was no supportive evidence (paragraph 3.10). The Committee also noted the pre-PBAC response arguments that re-treatment with ruxolitinib may be required after switching to momelotinib for patients experiencing adverse events or intolerance, to ensure ongoing JAK inhibitor treatment wherever possible. The PBAC considered it was reasonable to allow re-treatment with the initial therapy if patients experience adverse events or intolerance to the alternative therapy, but that this should not be unlimited. A limit of twice per lifetime for each JAK inhibitor was considered appropriate.

7.5 With respect to the PBS listing and restrictions, the PBAC considered:

- The proposed inclusion of the anaemia clinical criterion (Hgb < 100 g/L), which would indicate patients had at least moderate anaemia was reasonable;
- That JAK inhibitor experienced patients should have the option of switching treatment without needing to satisfy the disease-related symptoms requirement, and wording, as suggested in the PSCR and pre-PBAC response, would be appropriate: "Patient must have severe disease-related symptoms that are resistant, refractory or intolerant to available therapy, OR Patient must have intolerance to prior treatment with a JAK inhibitor for this condition." (paragraph 3.6); and
- The Committee noted the arguments for amending the authority levels in the submission compared to ruxolitinib (see paragraph 3.5) and agreed with the proposed reduced Authority levels to Telephone/Online listing for initial treatment (compared to Written Authority for ruxolitinib) and a Streamlined Authority listing for continuing therapy (compared to Telephone/Online for ruxolitinib).

7.6 The PBAC considered the PBS listing for ruxolitinib will need to be updated to align with the momelotinib restriction.

7.7 The PBAC accepted ruxolitinib was the appropriate comparator in both the treatment naïve and treatment experienced populations. It was noted patients who develop anaemia while being treated with ruxolitinib would remain on treatment with either dose modification and/or concomitant red blood cell transfusions. In the majority of patients who develop anaemia or thrombocytopenia, dose-adjusted ruxolitinib remains the preferred standard of care therapy because of rapid symptom rebound on dose interruption or treatment discontinuation of ruxolitinib (Ho, 2017) (paragraph 5.2).

7.8 The PBAC noted the submission was based on one head-to-head randomised trial comparing momelotinib to ruxolitinib in JAK inhibitor naïve patients (SIMPLIFY-1) and one head-to-head randomised trial comparing momelotinib to best available therapy (including ruxolitinib) in JAK inhibitor experienced patients (SIMPLIFY-2). The PBAC also noted supportive evidence from the MOMENTUM trial, a multicentre, randomised, double-blind trial investigating the efficacy and safety of momelotinib 200 mg once daily compared to danazol 300 mg twice daily in symptomatic and anaemic (Hgb < 100 g/L) adults with primary myelofibrosis, or post-PV or post-ET myelofibrosis (N=195), who were previously treated with a JAK inhibitor.

7.9 For treatment naïve patients (SIMPLIFY-1), rates of transfusion independence, transfusion dependence and mean RBC transfusions were all nominally statistically significantly in favour of momelotinib over ruxolitinib, in both the ITT population and the Hgb < 100 g/L subgroup (see Table 6). Similar proportions of patients had a splenic response at 24 weeks, in both the ITT population and the Hgb < 100 g/L subgroup (see Table 4). Fewer patients in the momelotinib arm (28.4%) had a total symptom score (TSS) reduction of ≥ 50% from baseline, compared to the ruxolitinib group (42.2%), and non-inferiority of momelotinib to ruxolitinib was not met (see paragraph 6.19). It was noted, a number of trial design factors may have contributed to this difference in TSS, and a post-hoc longitudinal mixed-effects model (MMRM) was conducted to provide a method to estimate the TSS treatment effect as a continuous variable; it was concluded based on this analysis that the while greater reductions in TSS scores from baseline were observed at Week 12 and Week 24 for the ruxolitinib treatment group compared to the momelotinib group, the differences (0.88 and 1.24 points, respectively) were considered small for a 70 point scale. Results of the post hoc MMRM analysis for the Hgb < 100 g/L subgroup were consistent with the ITT population, with similar mean differences between treatment arms (1.03 and 2.05 points, respectively) (see paragraphs 6.20 to 6.21). Overall, the PBAC accepted the submission claim that momelotinib was non-inferior in terms of effectiveness compared to ruxolitinib in JAK inhibitor naïve patients with myelofibrosis and moderate to severe anaemia.

7.10 For JAK inhibitor experienced patients (SIMPLIFY-2), the PBAC noted there were limitations with the SIMPLIFY-2 trial, particularly given the level at which ruxolitinib ultimately formed part of the best available therapy (BAT) arm of the study, and the plausible confounding effects of no washout period for the momelotinib arm prior to commencing study drug. However, the PBAC agreed with the ESC and considered, on balance, that the evidence was supportive of a conclusion that momelotinib was effective in JAK inhibitor experienced patients and the claim of a positive benefit/risk profile was reasonable. Importantly, momelotinib was at least as effective as BAT in splenic response and TSS (see Table 7), with a greater proportion of patients in the momelotinib arm (43.3%) being transfusion independent at Week 24 in the ITT population compared with the BAT group (21.2%), with results in the post hoc Hgb < 100 g/L subgroup consistent with the ITT population (see Table 8).

7.11 The PBAC noted that the MOMENTUM trial met the prespecified dual primary endpoints (statistically significant superiority of momelotinib over danazol for total symptom score response, and statistically significant non-inferiority for transfusion independence rate) (see paragraph 6.42).

7.12 For a comparative efficacy claim versus ruxolitinib in JAK experienced patients, the PBAC agreed with the ESC and considered the clinical evidence overall appears supportive of non-inferiority to ruxolitinib.

7.13 In SIMPLIFY-1 the adverse events were similar in both treatment arms, with the exception of Grade ≥ 3 adverse events that occurred in more patients treated with ruxolitinib than momelotinib, particularly treatment related Grade ≥ 3 anaemia adverse events (3.3% momelotinib versus 18.5% ruxolitinib). The overall higher reported incidence of anaemia in the ruxolitinib group compared to the momelotinib group (30.1% versus 8.4%) was assessed as directly related to ruxolitinib given its known myelosuppressive properties (see paragraph 6.44). The PBAC noted the higher rate of premature discontinuations in the momelotinib arm compared to ruxolitinib due to adverse events, with headache, dizziness, nausea, peripheral sensory neuropathy, fatigue, hypotension, flushing, and paraesthesia in the momelotinib group considered treatment related in a slightly higher proportion of patients than the ruxolitinib group (see Table 9 and paragraph 6.44). This reinforced the PBAC agreement to allow JAK inhibitor experienced patients to switch back to ruxolitinib if not tolerating momelotinib.

7.14 The PBAC accepted the claim of non-inferior overall safety compared to ruxolitinib and agreed with the submission that momelotinib provides a clinically meaningful improvement in anaemia-related outcomes and has a safety advantage in lowering the risk of anaemia adverse events compared to ruxolitinib.

7.15 The submission presented a CMA versus ruxolitinib, based on the SIMPLIFY-1 trial only. The PBAC considered this was appropriate as evidence in SIMPLIFY-2 was less reliable and dosing would be similar in practice across JAK inhibitor naive and treatment experienced patients.

7.16 The submission CMA included additional adverse event costs for thrombocytopenia, which the PBAC accepted. The submission also included cost offsets for the different rates of RBC transfusions, based on the mean number of RBC units over the 24 week double-blind period in SIMPLIFY-1. The PBAC noted ESCs concerns that the number of transfusions in clinical practice may be smaller than observed in the trial setting (see paragraph 6.68). However, PBAC noted the pre-PBAC response arguments that for patients with good symptom control, RBC transfusions should be considered rather than dose reductions. On balance, the PBAC considered the trial rates of transfusions were reasonably representative of what might be expected in clinical practice, and it was appropriate to account for the reduced cost of RBC transfusions in the CMA.

7.17 The PBAC noted the costs for RBC transfusion included only the cost per unit of RBC and the cost of transfusion administration. As noted by the submission, the approach

does not take into account other patient relevant benefits of avoiding transfusions such as fewer hospital visits, and as such is conservative.

7.18 The PBAC considered the following equi-effective doses appropriate (based on mean daily dose over 24 weeks from SIMPLIFY-1):

- momelotinib mean daily dose of 186.2 mg is equivalent to ruxolitinib mean daily dose of 26.2 mg.

7.19 The CMA resulted in a higher total drug cost for momelotinib over the treatment duration due to the reduced cost of RBC transfusions and shortened mean treatment duration associated with momelotinib treatment compared to ruxolitinib, based on data from the SIMPLIFY-1 trial.

7.20 The PBAC noted the DUSC considered the submission financial estimates were likely underestimated. The pre-PBAC response revised uptake rates in the treatment experienced population to match the naïve population, which the PBAC considered was appropriate. The PBAC also noted the DUSC provided updated PBS data as the 2018 ruxolitinib DUSC review data was considered to be too old. The PBAC considered the revised estimates should include both the revised uptake and revised ruxolitinib data (noting the results provided in the pre-PBAC response are based on published prices and would need to be updated to reflect effective prices) (see paragraphs 6.79 to 6.83 and Table 16).

7.21 The PBAC recommended that momelotinib should not be treated as interchangeable with any other drugs.

7.22 The PBAC advised that momelotinib is not suitable for prescribing by nurse practitioners.

7.23 The PBAC recommended that the Early Supply Rule should not apply.

7.24 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because momelotinib is not expected to provide a substantial and clinically relevant improvement in efficacy, over ruxolitinib, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.25 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
MOMELOTINIB					
momelotinib 200 mg tablet, 30	NEW	1	30	0	Omjjara
momelotinib 150 mg tablet, 30	NEW	1	30	0	Omjjara
momelotinib 100 mg tablet, 30	NEW	1	30	0	Omjjara

Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (immediate assessment)
	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.
	Administrative Advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) OR the Age-Adjusted DIPSS (aaDIPSS).
	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) or by telephone by contacting Services Australia on 1800 700 270.
	Indication: High risk and intermediate-2 risk myelofibrosis
	Treatment Phase: Initial treatment
	Clinical criteria:
	The condition must be either: (i) primary myelofibrosis, (ii) post-polycythemia vera myelofibrosis, (iii) post-essential thrombocythemia myelofibrosis, confirmed through a bone marrow biopsy report
	AND
	Clinical criteria:
	Patient must have a haemoglobin level of less than 100 g per L prior to commencing treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition
	Prescribing Instructions: Details of the following must be documented in the patient's medical records: (a) the bone marrow biopsy report confirming diagnosis of myelofibrosis (date, unique identifying number/code or provider number); and (b) a classification of risk of myelofibrosis according to either the IPSS, DIPSS, or the Age-Adjusted DIPSS.
	Administrative advice: A patient may only qualify for PBS-subsidised treatment under this restriction twice in a lifetime. Patients reinitiating PBS-subsidised treatment following pregnancy are exempt from this rule.
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: ☒ GENERAL - General Schedule (Code GE)

	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (immediate assessment)
	Indication: Intermediate-1 risk myelofibrosis
	Treatment Phase: Initial treatment
	Clinical criteria:
	The condition must be either: (i) primary myelofibrosis, (ii) post-polycythemia vera myelofibrosis, (iii) post-essential thrombocythemia myelofibrosis, confirmed through a bone marrow biopsy report
	AND
	Clinical criteria:
	Patient must have severe disease-related symptoms that are resistant, refractory or intolerant to available therapy
	AND
	Clinical criteria:
	Patient must have a haemoglobin level of less than 100 g per L prior to commencing treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition
	Prescribing Instructions: Details of the following must be documented in the patient's medical records: (a) the bone marrow biopsy report confirming diagnosis of myelofibrosis (date, unique identifying number/code or provider number); and ~~(b)~~ a classification of risk of myelofibrosis according to either the IPSS, DIPSS, or the Age-Adjusted DIPSS.
	Administrative advice: A patient may only qualify for PBS-subsidised treatment under this restriction twice in a lifetime. Patients reinitiating PBS-subsidised treatment following pregnancy are exempt from this rule.

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
MOMELOTINIB					
momelotinib 200 mg tablet, 30	NEW	1	30	5	omjjara
momelotinib 150 mg tablet, 30	NEW	1	30	5	omjjara
momelotinib 100 mg tablet, 30	NEW	1	30	5	omjjara
Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: ☒ GENERAL - General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required (Streamlined) [new code]				
	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.				
	Administrative Advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) or the Dynamic International Prognostic Scoring System (DIPSS) or the Age Adjusted DIPSS (aaDIPSS).				

	Indication: High risk and intermediate-2 risk myelofibrosis
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition.
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (Streamlined) [new code]
	Indication: Intermediate-1 risk myelofibrosis
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition.

8.2 Flow-on changes to the listing of ruxolitinib to align the listings, including the limit of two treatment attempts with each drug in a lifetime are required.

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
RUXOLITINIB					
ruxolitinib 5mg tablet, 56	10614P	2	112	0	Jakavi
ruxolitinib 10mg tablet, 56	10913J	1	56	0	Jakavi
ruxolitinib 15mg tablet, 56	10619X	1	56	0	Jakavi
ruxolitinib 20mg tablet, 56	10618W	1	56	0	Jakavi
Restriction Summary 13171 / Treatment of Concept: 13127					
	Category / Program: ☒ GENERAL - General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required (immediate assessment)				
	Administrative Advice: Special Pricing Arrangements apply.				
	Administrative Advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) OR the Age-Adjusted DIPSS (aaDIPSS).				
	Administrative Advice: No increase in the maximum quantity may be authorised for the 15 mg and 20 mg dose strengths.				
	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) or by telephone by contacting Services Australia on 1800 700 270.				
	Indication: High risk and intermediate-2 risk myelofibrosis				

	Treatment Phase: Initial treatment
	Clinical criteria:
	The condition must be either: (i) primary myelofibrosis, (ii) post-polycythemia vera myelofibrosis, (iii) post-essential thrombocythemia myelofibrosis, confirmed through a bone marrow biopsy report
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition
	Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction twice in a lifetime. Patients reinitiating PBS-subsidised treatment following pregnancy are exempt from this rule.
	Prescribing Instructions: Details of the following must be documented in the patient's medical records: (a) the bone marrow biopsy report confirming diagnosis of myelofibrosis (date, unique identifying number/code or provider number); and ~~(b)~~ a classification of risk of myelofibrosis according to either the IPSS, DIPSS, or the Age-Adjusted DIPSS
Restriction Summary 13172 / Treatment of Concept: 13173	
	Category / Program: ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (immediate assessment)
	Indication: Intermediate-1 risk myelofibrosis
	Treatment Phase: Initial treatment
	Clinical criteria:
	The condition must be either: (i) primary myelofibrosis, (ii) post-polycythemia vera myelofibrosis, (iii) post-essential thrombocythemia myelofibrosis, confirmed through a bone marrow biopsy report
	AND
	Clinical criteria:
	Patient must have severe disease-related symptoms that are resistant, refractory or intolerant to available therapy
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition
	Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction twice in a lifetime. Patients reinitiating PBS-subsidised treatment following pregnancy are exempt from this rule.
	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) or by telephone by contacting Services Australia on 1800 700 270.
	Prescribing Instructions: Details of the following must be documented in the patient's medical records: (a) the bone marrow biopsy report confirming diagnosis of myelofibrosis (date, unique identifying number/code or provider number); and ~~(b)~~ a classification of risk of myelofibrosis according to either the IPSS, DIPSS, or the Age-Adjusted DIPSS

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands

RUXOLITINIB					
ruxolitinib 5mg tablet, 56	10616R	2	112	5	Jakavi
ruxolitinib 10mg tablet, 56	10927D	1	56	5	Jakavi
ruxolitinib 15mg tablet, 56	10615Q	1	56	5	Jakavi
ruxolitinib 20mg tablet, 56	10617T	1	56	5	Jakavi

Restriction Summary 13174 / Treatment of Concept: 13128	
	Category / Program: ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (Streamlined)
	Administrative Advice: No increase in the maximum quantity may be authorised for the 15 mg and 20 mg dose strengths.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) or the Dynamic International Prognostic Scoring System (DIPSS) or the Age Adjusted DIPSS (aaDIPSS).
	Indication: High risk and intermediate-2 risk myelofibrosis
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition.
Restriction Summary 13129 / Treatment of Concept: 13130	
	Category / Program: ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (Streamlined)
	Indication: Intermediate-1 risk myelofibrosis
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition.

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

9 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.

10 Sponsor's Comment

GSK welcomes the PBAC's recommendation to list momelotinib (Omjjara®) on the PBS for the treatment of intermediate or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis in patients with moderate to severe anaemia and who are Janus kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.