7.01 FEDRATINIB, Capsule 100 mg, Inrebic®, Bristol-Myers Squibb Australia Pty Ltd.

1 Purpose of submission

1.1 The standard re-entry submission requested a General Schedule, Authority Required (Telephone/Online) listing of fedratinib for the treatment of patients with intermediate-2/high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis.

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

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

Component	Description
Population	Adult patients with intermediate-2 or high risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis who are Janus kinase (JAK) inhibitor naïve or post ruxolitinib or another JAK inhibitor; and intermediate-1 risk myelofibrosis patients with severe disease-related symptoms that are resistant, refractory or intolerant to available therapy (second line treatment).
Intervention	Fedratinib 400 mg (4 × 100 mg capsules) administered orally once a day.
Comparator	Ruxolitinib 5 mg to 25 mg twice daily, administered as 5 mg, 10 mg, 15 mg or 20 mg tablets for the population that is JAK inhibitor naïve. Best available therapy, comprised of suboptimal treatment with ruxolitinib for the majority of patients, along with other treatments such hydroxyurea, interferon alfa, prednisone, or busulfan for a small proportion of patients, for the population previously treated with ruxolitinib or another JAK inhibitor.
Outcomes	Spleen volume reduction; myelofibrosis-associated symptoms; quality of life, adverse events.
Clinical claim	In consideration of the totality of evidence presented for fedratinib in the original submission and this resubmission, the clinical claim for fedratinib is one of non-inferiority overall for both efficacy and safety compared with ruxolitinib.

Source: Table 4-5, p18-20, p76 of the resubmission.
Abbreviations: JAK, Janus kinase.

2 Background

Registration status

2.1 Fedratinib was registered on the Australian Register of Therapeutic Goods on 13 February 2025 for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who are JAK inhibitor naïve or have been treated with ruxolitinib.

2.2 The product information includes a black box warning on the risks of serious and fatal encephalopathy, including Wernicke's, associated with fedratinib and that the risk of

Wernicke's encephalopathy is reduced via thiamine monitoring and prophylaxis with daily oral thiamine.

2.3 Fedratinib is subject to additional monitoring in Australia under the Black Triangle Scheme.

Previous PBAC consideration

2.4 Table 2 summarises the key matters of concern identified at the May 2025 PBAC meeting and how these were addressed in the resubmission.

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
Proposed restriction	
The PBAC noted the advice of the ESC and Pre-PBAC Response that noted the available evidence for fedratinib in a first-line setting (the JAKARTA trial) and agreed with the ESC that it would be simpler for patients and clinicians if a potential future listing for fedratinib was line agnostic alongside ruxolitinib and momelotinib and expressed a preference for such an approach (para 7.3, fedratinib PBAC minutes, May 2025 PBAC meeting).	A line agnostic listing based on the PBS restrictions for ruxolitinib and momelotinib was proposed.
The PBAC noted the restrictions for fedratinib should consider the inclusion of both an initial and continuing treatment phase, similar to the current PBS restriction structure for ruxolitinib and momelotinib; a criterion that the treatment must be sole PBS subsidised JAK inhibitor for the condition; include prescribing instructions to document the details of the patient's medical records for the bone marrow biopsy report confirming diagnosis of myelofibrosis and risk classification based on IPSS, DIPSS or age-adjusted DIPSS (consistent with the listings of ruxolitinib and momelotinib); and should include a caution that thiamine levels must be monitored whilst on treatment, as per the approved TGA boxed warning (para 7.6, fedratinib PBAC minutes, May 2025 PBAC meeting).	The proposed restriction addressed all the issues identified by the PBAC.
Clinical evidence	
The PBAC considered overall the evidence supports a conclusion that fedratinib is effective in myelofibrosis in the requested population. However, the PBAC considered there is a lack of long-term comparative efficacy and safety data for fedratinib in this setting (para 7.6, fedratinib PBAC minutes, May 2025 PBAC meeting).	The lack of long-term comparative efficacy and safety data was not addressed in the resubmission.
The PBAC considered that, if a first-line or line agnostic listing is sought, a new submission should be based primarily on the first line evidence from the JAKARTA trial (with the FREEDOM-2 evidence supportive of use in later line therapy and in patients who are intolerant or who do not respond/lose response to ruxolitinib) (para 7.13, fedratinib PBAC minutes, May 2025 PBAC meeting).	The resubmission was based primarily on evidence from the JAKARTA trial.
Economic Issues	
Overall, the PBAC considered the approach of a line agnostic listing on a cost-minimisation basis with ruxolitinib may be reasonable (para 7.3, fedratinib PBAC minutes, May 2025 PBAC meeting).	The resubmission requested a line agnostic listing on a cost-minimisation basis with ruxolitinib.
Financial Issues	
The PBAC considered the market share approach underestimated the market, as it failed to account for market expansion with the recent PBS listing of momelotinib and utilisation of non-JAK-inhibitor therapies (para 7.12, fedratinib PBAC minutes, May 2025 PBAC meeting).	The resubmission did not account for the potential market expansion associated with the recent PBS listing of momelotinib or utilisation of non-JAK inhibitor therapies.

Source: Fedratinib PBAC minutes, May 2025 PBAC meeting; Sections 1-4 of the resubmission.
Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; IPSS, International Prognostic Scoring System; JAK, Janus kinase; para, paragraph.

3 Requested listing

3.1 Secretariat suggestions and additions proposed are shown in italics and deletions are in strikethrough.

High-risk and intermediate-2 risk myelofibrosis

Initial/Continuing treatment

MEDICINAL PRODUCT medicinal product pack		Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
FEDRATINIB						
Fedratinib 100 mg capsule, 120		$10,515.60 (published) $[redacted] (effective)	1	120	5	Inrebic
Restriction Summary [new1] / Treatment of Concept: [new1A]						
Concept ID (for internal Dept. use)		**Category / Program:** ☒GENERAL - General Schedule (Code GE)				
		Prescriber type: ☒Medical Practitioners				
		Restriction type: ☒Authority Required – immediate assessment ~~/real time assessment by Services Australia (telephone/online application avenues)~~				
Prescribing rule level		***Administrative Advice:*** *No increase in the maximum quantity or number of units may be authorised.*				
		Administrative Advice: *No increase in the maximum number of repeats may be authorised.*				
		Administrative Advice: Special Pricing Arrangements apply.				
		Administrative Advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (OPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) OR the Age-Adjusted DIPSS (aaDIPSS).				
		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~~. *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 888 333.*				
		Indication: High-risk and intermediate-2 risk myelofibrosis				
		Treatment Phase: Initial treatment				
		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:				
		The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition				
		Population criteria:				
		Patient must be at least 18 years of age.				

	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
	Caution: Thiamine levels should be assessed as per the approved Therapeutic Goods Administration (TGA) Product Information (PI) prior to receiving treatment and should be closely monitored throughout the treatment period.

MEDICINAL PRODUCT medicinal product pack	**Dispensed Price for Max. Qty**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
FEDRATINIB					
Fedratinib 100 mg capsule, 120	$10,515.60 (published) $[redacted] (effective)	1	120	5	Inrebic

Restriction Summary [new2] / Treatment of Concept: [new2A]		
Concept ID (for internal Dept. use)		**Category / Program:** ☒GENERAL – General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required – streamlined [new code]
Prescribing rule level		***Administrative Advice:*** *No increase in the maximum quantity or number of units may be authorised.*
		Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
		Administrative Advice: Special Pricing Arrangements apply.
		Administrative Advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (OPSS) 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: 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

Intermediate-1 risk myelofibrosis
Initial/continuing treatment

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
FEDRATINIB					
Fedratinib 100 mg capsule, 120	$10,515.60 (published) $[redacted] (effective)	1	120	5	Inrebic

Restriction Summary [new3] / Treatment of Concept: [new3A]		
Concept ID (for internal Dept. use)		**Category / Program:** ☒ GENERAL – General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required – immediate assessment ~~/real time assessment by Services Australia (telephone/online application avenues)~~
Prescribing rule level		***Administrative Advice:*** *No increase in the maximum quantity or number of units may be authorised.*
		Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
		Administrative Advice: Special Pricing Arrangements apply.
		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: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (OPSS) 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.~~ *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 888 333.*
		Indication: intermediate-1 risk myelofibrosis
		Treatment Phase: Initial treatment
		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;
		OR
		Patient must have intolerance to prior treatment with a JAK inhibitor for this condition
		AND
		Clinical criteria:
		The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition
		Population criteria:

	Patient must be at least 18 years of age.
	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
	Caution: Thiamine levels should be assessed as per the approved Therapeutic Goods Administration (TGA) Product Information (PI) prior to receiving treatment and should be closely monitored throughout the treatment period.

MEDICINAL PRODUCT medicinal product pack	**Dispensed Price for Max. Qty**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
FEDRATINIB					
Fedratinib 100 mg capsule, 120	$10,515.60 (published) $[redacted] (effective)	1	120	5	Inrebic

Restriction Summary [new1] / Treatment of Concept: [new1A]		
Concept ID (for internal Dept. use)		**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required – streamlined [new code]
Prescribing rule level		***Administrative Advice:*** *No increase in the maximum quantity or number of units may be authorised.*
		Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
		Administrative Advice: Special Pricing Arrangements apply.
		Administrative Advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (OPSS) 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: 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
		~~**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.~~

	Caution: Thiamine levels should be assessed as per the approved Therapeutic Goods Administration (TGA) Product Information (PI) prior to receiving treatment and should be closely monitored throughout the treatment period.

3.2 The submission proposed a special pricing arrangement with a published DPMQ of $10,515.93 and an effective DPMQ of $[redacted] per pack of 120 capsules.

3.3 The proposed PBS restriction is broader than the TGA indication for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus kinase (JAK) inhibitor naïve or have been treated with ruxolitinib. The proposed restriction would allow use of fedratinib in patients who are neither JAK inhibitor naïve nor previously treated with ruxolitinib (i.e. patients who have been treated with momelotinib). The proposed restriction does not limit use to adults, while the TGA indication is for adult patients only.

3.4 The proposed restriction is consistent with the PBS restrictions for ruxolitinib and momelotinib for myelofibrosis (except for the anaemia requirements for momelotinib). The ESC considered the line agnostic listing aligned with PBS restrictions for ruxolitinib and momelotinib was appropriate.

3.5 The submission did not request for nurse practitioners to be eligible PBS prescribers of fedratinib. As part of the nurse practitioner/endorsed midwife prescribing review, the PBAC considered a list of oncology and haematology medicines listed on the General Schedule, and medicines listed on the Section 100 program that had been identified by stakeholders as being suitable for prescribing by nurse practitioners. The PBAC noted the stakeholder feedback did not include the comparator medicines, ruxolitinib nor momelotinib. Therefore, the PBAC did not review the suitability of nurse practitioner prescribing of these medicines. Ruxolitinib and momelotinib are currently limited to prescribing by medical practitioners.

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

4 Population and disease

4.1 Myelofibrosis is a type of Philadelphia chromosome-negative neoplasm affecting myeloid stem cells. Abnormal clonal proliferation of stem cells and an associated release of pro-inflammatory cytokines results in progressive bone marrow fibrosis, which may lead to the development of cytopaenias (i.e., anaemia, thrombocytopenia, and leukopenia) due to impairment of normal haematopoiesis. Compensatory production of blood cells in other organs (extramedullary haematopoiesis) leads to enlargement of the spleen and liver. Symptoms of myelofibrosis include fatigue, shortness of breath, pain associated with splenomegaly, bruising/bleeding, low grade fever, night sweats, bone pain, and weight loss. Some patients may be asymptomatic.

4.2 The resubmission positioned fedratinib as an alternative treatment option to ruxolitinib and momelotinib in JAK-inhibitor naïve patients unsuitable for allogeneic HSCT, with either: intermediate-2/high-risk myelofibrosis, or intermediate-1 risk

myelofibrosis with severe disease-related symptoms that are resistant, refractory or intolerant to available therapy.

4.3 Fedratinib was also positioned as an alternative to available therapies (ruxolitinib with or without other therapies, momelotinib, hydroxyurea, peginterferon alfa-2a, busulfan, prednisone) in patients with intermediate/high-risk myelofibrosis who experience persistent symptoms despite prior treatment with a JAK-inhibitor.

4.4 The recommended dose of fedratinib for patients with a baseline platelet count ≥50 × 10^9/L is 400 mg administered orally once a day. The product information states that fedratinib has not been studied in patients with a baseline platelet count <50 × 10^9/L. Dose modification is required for patients with severe renal impairment (creatinine clearance of 15 to 29 mL/min), patients using strong CYP3A4 inhibitors, and patients with specified Grade ≥3 haematologic/non-haematologic toxicities

4.5 Due to the association of fedratinib with the development of Wernicke's encephalopathy, assessment of thiamine levels and correction of thiamine deficiency (if detected) should be undertaken prior to fedratinib initiation. Additionally, patients should receive prophylaxis with oral thiamine 100 mg daily and have thiamine levels assessed periodically (as clinically indicated) while on treatment with fedratinib. Fedratinib should be immediately discontinued if Wernicke's encephalopathy is suspected.

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

5 Comparator

5.1 The resubmission nominated best available therapy (BAT) as the comparator for the population previously treated with ruxolitinib. The PBAC previously considered that BAT was an appropriate comparator for patients who have had prior ruxolitinib treatment (para 7.7, fedratinib PBAC minutes, May 2025 PBAC meeting).

5.2 The resubmission nominated ruxolitinib as the comparator for the population that is JAK inhibitor naïve. Ruxolitinib is an appropriate comparator for JAK inhibitor naïve patients.

5.3 The resubmission noted the recent PBS listing of momelotinib, a selective JAK1/JAK2 inhibitor that also inhibits activin A receptor type 1 (ACVR1), however, maintained that the patient groups treated with fedratinib and momelotinib are mutually exclusive for the majority of patients (para 5.4, fedratinib PBAC minutes, May 2025 PBAC meeting). The ESC considered there was likely to be limited overlap in the populations who would be considered for fedratinib and momelotinib, as momelotinib is restricted to patients with baseline haemoglobin of less than 100 g per litre and has demonstrated benefits in terms of reducing anaemia and would generally be a preferred treatment in those patients. This was also consistent with recently updated treatment guidelines and as such the ESC considered ruxolitinib to be the appropriate main comparator for JAK inhibitor naïve patients.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer inputs

6.2 The PBAC noted and welcomed the input from individuals (1) and organisations (2) via the Office of Health Technology Assessment Consultation Hub. The individual input was provided by someone who would like to access fedratinib to treat own health condition, but has never used fedratinib. The sole contributor described being continuously sick with no relief from the symptoms of myelofibrosis. Despite trying four different medications, including injections, the contributor stated they all appear to work temporarily, but then cease being effective. The input stated that fedratinib is important as it provides another option for a disease with limited medications and could possibly slow down the progression of the disease, or at least provide some relief from its side-effects.

6.3 The PBAC noted the advice received from the Myeloproliferative Neoplasms (MPN) Alliance Australia and Rare Cancers Australia. MPN Alliance Australia noted that myelofibrosis patients have the shortest life expectancy of MPN patients (other than those who progress to acute myeloid leukaemia). Therefore, being able to access the most appropriate JAK inhibitor when it is clinically needed, rather than having to fail ruxolitinib first, will allow clinicians to tailor the best treatment option for that patient in as timely a manner as possible. Having equal first-line access to fedratinib along with momelotinib will hopefully help avoid any additional adverse impacts that may arise from any initial ruxolitinib treatment. The input also welcomed the proposal to make fedratinib available to all intermediate myelofibrosis patients, and not limited to intermediate-2+ and high-risk patients as in the original submission.

6.4 Rare Cancers Australia stated there is much uncertainty for patients with this diagnosis as many of them are required to 'watch and wait' for bone marrow transplant options. Many, who are transfusion dependent, report the negative effects on their quality of life living this way, such as being fatigued, short of breath and pale due to being anaemic. Current treatments can come with significant side effects and may not be suitable for all patients. Patients often find themselves anaemic, requiring intermittent infusions. The input described that patients find the reported advantages of fedratinib appealing such as an overall improvement in the total symptom score, reducing symptoms such as fatigue, discomfort and bone pain and potentially achieve transfusion independency. Patients are hopeful that this treatment could significantly improve their quality of life, at any line of treatment. The input noted that patients should be aware of possible side effects which can include, but are not limited to, bleeding gums, chills, cough and nausea. Rare Cancers Australia noted that their patients emphasised the importance of discussing these potential side effects with their healthcare providers to determine if they are manageable in their individual

cases. The input included a patient experience with this condition which described the health and financial challenges they have faced to manage this condition.

Clinical trials

6.5 No head-to-head trials of fedratinib and ruxolitinib in the first line (JAK inhibitor naïve) setting were available. The resubmission was based on an indirect comparison of one placebo-controlled fedratinib trial (JAKARTA) and two ruxolitinib trials (one placebo-controlled trial (COMFORT-I) and one BAT-controlled trial (COMFORT-II)) in adults with intermediate-2 or high risk myelofibrosis who had not received prior treatment with a JAK inhibitor. Supportive data was provided from single-arm studies inclusive of patients with intermediate-1 risk myelofibrosis (fedratinib: JAKARTA 2, FREEDOM; ruxolitinib: JUMP, ROBUST, Barosi 2012).

6.6 The resubmission argued that the claim of superiority of fedratinib over BAT in the second line (ruxolitinib-experienced) setting was accepted by the PBAC in the May 2025 consideration of fedratinib. At the May 2025 meeting, the PBAC did not recommend the PBS listing of fedratinib for the treatment of patients with intermediate-2 and high-risk myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who have had prior ruxolitinib treatment. The primary reason for this outcome was due to the economic analysis provided in the submission (paras 7.1 and 7.2, fedratinib PBAC minutes, May 2025 PBAC meeting). The PBAC considered overall the evidence supports a conclusion that fedratinib is effective in myelofibrosis in the requested population. However, the PBAC considered there is a lack of long-term comparative efficacy and safety data for fedratinib in this setting (para 7.8, fedratinib PBAC minutes, May 2025 PBAC meeting). As no new publications or updated data were located in the resubmission's literature search, no further details on this population were provided in the resubmission. Details of the FREEDOM-2 trial, considered previously by the PBAC at the May 2025 PBAC meeting, have been included in the current commentary.

6.7 Efficacy and safety data from the FREEDOM-2 trial and safety data from the JAKARTA trial and single-arm fedratinib studies (FREEDOM, JAKARTA 2) were previously considered by the PBAC in the May 2025 fedratinib submission. The ruxolitinib trials (COMFORT-I and COMFORT-II) and single arm studies (JUMP, ROBUST, Barosi 2012) were previously considered by the PBAC in ruxolitinib submissions from July 2013, July 2014 and March 2015. The efficacy data from the JAKARTA, FREEDOM and JAKARTA 2 studies have not been previously considered by the PBAC.

6.8 Details of the trials presented in the resubmission are provided in Table 3.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Fedratinib trials		
FREEDOM-2	A Phase 3, multicenter, open-label, randomized study to evaluate the efficacy and safety of fedratinib compared to best available therapy in subjects with DIPSS-Intermediate or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis and previously treated with ruxolitinib: The "FREEDOM-2" trial. Harrison CN, Mesa R, Talpaz M, *et al*. Efficacy and safety of fedratinib in patients with myelofibrosis previously treated with ruxolitinib (FREEDOM2): Results from a multicentre, open-label, randomised, controlled phase 3 trial.	Clinical Study Report, August 2023 *Lancet Haematology* 2024; 11(10):e729-e740
JAKARTA	A phase 3, multicenter, randomized, double-blind, placebo-controlled, 3-arm study of SAR302503 in patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis with splenomegaly. Pardanani A, Harrison C, Cortes JE, et al. Safety and efficacy of fedratinib in patients with primary or secondary myelofibrosis: a randomized clinical trial. Pardanani A, Tefferi A, Masszi T, et al. Updated results of the placebo-controlled, phase III JAKARTA trial of fedratinib in patients with intermediate-2 or high-risk myelofibrosis. Mesa RA, Schaap N, Vannucchi AM, et al. Patient-reported effects of fedratinib, an oral, selective inhibitor of Janus kinase 2, on myelofibrosis-related symptoms and health-related quality of life in the randomized, placebo-controlled, phase III JAKARTA trial.	Clinical Study Report, December 2018 *JAMA Oncology* 2015; 1(5): 643-651. *British J Haematology* 2021; 195 (2): 244-248. *Hemasphere* 2021; 5(5):e553
JAKARTA 2	A Phase II, multicenter, open-label, single-arm study of SAR302503 in subjects previously treated with ruxolitinib and with a current diagnosis of intermediate or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis. Harrison CN, Schaap N, Vannucchi AM, et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA 2): a single-arm, open-label, non-randomised, phase 2, multicentre study. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib improves myelofibrosis-related symptoms and health-related quality of life in patients with myelofibrosis previously treated with ruxolitinib: patient-reported outcomes from the phase II JAKARTA2 trial.	Clinical Study Report, December 2018 Clinical Study Report Addendum, December 2018 *Lancet Haematology* 2017; 4(7): e317-e324 *Hemasphere* 2021; 5(5): e562.
FREEDOM	A Phase 3B, multicenter, single-arm, open-label efficacy and safety study of fedratinib in subjects with DIPSS-Intermediate or High Risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis and previously treated with ruxolitinib: The FREEDOM trial. Gupta V, Yacoub A, Mesa RA, et al. Safety and efficacy of fedratinib in patients with myelofibrosis previously treated with ruxolitinib: Primary analysis of FREEDOM trial.	Clinical Study Report, July 2022 *Leukemia & Lymphoma* 2024; 65(9): 1314-1324
Ruxolitinib trials		
COMFORT-I	Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety and survival with ruxolitinib in patients with myelofibrosis: results of a median 2-year follow-up of COMFORT-I. Mesa RA Gotlib J, Gupta V, et al. Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patient-reported outcomes in COMFORT-I: a randomized, double-blind, placebo-controlled trial.	*N Engl J Med* 2012; 366(9): 799-807. *Haematologica* 2013 98(12):1865-1871. *J Clin Oncol* 2013; 31(10): 1285-1292.

Trial ID	Protocol title/ Publication title	Publication citation
	Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I.	*Haematologica* 2015; 100(4): 479-488.
	Vannucchi AM, Kantarjian HM, Kiladjian J-J, et al. A pooled analysis of overall survival in COMFORT-I and COMFORT-II, 2 randomized phase III trials of ruxolitinib for the treatment of myelofibrosis.	*Haematologica* 2015; 100(9): 1139-1145.
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	Verstovsek S, Gotlib J, Mesa RA, et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and-II pooled analyses.	*J Hematol Oncol* 2017; 10: 156.
COMFORT-II	Harrison C, Kiladjian J-J, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis.	*N Engl J Med* 2012; 366(9): 787-798.
	Harrison CN, Mesa RA, Kiladjian J-J, et al. Health-related quality of life and symptoms in patients with myelofibrosis treated with ruxolitinib versus best available therapy.	*British J Haematology* 2013; 162(2): 229-239.
	Cervantes F, Vannucchi AM, Kiladjian J-J, et al. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis.	*Blood* 2013; 122(25): 4047-4053.
	Vannucchi AM, Kantarjian HM, Kiladjian J-J, et al. A pooled analysis of overall survival in COMFORT-I and COMFORT-II, 2 randomized phase III trials of ruxolitinib for the treatment of myelofibrosis.	*Haematologica* 2015; 100(9): 1139-1145.
	Harrison CN, Vannucchi AM, Kiladjian J-J, et al. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis.	*Leukemia* 2016; 30(8): 1701-1707.
	Verstovsek S, Gotlib J, Mesa RA, et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and-II pooled analyses.	*J Hematol Oncol* 2017; 10: 156.
JUMP	Al-Ali HK, Griesshammer M, le Coutre P, et al. Safety and efficacy of ruxolitinib in an open-label, multicenter, single-arm phase 3b expanded-access study in patients with myelofibrosis: a snapshot of 1144 patients in the JUMP trial.	*Haematologica* 2016; 101(9): 1065.
	Al-Ali HK, Griesshammer M, Foltz L, et al. Primary analysis of JUMP, a phase 3b, expanded-access study evaluating the safety and efficacy of ruxolitinib in patients with myelofibrosis, including those with low platelet counts.	*British J Haematology* 2020; 189(5): 888-903.
ROBUST	Mead AJ, Milojkovic D, Knapper S, et al. Response to ruxolitinib in patients with intermediate-1–, intermediate-2–, and high-risk myelofibrosis: results of the UK ROBUST Trial.	*British J Haematology* 2015; 170(1): 29-39.
Barosi 2012	Barosi G, Agarwal M, Zweegman S, et al. An individual patient supply program for ruxolitinib for the treatment of patients with primary myelofibrosis (PMD), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF).	*Blood* 2012; 21:2844

Source: Table 10, pp32-33; Table 11, p33 of the resubmission.
Note: Trials seen previously by the PBAC in the May 2025 consideration for fedratinib are shaded in blue.

6.9 The key features of the randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes
Fedratinib vs. placebo					
FREEDOM-2	201	Phase 3, multicentre, randomised, open label trial; 24-week randomised period with ongoing follow-up	*High*	Adults with high or intermediate-2 risk primary, post-PV or post-ET myelofibrosis who were relapsed/refractory or intolerant to ruxolitinib.	Spleen volume response rate, MFSAF TSS response rate, quality of life, overall survival, safety
JAKARTA	289	Phase 3, multicentre, double blind, 3 arm, placebo controlled RCT; 24 week randomised period with ongoing follow-up	*Unclear*	Adults with high or intermediate-2 risk primary, post-PV or post-ET myelofibrosis who had no prior JAK inhibitor treatment	Spleen volume response rate, MFSAF TSS response rate, quality of life, safety
Ruxolitinib vs. placebo or best available therapy					
COMFORT-I	309	Phase 3, multicentre, double-blind, placebo-controlled RCT; 24 week randomised period with ongoing follow-up	*Low*	Adults with intermediate-2 or high risk primary myelofibrosis, post-ET or post-PV myelofibrosis who had no prior therapy with JAK inhibitors and were refractory/intolerant to available therapies	Spleen volume response rate, MFSAF TSS response rate, quality of life, overall survival, safety
COMFORT-II	219	Phase 3, multicentre, randomised, open-label trial; 48 week randomised period with ongoing follow-up	*High*	Adults with intermediate-2 or high risk primary myelofibrosis, post-ET or post-PV myelofibrosis who had no prior therapy with JAK inhibitors	Spleen volume response rate, progression or leukaemia free survival, overall survival, safety

Source: Table 12, p37; Table 13, pp39-41; Table 15, pp43-44; Table 22, p53 of the resubmission; Table 3, p8 of the May 2025 fedratinib commentary.
Abbreviations: ET, essential thrombocythaemia; JAK, Janus kinase; MFSAF, Myelofibrosis Symptom Assessment Form; PV, polycythaemia vera; RCT, randomised controlled trial; TSS, total symptom score.
Note: Trials seen previously by the PBAC in the May 2025 consideration for fedratinib are shaded in blue.

6.10 The open label FREEDOM-2 trial randomised patients to treatment with either fedratinib 400 mg once daily or best available therapy for 24 weeks. In the best available therapy arm, 77.6% of patients were treated with ruxolitinib. Patients in the best available therapy arm could switch from best available therapy to fedratinib treatment at any time before the Cycle 6 response assessment in the event of a confirmed progression of splenomegaly (by MRI/CT scan) or after the Cycle 6 response assessment. Subjects were allowed to continue study treatment beyond the initial 24 week period until the occurrence of unacceptable toxicity, lack of therapeutic effect, progression of disease or withdrawal of consent. Further details of the FREEDOM-2 trial design and patient characteristics are in Sections 2.3 and 2.4 of the commentary.

6.11 The JAKARTA trial was a three-arm placebo-controlled trial, with the two active treatment arms consisting of fedratinib 400 mg or fedratinib 500 mg daily. The resubmission noted that the 500 mg daily dose is not used in clinical practice nor is it TGA approved, and results from this arm of the trial were not presented in the

resubmission. This was appropriate. The overall risk of bias for the JAKARTA trial was unclear, due to the sponsor of the trial changing multiple times throughout the clinical development program, and the full clinical hold imposed by the FDA across the fedratinib clinical development program which meant that all patients permanently discontinued fedratinib treatment early (see paragraph 6.13 below). In addition, the JAKARTA trial was limited to patients with intermediate-2 or high risk myelofibrosis only. There was no randomised controlled trial evidence for the intermediate-1 population, which was limited to single-arm data.

6.12 Patients in the JAKARTA trial were randomised to treatment with fedratinib or placebo for 24 weeks (divided into 6 × 28 day cycles), but continued to receive their assigned study treatment as long as they were benefitting (defined as complete or partial remission, clinical improvement, or stable disease, and no disease progression or relapse, or unacceptable toxicity requiring treatment discontinuation). Patients in the placebo arm could switch to fedratinib treatment after disease progression, defined as an increase in spleen volume of ≥25% from baseline, leukaemic transformation, or an increase in peripheral blood blast percentage of ≥20%. There were 71 patients from the placebo arm who crossed over to one of the two fedratinib arms (10 of whom crossed over prior to the end of Cycle 6). Patients who crossed over after disease progression were considered to be non-responders.

6.13 Following notification of cases consistent with events of Wernicke's encephalopathy in subjects treated with fedratinib, the fedratinib clinical development program was terminated in November 2013, at which time all subjects worldwide were permanently discontinued from fedratinib treatment, given the option to receive thiamine supplementation for at least 90 days and followed during this period. At the time of study termination, 144 patients in the JAKARTA trial were still receiving fedratinib (including 51 of 96 patients in the 400 mg fedratinib arm, and 26 of 35 placebo patients who crossed over to the 400 mg fedratinib arm). The clinical hold for fedratinib was lifted in August 2017, with provisions for the need for risk-mitigation strategies for Wernicke's encephalopathy.

6.14 The COMFORT-I trial was a double-blind, placebo-controlled randomised trial comparing ruxolitinib at a starting dose of 15 mg or 20 mg twice daily (determined by baseline platelet count: 15 mg for ≥100 to 200 × 10^9/L, and 20 mg for >200 × 10^9/L) to placebo. The COMFORT-II trial was an open label trial, with patients randomised in a 2:1 ratio to ruxolitinib 15 mg or 20 mg twice daily (determined by baseline platelet count as above) or best available therapy, which included any commercially available agents as monotherapy or in combination, or no therapy at all. In both ruxolitinib trials, the ruxolitinib dose could be increased up to 25 mg twice daily, or decreased in response to adverse events, with treatment continuing while the patient continued to derive a clinical benefit. Patients in the placebo arm of the COMFORT-I trial or best available therapy arm of the COMFORT-II trial could cross over to active treatment with ruxolitinib on disease progression.

Comparative effectiveness

Fedratinib trials

6.15 Results from the FREEDOM-2 trial comparing fedratinib and best available therapy in patients with intermediate-2 or high risk myelofibrosis who had received previous treatment with ruxolitinib were not presented in the resubmission. Results from the May 2025 submission for the primary endpoint and key secondary outcomes at Week 24 from FREEDOM-2 are briefly summarised in Table 5.

Table 5: Results of primary and key secondary outcomes from FREEDOM-2, ITT population

Outcome at week 24	Fedratinib N = 134	BAT N = 67	Difference in proportion (95% CI)
≥35% spleen volume reduction, n (%)	48 (35.8%)	4 (6.0%)	**29.6 (19.9, 39.4)**
≥25% spleen volume reduction, n (%)	63 (47.0%)	9 (13.4%)	**33.5 (21.9, 45.1)**
Spleen response by palpation, n (%)	38 (28.4%)	5 (7.7%)	**19.9 (10.0, 29.7)**
≥50% reduction in MFSAF TSS, n (%)	43 (34.1%)	11 (16.9%)	**17.1 (4.8, 29.4)**

Source: Table 4, p10, Table 5, p11 of the May 2025 fedratinib commentary.
Abbreviations: BAT, best available therapy; CI, confidence interval; ITT, intent-to-treat; MFSAF, myelofibrosis symptom assessment form; TSS, total symptom score.
Bold indicates statistically significant results.

6.16 In the FREEDOM-2 trial, a statistically significantly greater proportion of patients treated with fedratinib achieved at least a 35% spleen volume reduction and at least 50% reduction in MFSAF total symptom scores from baseline compared to patients in the best available therapy arm.

6.17 Quality of life in the FREEDOM-2 trial was measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EQ-5D-5L visual analogue scale and utility score (using the US value set). For the EORTC QLQ-C30, low questionnaire completion rates and clinically important baseline score differences between treatment arms, favouring fedratinib, limit the usefulness of results. Although questionnaire completion rates were similarly low for the EQ-5D-5L, there were no notable differences in baseline scores. Both treatment groups had increased mean EQ-5D-5L VAS and utility scores (indicating improvement) from baseline during the treatment period through to the end of Cycle 6. Mean change from baseline in the VAS score was greater in the fedratinib arm than the best available therapy arm, while change in utility scores was similar across treatments. Differences between treatment arms were not assessed statistically.

6.18 Results of the primary and key secondary spleen response outcomes from the JAKARTA trial in patients with intermediate-2 or high risk myelofibrosis with no prior treatment with a JAK inhibitor are summarised in Table 6.

Table 6: Results of primary and key secondary spleen response outcomes from JAKARTA, ITT population

Outcome at week 24	Fedratinib 400 mg N = 96	Placebo N = 96	Difference in proportion (95% CI)
Spleen volume reduction outcomes at Week 24 (end of Cycle 6)			
Primary outcome: Patients with ≥35% SVR with MRI/CT confirmation 4 weeks later, n (%)	35 (36.5)	1 (1.0)	**35.42 (24.2, 46.7)**
Patients with ≥35% SVR with no confirmation, n (%)	45 (46.9)	1 (1.0)	**45.83 (34.2, 57.5)**
Patients with ≥25% spleen volume reduction with MRI/CT confirmation 4 weeks later, n (%)	47 (49.0)	2 (2.1)	**46.88 (35.0, 58.8)**

Source: Table 23, p57 of the resubmission; JAKARTA clinical study report

Abbreviations: CI, confidence interval; CT, computed tomography; ITT, intent-to-treat; MRI, magnetic resonance imaging; SVR, spleen volume reduction.

Note: The JAKARTA clinical study report noted that 10 patients in the fedratinib 400 mg arm did not have confirmation of ≥35% spleen volume reduction 4 weeks after the end of Cycle 6, with 6 patients having a spleen volume reduction of less than 35% (ranging from 13% to 34% spleen volume reduction) and the remainder with no scans performed or scans outside of the required time window for confirmation. One patient with spleen volume reduction of 13% at the time of the confirmatory scan had permanently discontinued treatment after the end of Cycle 6 assessment.

Bold indicates statistically significant results.

6.19 In the JAKARTA trial, fedratinib 400 mg was associated with a statistically significantly greater proportion of responders compared to placebo for the primary and key secondary spleen response outcomes. For the secondary outcome of duration of spleen response, follow-up was subject to extensive censoring due to the early termination of the study, and ranged from 0 to 18.2 months for the 400 mg fedratinib arm. Median duration of spleen response in the fedratinib 400 mg arm was 18.2 months. Six patients experienced disease progression or death during the trial. One patient in the placebo arm demonstrated a spleen response during the first 6 treatment cycles, then crossed over to receive fedratinib 500 mg, and continued to demonstrate a response until the end of the study.

6.20 Results of the key secondary outcome from JAKARTA, proportion of patients with at least a 50% reduction in MFSAF total symptom scores from baseline to the end of Cycle 6 (in patients with a non-missing baseline total symptom score) are summarised in Table 7.

Table 7: Proportion of patients with at least 50% reduction in MFSAF total symptom scores from baseline to end of Cycle 6, JAKARTA, ITT population with non-missing baseline total symptom score

Outcome at week 24	Fedratinib 400 mg N = 91	Placebo N = 85	Difference in proportion (95% CI)
≥50% reduction in TSS, n (%)	36 (39.6)	7 (8.2)	**31.33 (18.0, 44.6)**

Source: Table 24, p57 of the resubmission

Abbreviations: ITT, intent-to-treat; MFSAF, Myelofibrosis Symptom Assessment Form; TSS, total symptom score.

Note: The MFSAF asks patients to report myelofibrosis associated symptoms experienced within the prior 7 days, including night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on the left side, and bone or muscle pain. Each symptom is scored from 0 to 10, with the total symptom score (0 to 60) the sum of the scores for the 6 symptoms, and higher scores corresponding to more severe symptoms. Two (2.1%) fedratinib 400 mg treated subjects and 4 (4.2%) placebo-treated subjects had a baseline TSS of zero (no symptoms).

Bold indicates statistically significant results.

6.21 A statistically significantly greater proportion of patients treated with fedratinib 400 mg achieved at least a 50% reduction in MFSAF total symptom scores compared to patients in the placebo arm. Results in the symptom analysis population (fedratinib 400 mg n = 89, placebo n = 81) that additionally excluded patients with a baseline TSS of zero, were consistent with the ITT population results.

6.22 Quality of life in the JAKARTA trial was an exploratory outcome measured by the EQ-5D-5L utility score (value set not specified) and visual analogue scale (VAS). Patients in the fedratinib 400 mg arm had increased mean EQ-5D-5L VAS and utility scores (indicating improvement) from baseline to the end of Cycle 6, while a slight decrease in scores was noted in the placebo arm. Differences between treatment arms were not assessed statistically.

6.23 Analyses of survival outcomes were not performed as planned in the JAKARTA trial due to the early termination of the study.

Indirect comparison with ruxolitinib

6.24 The resubmission presented the results of an indirect treatment comparison of one fedratinib trial (JAKARTA), and two ruxolitinib trials (COMFORT-I and COMFORT-II) of patients with intermediate-2 or high risk myelofibrosis who had not received previous treatment with a JAK inhibitor. The resubmission argued that despite the differences in study design, inclusion and exclusion criteria, endpoint definitions and baseline characteristics, the JAKARTA, COMFORT-I and COMFORT-II trials were considered sufficiently homogenous and similar to perform standard indirect treatment comparisons.

6.25 Noting that treatment-effect modifiers may potentially confound results in an anchored ITC, the resubmission conducted a matching adjusted indirect comparison (MAIC) to explore the potential impact of treatment effect modifiers on the results. However, data for only one of two identified potential treatment effect modifiers, JAK2 mutation status, was available across all trials. There were no adjusted analyses conducted for the outcome of total symptom score response as no potential treatment effect modifiers were identified for this endpoint. Given differences in trial eligibility criteria for baseline platelet counts (≥50 × 10^9/L in the JAKARTA trial compared to ≥100 × 10^9/L in the COMFORT trials), the resubmission also conducted indirect treatment comparisons of the subgroup of JAKARTA patients with baseline platelet counts ≥100 × 10^9/L, consistent with the eligibility requirements of the COMFORT-I and COMFORT-II trial populations.

6.26 The resubmission assumed that the best available therapy arm of the COMFORT-II trial was a common comparator to placebo, based on a post hoc comparison of baseline characteristics, spleen volume and spleen length response, patient-reported outcomes and adverse events of the COMFORT-I (n = 154) and COMFORT-II (n = 73) control arms (Mesa 2014). The resubmission argued that the study concluded that BAT provides little improvement in splenomegaly, symptoms or quality of life compared with placebo. The BAT arm of the COMFORT-II trial included 49 patients (67%) who received any active therapy (the most commonly used agents were hydroxyurea and glucocorticoids) and 24 patients (33%) who received no therapy during the randomised treatment phase. When the BAT arm of COMFORT-II was separated into active versus no treatments, a clinically significant mean change from baseline in global health status was noted in the BAT active treatment group, and a comparison of palpable spleen length over time showed a decrease in spleen length at Week 24 in

the BAT active treatment group compared to no change in the overall BAT arm and an increase in spleen length in the placebo arm. The study authors noted that the comparison between control arms was limited by differences in patient populations and eligibility and inclusion criteria of the two trials. It is unclear if the assumption of comparable control arms for the purposes of an anchored indirect comparison was reasonable.

6.27 The results of the indirect comparisons for the proportion of subjects achieving ≥35% spleen volume reduction from baseline to Week 24, including an analysis using the subgroup of JAKARTA trial patients with platelets ≥100 × 10^9/L, are presented in Table 8.

Table 8: Summary of results of the indirect comparison for ≥35% spleen volume reduction

Analysis performed	JAKARTA		COMFORT-I		COMFORT-II	
	FED 400 mg	PBO	RUX	PBO	RUX	BAT
≥35% spleen volume reduction from baseline to Week 24 (using JAKARTA ITT population)						
Absolute responses, n/N (%)	45/96 (46.9)	1/95 (1.0)	65/155 (41.9)	1/153 (0.7)	46/144 (31.9)	0/72 (0)
Bucher ITC, Risk Difference (95% CI)			4.6% (-8.3, 17.4)		13.9% (1.2, 26.6)	
MAIC (Bucher), Risk Difference (95% CI) [a]			7.9% (-5.2, 20.9)		16.3% (3.5, 29.0)	
Frequentist NMA, Risk Difference (95% CI)			9.4% (-2.2, 20.9)			
MAIC (frequentist NMA), Risk Difference (95% CI) [a]			12.3% (0.6, 24.0)			
≥35% spleen volume reduction from baseline to Week 24 (using JAKARTA subgroup with platelets ≥100 × 10^9/L)						
Absolute responses, n/N (%)	40/82 (48.8)	1/77 (1.3)	65/155 (41.9)	1/153 (0.7)	46/144 (31.9)	0/72 (0)
Bucher ITC, Risk Difference (95% CI)			6.2% (-7.4, 19.8)		15.5% (2.1, 29.0)	
MAIC (Bucher), Risk Difference (95% CI) [a]			10.4% (-3.2, 24.1)		18.5% (5.1, 31.9)	
Frequentist NMA, Risk Difference (95% CI)			11.0% (-1.4, 23.4)			
MAIC (frequentist NMA), Risk Difference (95% CI) [a]			14.7% (2.4, 27.1)			

Source: Table 26, p67 of the resubmission; Table 11, Attachment 12 of the resubmission.
Abbreviations: BAT, best available therapy; FED, fedratinib; ITC, indirect treatment comparison; MAIC, matched adjusted indirect comparison; NMA, network meta-analysis; PBO, placebo; RUX, ruxolitinib
[a] The MAIC included an adjustment for JAK2 status at baseline (mutant or wildtype).

6.28 The network meta-analysis including both COMFORT trials demonstrated comparable spleen volume reduction rates in patients treated with fedratinib 400 mg compared to ruxolitinib while the MAIC analysis, adjusted for the imbalance in JAK2 mutation status, resulted in greater proportions of fedratinib-treated patients with ≥35% spleen volume reduction compared to ruxolitinib. Indirect comparisons of the JAKARTA trial with the COMFORT-I trial, regardless of approach (Bucher ITC or MAIC), demonstrated comparable proportions of patients with spleen volume response, while the comparison with the COMFORT-II trial resulted in higher proportions of fedratinib treated patients with spleen volume response compared to ruxolitinib. Results of the comparisons using the subgroup of JAKARTA patients with platelets ≥100 × 10^9/L were consistent with the ITT population comparison.

6.29 The results of the indirect comparisons should be interpreted with caution due to differences in common reference arms, eligibility criteria, and outcome definitions between the trials. Additionally, overall survival and progression-free survival comparisons could not be conducted due to early termination of the JAKARTA trial,

and only one ruxolitinib trial was suitable for inclusion in the total symptom score comparison. While the results of the MAIC analyses were generally consistent with the unadjusted results, only one of the two identified treatment effect modifiers were included for matching in the spleen size comparison. It is unclear whether all relevant treatment effect modifier variables were identified, as the resubmission did not present the results of any literature searches for additional treatment effect modifiers that were not identified in the post hoc analyses of the JAKARTA trial. The resubmission also noted that the indirect comparisons were post hoc analyses and were not powered a priori to show a statistically significant result.

6.30 The Pre-Sub-Committee Response (PSCR) acknowledged early termination of the fedratinib clinical development program meant no overall survival or progression-free survival analyses could be conducted. However, the PSCR presented a descriptive comparison of the common reference arms, inclusion criteria and outcome definitions, and argued it was reasonable to conclude the noted differences were likely to have a negligible impact on the overall conclusion of non-inferior comparative effectiveness. In addition, the PSCR argued that for the MAIC approach, matching was not undertaken for the outcome of total symptom score because no treatment effect modifiers were identified for that outcome.

Single arm studies

6.31 The resubmission included supportive clinical data inclusive of intermediate-1 risk patients from single arm studies of fedratinib (JAKARTA 2 and FREEDOM) and ruxolitinib (ROBUST, JUMP, Barosi 2012) in Appendix 1 of the resubmission. The resubmission acknowledged the limited data for fedratinib in the intermediate-1 risk subgroup, but noted that this was also the case for ruxolitinib. The resubmission noted that a brief summary of results from the JAKARTA 2 and FREEDOM studies was included in the May 2025 fedratinib submission, and that the PBAC has previously considered the ruxolitinib studies as part of the March 2015 ruxolitinib submission. Data from these studies were summarised in the resubmission with a focus on data pertaining to patients with intermediate-1 risk myelofibrosis.

6.32 The JAKARTA 2 and FREEDOM fedratinib studies both presented results for ≥35% SVR response rate in the ITT population and the subgroup of patients with intermediate-1 disease. In the JAKARTA 2 study, 40/83 (48.2%) patients in the ITT population and 8/13 (61.5%) patients in the intermediate-1 subgroup achieved spleen response at the end of week 24. In the JAKARTA 2 'stringent cohort' which used stricter definitions for patients who were refractory, intolerant or resistant to treatment with ruxolitinib, 24/79 (30.4%) patients in the ITT population and 2/11 (18.2%) patients in the intermediate-1 subgroup achieved spleen response. In the FREEDOM study 9/35 (25.7%) patients in the ITT population and 4/13 (30.8%) patients in the intermediate-1 risk subgroup achieved spleen response at week 24.

6.33 There were limited data available to compare fedratinib to ruxolitinib in the intermediate-1 risk subgroups.

Comparative harms

6.34 Adverse events during the randomised phase of the FREEDOM-2 trial are summarised in Table 9.

Table 9: Summary of key adverse events in the FREEDOM-2 trial safety population, randomised treatment phase

Adverse events during the randomised treatment phase (24 weeks), n (%)	Fedratinib N = 134	BAT N = 67
Any TEAE	132 (98.5)	65 (97.0)
Treatment-related TEAE	109 (81.3)	23 (34.3)
Serious TEAE	44 (32.8)	16 (23.9)
Serious treatment-related TEAE	20 (14.9)	2 (3.0)
Grade ≥3 TEAE	88 (65.7)	29 (43.3)
Grade ≥3 treatment-related TEAE	52 (38.8)	8 (11.9)
TEAE leading to death	7 (5.2)	1 (1.5)
Treatment related TEAE leading to death	1 (0.7)	0 (0)
TEAE leading to dose reduction	41 (30.6)	7 (10.4)
TEAE leading to dose interruption	42 (31.3)	4 (6.0)
TEAE leading to permanent treatment discontinuation	13 (9.7)	4 (6.0)
AE of special interest	88 (67.5)	27 (40.3)
Treatment-related AE of special interest	42 (31.3)	8 (11.9)
Commonly reported adverse events		
Diarrhoea	56 (41.8)	2 (3.0)
Nausea	49 (36.6)	10 (14.9)
Constipation	28 (20.9)	6 (9.0)
Vomiting	21 (15.7)	3 (4.5)
Abdominal pain	12 (9.0)	9 (13.4)
Anaemia	52 (38.8)	23 (34.3)
Thrombocytopenia	36 (26.9)	11 (16.4)
Encephalopathy	18 (13.4)	2 (3.0)
Wernicke's encephalopathy	1 (0.7)	0 (0)

Source: Table 47, pp77-80 of the submission.

Abbreviations: AE, adverse event; TEAE, treatment emergent adverse event.

Note: Adverse events of special interest included: encephalopathy including confirmed and suspected cases of Wernicke's encephalopathy, thiamine levels below normal range with or without signs or symptoms of Wernicke's encephalopathy, new malignancy after start of study treatment, progression of myelofibrosis to acute myeloid leukaemia, cardiac failure or cardiomyopathy, Grade 3 or 4 hyperlipasemia or hyperamylasemia or events of pancreatitis, Grade 3 or 4 ALT or AST or total bilirubin elevation or events of hepatotoxicity, Grade 3 or 4 anaemia, Grade 3 or 4 thrombocytopenia, pregnancy, overdose.

Note: Data seen previously by the PBAC in the May 2025 consideration for fedratinib are shaded in blue.

6.35 In the FREEDOM-2 trial, almost all patients in both treatment arms reported a treatment emergent adverse event during the first 6 cycles (24 weeks) of treatment, however a greater proportion of patients in the fedratinib arm reported adverse events of all types (treatment-related, serious, grade ≥3), and adverse events leading to death, dose reduction, dose interruption or treatment discontinuation, compared to patients in the best available therapy arm. The most frequently reported adverse events in the fedratinib arm were gastrointestinal events (diarrhoea, nausea, constipation, or vomiting), anaemia and thrombocytopenia. The overall incidence of Grade 3 or 4 thrombocytopenia was higher in the fedratinib arm than the best available therapy arm, as was the incidence of Grade 3 or 4 anaemia. The incidence of Grade 3 or 4 gastrointestinal disorders (including upper abdominal pain, diarrhoea and gastrointestinal haemorrhage reported for more than 1 patient in the fedratinib arm)

was also higher in the fedratinib arm compared to the best available therapy arm. The May 2025 submission noted that these adverse events are consistent with all prior studies of fedratinib in myelofibrosis, and argued that the lower incidence of treatment emergent adverse events in the best available therapy arm were due to the majority of patients continuing treatment with previously-received ruxolitinib, rather than receiving a new treatment for which they had no prior exposure. In the best available therapy arm, the most frequently reported adverse events were anaemia, asthenia, thrombocytopenia, nausea and fatigue.

6.36 Encephalopathy-related events were reported in the FREEDOM-2 trial for 13.4% of patients in the fedratinib arm (3.0% in the best available therapy arm), including one case of Wernicke's encephalopathy (grade 1, non-serious, with symptoms resolved within 24 hours with thiamine supplementation). Thiamine levels below normal range were reported for 16.4% of fedratinib-treated patients compared to 3.0% in the best available therapy arm. It is unclear whether the incidence of encephalopathy events during the trial would be representative of clinical practice, given the product information states that all patients should receive prophylaxis with oral thiamine whilst on treatment with fedratinib, while in the trial only 64.5% of patients in the fedratinib arm received thiamine supplementation.

6.37 A naïve comparison of adverse events reported in the JAKARTA, COMFORT-I and COMFORT-II trials are presented in Table 10. Adverse events for the JAKARTA and COMFORT-I trials were reported up to Week 24, while the COMFORT-II trial reported adverse events to Week 48.

Table 10: Adverse events reported in the JAKARTA, COMFORT-I and COMFORT-II trials (to Week 24/48)

% patients	JAKARTA (24 Weeks)		COMFORT-I (24 Weeks)		COMFORT-II (48 Weeks)	
	FED 400 mg	PBO	RUX	PBO	RUX	BAT
Any AE	99.0	93.7	97.4	98.0	99.3	90.4
Serious AE	20.8	23.2	27.7	35.1	30.1	28.8
Grade 3 or 4 AE	52.1	30.5	47.1	44.4	41.8	24.7
Discontinuation due to AE	13.5	8.4	11.0	10.6	8.2	5.5
Death due to AE	1.0	6.3	5.8	7.3	4.1	5.5
Haematological AE (Grade 3 or 4)						
Anaemia	41.7 [a]	24.2 [a]	45.2 [a]	19.2 [a]	42	31
Thrombocytopaenia	11.4 [a]	9.5 [a]	12.9 [a]	1.3 [a]	8	7
Non-haematological AEs						
Diarrhoea (any grade)	65.6	15.8	23.2	21.2	23	12
Diarrhoea (Grade 3 or 4)	5.2	0	1.9	0	1	0
Nausea (any grade)	61.5	14.7	14.8	19.2	13	7
Nausea (Grade 3 or 4)	0	0	0	0.7	1	0
Vomiting (any grade)	38.5	5.3	12.3	9.9	NR	NR
Vomiting (Grade 3 or 4)	3.1	0	0.6	0.7	NR	NR

Source: Table 13, Attachment 12 of the resubmission

Abbreviations: AE, adverse event; BAT, best available therapy; FED, fedratinib; NR, not reported; PBO, placebo; RUX, ruxolitinib

[a] The ITC report (Attachment 12 of the resubmission) noted that proportions of patients experiencing Grade 3 or 4 anaemia or thrombocytopaenia adverse events in JAKARTA and COMFORT-I were derived based on laboratory values. The JAKARTA clinical study report had smaller proportions of patients with Grade 3 or 4 treatment emergent adverse events of anaemia (fedratinib 400 mg, 30.2%; placebo 7.4%) and thrombocytopaenia (fedratinib 400 mg, 5.2%; placebo 6.3%).

6.38 Almost all patients across all treatment and control arms reported at least one adverse event. The incidence of discontinuation due to an adverse event, and Grade 3 or 4 adverse events was numerically higher for fedratinib treated patients compared to those treated with ruxolitinib, while greater proportions of ruxolitinib treated patients experienced serious adverse events and deaths due to adverse events. The incidence of Grade 3 or 4 anaemia and thrombocytopaenia (derived from laboratory values) were similar in the fedratinib and ruxolitinib treatment arms.

6.39 There was a larger proportion of fedratinib-treated patients who experienced diarrhoea, nausea or vomiting of any grade compared to patients treated with ruxolitinib. The resubmission noted that at the time of the JAKARTA study, anti-emetic prophylaxis was not provided to subjects which could explain the increased incidence of nausea and vomiting.

6.40 The assessment of the relative safety of fedratinib and ruxolitinib in the first-line setting was limited by the naïve comparison, and differences in populations and treatment durations between trials.

6.41 The resubmission noted that there were 4 potential cases of Wernicke's encephalopathy (including one confirmed case) reported in the JAKARTA trial, all of which were reported in the fedratinib 500 mg arm in patients who had predisposing factors known to increase the risk of Wernicke's encephalopathy in any population. The resubmission stated that this risk is now managed by thiamine level testing and ongoing thiamine supplementation, as recommended in the fedratinib Product Information.

Benefits/harms

6.42 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

6.43 In consideration of the totality of evidence presented for fedratinib in the May 2025 submission and the current resubmission, the resubmission described fedratinib as non-inferior in terms of efficacy and safety compared to ruxolitinib.

6.44 The claim of non-inferior efficacy presented in the submission was adequately supported by the evidence presented in the resubmission. However, the following issues should be considered:

- The early termination of the JAKARTA trial meant that planned survival outcomes could not be assessed, and available data for long term safety of fedratinib for first line treatment of myelofibrosis was limited.
- Interpretation of the results of the indirect comparison of fedratinib and ruxolitinib in the first line setting was limited by differences in trial eligibility criteria and different outcomes across the included trials, and limited available information from the ruxolitinib trials to allow adjustment for potential treatment effect modifiers in the matched adjusted indirect comparison.

- At the May 2025 meeting, the PBAC considered that the claim of superior comparative effectiveness compared to best available therapy [in the second line setting] was reasonable (para 6.38, fedratinib PBAC minutes, May 2025 PBAC meeting). However, the PBAC considered there is a lack of long-term comparative efficacy and safety data for fedratinib in this setting (para 7.8, fedratinib PBAC minutes, May 2025 PBAC meeting).
- There were limited data available to compare fedratinib to ruxolitinib in the subgroup of patients with intermediate-1 risk myelofibrosis.

6.45 The ESC considered that whilst there were some uncertainties with the data arising from both the early termination of the JAKARTA trial and differences between the fedratinib and ruxolitinib trials, the clinical claim of non-inferior comparative effectiveness was overall reasonable.

6.46 The claim of non-inferior safety was not adequately supported by the evidence presented in Section 2 of the resubmission.

- The comparison of adverse events for fedratinib and ruxolitinib in the first line setting was limited to a descriptive analysis only, however the naïve comparison of adverse events suggested that there was a higher incidence of Grade 3 or 4 adverse events, and gastrointestinal adverse events of any grade reported in the fedratinib treatment arms compared to the ruxolitinib treatment arms.
- At the May 2025 meeting, for treatment of patients with intermediate-2 and high-risk myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who have had prior ruxolitinib treatment, the PBAC considered that the claim of inferior comparative safety of fedratinib compared to best available therapy [predominantly ruxolitinib] was reasonable (para 6.39, fedratinib PBAC minutes, May 2025 PBAC meeting). The PBAC considered the safety profile of fedratinib raised concerns, particularly given the observed rate of encephalopathy, including Wernicke's (or suspected cases associated with thiamine levels below normal range). The Committee noted the TGA registration includes a box warning and states that all patients should receive prophylaxis with oral thiamine whilst on treatment with fedratinib (para 7.9, fedratinib PBAC minutes, May 2025 PBAC meeting).

6.47 The PSCR and pre-PBAC response acknowledged Grade 3 or 4 adverse events and gastrointestinal events of any grade were reported in more patients treated with fedratinib compared to ruxolitinib, but that these events could be readily mitigated through the use of anti-emetic treatments and the cost minimisation approach (presented in the following section) includes offsets for these medicines. With respect to Wernicke's encephalopathy, the PSCR stated an extensive review suggested the events were most likely a consequence of poor control of the aforementioned gastrointestinal adverse events in undernourished patients, and noted provisions for the need for risk mitigation strategies are outlined in the Product Information for fedratinib.

6.48 The ESC considered the claim of non-inferior comparative safety was not supported, given the types and severity of adverse events observed for fedratinib relative to ruxolitinib, as well as the identified risk of Wernicke's encephalopathy. The ESC considered a claim of inferior comparative safety to ruxolitinib was more appropriate. The ESC acknowledged risk mitigation strategies for Wercnicke's encephalopathy, such as thiamine monitoring and supplementation, are outlined in the approved Product Information and proposed for inclusion in the PBS listing. The pre-PBAC response accepted the clinical claim of inferior safety based on the ESC's concerns.

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

6.50 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data. However, the PBAC considered that the claim of inferior comparative safety in the pre-PBAC response was reasonable and adequately supported by the data.

Economic analysis

6.51 The resubmission applied a cost-minimisation approach (CMA) to calculating the proposed effective price for fedratinib compared to ruxolitinib for patients with intermediate-1, intermediate-2 or high risk myelofibrosis across all lines of therapy (see Table 11).

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

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, efficacy is assumed to be at least non-inferior
Therapeutic claim: safety	Based on evidence presented in Section 2, safety is assumed to be non-inferior
Evidence base	Indirect treatment comparison of fedratinib and ruxolitinib in the first line treatment setting (intermediate-2 and high risk patients; JAKARTA, COMFORT-I, COMFORT-II trials); direct comparison of fedratinib and BAT (predominantly ruxolitinib) in the second line treatment setting (intermediate-2 and high risk patients; FREEDOM-2 trial); naïve comparison of fedratinib and ruxolitinib in intermediate-1 risk patients (single arm studies).
Equi-effective doses	Fedratinib 349.96 mg/day is equivalent to ruxolitinib 27.1 mg/day [a]
Direct medicine costs	Fedratinib = $[redacted] per day; ruxolitinib = $[redacted] per day (at assumed effective AEMP)
Other costs or cost offsets	Adverse event treatment at $0.44 per day for fedratinib only (treatment of diarrhoea $0.23 per day; thiamine monitoring $0.17 per day; thiamine supplementation $0.04 per day). The resubmission noted that the Product Information for fedratinib also recommends prophylactic anti-emetic therapy (e.g. 5-HT3 receptor antagonists), however costs for these were not included in the cost-minimisation approach.

Source: Table 30, p79 of the resubmission.

Abbreviations: AEMP, approved ex-manufacturer price; BAT, best available therapy.

[a] The fedratinib dose was based on the recommended 400 mg daily dose, multiplied by the trial-based mean relative dose intensity during the total treatment period in the first line setting (JAKARTA trial; 92.8%, equivalent to 371.2 mg/day), and the second line setting (FREEDOM-2 trial; 86.9%, equivalent to 347.6 mg/day), weighted by an assumed 10%/90% utilisation in first and second line, respectively. No mean dose or relative dose intensities were reported in the ruxolitinib trial publications, so the resubmission used the average daily dose of 27.1 mg/day sourced from a DUSC utilisation report for ruxolitinib (2018).

6.52 The equi-effective doses were estimated as fedratinib 349.96 mg per day and ruxolitinib 27.1 mg per day. The resubmission stated that the PBAC has previously accepted a steady state ruxolitinib dose of 26.2 mg/day when determining the cost-

minimisation analysis for momelotinib. The momelotinib submission calculated equi-effective doses using ruxolitinib dose distributions and mean duration of exposure from a head to head trial of momelotinib and ruxolitinib. The resubmission also noted that the mean maximum daily ruxolitinib dose in the FREEDOM-2 trial (as part of the BAT arm) was 27 mg/day. There was no evidence to support the equi-effectiveness of the mean daily fedratinib dose from the JAKARTA and FREEDOM-2 trials with the mean daily ruxolitinib dose based on utilisation in clinical practice from the 2018 DUSC report.

6.53 The PSCR argued the CMA inputs were reasonable, as the fedratinib steady-state dosing was derived from the Phase 3 clinical trials and the inputs for ruxolitinib were derived from a DUSC analysis from 2018, with that analysis concluding the average dose used in practice was similar to that predicted from the clinical trial setting (pg 2, Ruxolitinib DUSC Public Release Document, September 2018 DUSC meeting). However, the PSCR also stated the Sponsor was amenable to using ruxolitinib dose distribution and equi-effective dose inputs based on the momelotinib submission, given the view expressed by the DUSC in November 2024 that the data in the 2018 review was too old (paragraph 6.80, momelotinib Public Summary Document [PSD], November 2024 PBAC meeting).

6.54 The ESC considered using ruxolitinib dose distribution and equi-effective dose inputs from the momelotinib submission (based on the SIMPLIFY-1 trial) was reasonable, as this was the most recent source of inputs for determining relativities in myelofibrosis on the PBS, and recognising views expressed by the DUSC regarding the age of the previous ruxolitinib review. Dose distributions for ruxolitinib in the momelotinib submission were 5 mg 23.6%; 10 mg 17.43%; 15 mg 19.32%; 20 mg 35.51%; and 25 mg 3.38%.

6.55 The cost-minimisation approach incorporated adverse event costs for fedratinib only. Costs for prophylactic anti-emetic therapy were not included in the cost-minimisation approach as 5-HT3 receptor antagonists (such as ondansetron) are not PBS-listed for this indication and would not generally incur a public cost. The evaluation suggested costs for prophylactic anti-emetic therapy should have been included in the estimation of adverse event costs.

6.56 The cost per day for the average ruxolitinib dose of 27.1 mg was estimated in the resubmission by using the cost per mg for each pack size of ruxolitinib to calculate a weighted price by ruxolitinib PBS prescribing by dose (Table 12). The resubmission applied a [redacted]% rebate to the published AEMP of ruxolitinib to approximate the effective AEMP, noting that this will be amended to the correct value once the true effective price for ruxolitinib is known.

Table 12: Approach to calculating cost of daily ruxolitinib dose in the resubmission

Ruxolitinib dose	Published AEMP	Total mg/pack	Cost per mg	Cost / day (Published AEMP)	PBS utilisation by dose	Cost / day (Effective AEMP) [a]
5 mg (112 tablets)	$4,750.00	560 mg	$8.48	$229.87	12.43%	$
10 mg (56 tablets)	$4,750.00	560 mg	$8.48	$229.87	26.75%	$
15 mg (56 tablets)	$4,750.00	840 mg	$5.65	$153.24	23.51%	$
20 mg (56 tablets)	$4,750.00	1,120 mg	$4.24	$114.93	37.31%	$
Price per day for ruxolitinib				**$168.97**		**$**

Source: Table 33, p82 of the resubmission
Abbreviations: AEMP, approved ex-manufacturer price
[a] The resubmission estimated effective AEMP for ruxolitinib by applying an assumed % rebate to the published AEMP.

6.57 The evaluation noted the resubmission's approach calculates daily costs by dose that would not be realised in practice (e.g. a 5 mg ruxolitinib dose with a higher cost per mg would not be used in a patient receiving 27.1 mg per day). Calculating weighted costs per day based on the dose distribution from PBS/RPBS script data was not appropriate as it does not account for the 25 mg twice daily dose, or for treatment adherence, which were included in the DUSC analysis used to derive the average daily dose (based on the total amount of drug supplied divided by the number of days of treatment). A preferred approach would be to calculate a weighted average cost by the distribution of actual daily doses (such as from the 2018 DUSC utilisation report). The PSCR argued dose modification of ruxolitinib information in the TGA Product Information allows for dose increases in increments of 5 mg (twice daily) up to the maximum 25 mg twice daily dose, and therefore it was reasonable to consider use of the 5 mg form in the CMA. The ESC agreed with the evaluation and considered the approach undertaken in the commentary, based on a weighted average cost by the distribution of actual daily doses, was more appropriate.

6.58 Results of the resubmission's cost-minimisation approach are presented in Table 13.

Table 13: Results of the cost-minimisation approach

Description	Amount
Ruxolitinib	
Daily dose of ruxolitinib (DUSC 2018 utilisation report – average daily dose)	27.1 mg
Cost per day (based on published AEMP of $4,750.00 and average dose of 27.1 mg/day, cost weighted by PBS/RPBS utilisation statistics by dose from June 2024 – May 2025)	$168.97
Cost per day with % rebate (equates to assumed effective AEMP of $)	$
Fedratinib	
Cost per day of fedratinib (equates to price per day of ruxolitinib)	$
Less cost per day for adverse event treatments ($0.44 /day)	$
Daily dose of fedratinib (PI recommended dose of 400 mg/day adjusted with trial-based relative dose intensities in first and second line and assumed 10%/90% utilisation split across first and second line, respectively)	349.96 mg
Cost per mg for fedratinib	$
Cost per 100 mg fedratinib capsule	$
AEMP per pack fedratinib (120 × 100 mg capsules)	**$**

Source: Table 34, p83 of the resubmission.
Abbreviations: AEMP, approved ex-manufacturer price; DUSC, Drug Utilisation Sub Committee; PI, Product Information

6.59 The resubmission's approach resulted in an effective AEMP per pack of 120 tablets of $.

6.60 Given the lack of evidence to support the equi-effective doses, the approach to calculating the average daily cost of ruxolitinib based on costs that would not be realised in practice, and the inability to incorporate a measure of treatment adherence for ruxolitinib, sensitivity analyses were conducted during the evaluation to incorporate alternative sources of ruxolitinib utilisation by dose, and omitting the relative dose distribution for fedratinib. The results of sensitivity analyses conducted during the evaluation are presented in Table 14.

Table 14: Sensitivity analyses (based on published AEMP for ruxolitinib with assumed [redacted]% rebate)

Approach	Amount
Resubmission's approach without fedratinib RDI adjustment	
Cost per day of fedratinib based on cost per day of ruxolitinib	$[redacted]
Less cost for adverse event treatments ($0.44)	$[redacted]
Fedratinib AEMP per pack (120×100 mg), 30 days supply	**$[redacted]**
Ruxolitinib dose distribution in the September 2018 DUSC ruxolitinib review without RDI adjustment	
Cost per day of fedratinib based on cost per day of ruxolitinib (based on the dose distribution from the DUSC 2018 ruxolitinib report) [a]	$[redacted]
Less cost for adverse event treatments ($0.44)	$[redacted]
Fedratinib AEMP per pack (120×100 mg), 30 days supply	**$[redacted]**
Ruxolitinib dose distribution in the November 2024 momelotinib submission without RDI adjustment	
Cost per day of fedratinib based on cost per day of ruxolitinib (based on the dose distribution from the November 2024 momelotinib PSD [b]) (fedratinib dose 400 mg)	$[redacted]
Less cost for adverse event treatments ($0.44)	$[redacted]
Fedratinib AEMP per pack (120×100 mg), 30 days supply	**$[redacted]**
Ruxolitinib dose distribution in the November 2024 momelotinib submission with RDI adjustment	
Cost per day of fedratinib based on cost per day of ruxolitinib (based on the dose distribution from the November 2024 momelotinib PSD [b]) with RDI adjustment (fedratinib dose 349.96 mg)	**$[redacted]**
Less cost for adverse event treatments ($0.44)	**$[redacted]**
Fedratinib AEMP per pack (120×100 mg), 30 days supply	**$[redacted]**

Source: Constructed during the evaluation based on the 'Attachment 14 – Fedratinib Cost-Minimisation Analysis' spreadsheet provided with the resubmission.

Abbreviations: AEMP, approved ex-manufacturer price; DUSC, Drug Utilisation Sub Committee; RDI, relative dose intensity.

Note: Based on the published AEMPs for ruxolitinib with assumed [redacted]% rebate ($[redacted] for 56 × 5 mg tablets; $[redacted] for 56 × 10 mg, 15 mg and 20 mg tablets)

[a] Table 6, September 2018 DUSC analysis of ruxolitinib (5 mg 15%; 10 mg 27%; 15 mg 29%; 20 mg 25%; 25 mg 4%), divided by 28 days per pack of ruxolitinib).

[b] Ruxolitinib dose distributions from Table 12, momelotinib PSD, November 2024 PBAC meeting (5 mg 23.6%; 10 mg 17.43%; 15 mg 19.32%; 20 mg 35.51%; 25 mg 3.38%).

6.61 The sensitivity analyses indicated that the price of fedratinib was sensitive to the inclusion of the relative dose intensity adjustment for fedratinib, as well as alternative approaches to costing ruxolitinib that did not include costs that that would not be realised in practice.

Drug cost/patient/year

6.62 Table 15 presents a comparison of drug costs per patient per year for fedratinib and ruxolitinib included in the cost-minimisation approach and the financial estimates. The estimates presented in the resubmission were based on the assumed effective prices of ruxolitinib ([redacted]% rebate on the published AEMP).

Table 15: Drug cost per patient for fedratinib and ruxolitinib (based on published AEMP for ruxolitinib with assumed [redacted]% rebate)

	Cost-minimisation approach	Financial estimates
Fedratinib 100 mg dose strength	$[redacted] [a]	$[redacted] [d]
Ruxolitinib 5 mg dose strength	$[redacted] [b]	$[redacted] [d]
Ruxolitinib 10 mg dose strength	$[redacted] [b]	$[redacted] [d]
Ruxolitinib 15 mg dose strength	$[redacted] [b]	$[redacted] [d]
Ruxolitinib 20 mg dose strength	$[redacted] [b]	$[redacted] [d]
Ruxolitinib 25 mg dose strength	-	$[redacted] [d]
Weighted average ruxolitinib	$[redacted] [c]	-

Source: Constructed during the evaluation based on 'Attachment 14 - Fedratinib Cost-Minimisation Analysis' and 'Attachment 15 - Fedratinib_ MF_Utilisation and Cost Model' spreadsheets provided with the submission.

Abbreviations: AEMP, approved ex-manufacture price; DPMQ, dispensed price for maximum quantity.

[a] Derived based on the weighted average cost per day calculated for ruxolitinib (AEMP $[redacted]) minus the costs associated with thiamine testing and supplementation and the costs of an antidiarrhoeal ($0.44); adjusted for the weighted average relative dose intensity for fedratinib from the JAKARTA and FREEDOM-2 trials (87.49%), with the resulting cost per mg used to derive a price per pack of fedratinib 120×100 mg (DPMQ $[redacted]). The DPMQ was multiplied by the relative dose in intensity (87.49%), divided by 30 days of treatment and multiplied by the 365.25 days to derive the cost per year.

[b] The published AEMPs for ruxolitinib ($2,375.00 per pack of ruxolitinib 56×5 mg; $4,750 per pack of 56×10/15/20 mg) were used to derive an average cost per mg (5 mg $8.48; 10 mg $8.48; 15 mg $5.65; 20 mg $4.24); multiplied by the average daily dose of ruxolitinib from the 2018 DUSC utilisation report for ruxolitinib (27.1 mg); and adjusted for an assumed [redacted]% special pricing arrangement rebate. Including fees and mark-ups, the average cost per day (5 mg $[redacted]; 10 mg $[redacted]; 15 mg $[redacted]; 20 mg $[redacted]) was multiplied by 365.25 days to derive the cost per year.

[c] The weighted average cost per day of ruxolitinib was derived by multiplying the average cost per day for each dose strength by the distribution of use based on PBS/RPBS utilisation statistics from June 2024 – May 2025. The weighted average cost per day ($[redacted], inclusive of fees and markups) was multiplied by 365.25 days to derive the cost per year.

[d] Based on assumed script equivalence of 6.52 scripts of ruxolitinib 112×5 mg tablets (assuming 2 packs per script); 13.04 scripts of ruxolitinib 56×10/15/20 mg tablets; and for ruxolitinib 25 mg twice daily – 13.04 scripts of ruxolitinib 56×5 mg tablets (assuming 1 pack per script) and 13.04 scripts of ruxolitinib 56×20 mg tablets; is equivalent to 10.65 scripts of fedratinib 120×100 mg capsules (400 mg daily×87.49% relative dose intensity×12.175 scripts). Ruxolitinib DPMQs were adjusted for an assumed [redacted]% special pricing arrangement rebate (112×5 mg tablets $[redacted]; 56×5 mg tablets $[redacted]; 56×10/15/20 mg tablets $[redacted]). The DPMQ for fedratinib 120×100 mg capsules ($[redacted]) was derived from the submission's cost-minimisation approach.

Estimated PBS usage & financial implications

6.63 This submission was not considered by DUSC.

6.64 The resubmission used a market share approach to estimate the utilisation and financial implications of a line agnostic PBS/RPBS listing for fedratinib for the treatment of patients with intermediate/high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis.

6.65 Table 16 presents the key inputs used to derive the financial estimates.

Table 16: Key inputs for financial estimates

Data	Value applied and source	Comment
Eligible population		
Ruxolitinib scripts	Ruxolitinib PBS initial and continuing treatment scripts for intermediate-1, intermediate-2 and high risk myelofibrosis, dispensed from June 2024 to May 2025, with an estimated annual growth rate of 6.37% based on ruxolitinib scripts between 2020 and 2024, extrapolated over initial 6 years of fedratinib listing (June 2026 to May 2031).	This appeared reasonable, although the Utilisation and Cost Model Workbook template specifies that service volumes should be based on the last full calendar year. The market share approach will not account for eligible patients who have discontinued ruxolitinib treatment. The projected growth rate for ruxolitinib may be an underestimate. DUSC previously considered an average annual growth rate of 9.1%, applied in the

Data	Value applied and source	Comment
		November 2024 momelotinib submission, to be an underestimate (Table 13, momelotinib PSD, November 2024 PBAC meeting).
Treatment utilisation		
Uptake rate for fedratinib	Assumed [redacted]% uptake across all lines of therapy, informed by clinician input. The resubmission noted that the PBAC previously considered it appropriate to match momelotinib uptake rates in the treatment experienced population with the naïve population (para 7.20, momelotinib PSD, November 2024 PBAC meeting).	The clinician input informing this assumption was not provided in the resubmission. A clinician survey of 11 haematologists included with the resubmission (also provided in the previous submission) only asked clinicians about potential uptake of fedratinib as a second-line treatment after ruxolitinib. While the representativeness of the sample is unclear, the majority of clinicians expected relatively high uptake of fedratinib, and the resubmission's estimates may underestimate fedratinib uptake. The assumption of constant uptake over the initial 6 years of listing may not be reasonable. The impact of the recent listing of momelotinib on the uptake of fedratinib is unclear.
Fedratinib relative dose intensity	87.49%; weighted average relative dose intensity across first and second line use based on mean RDI from JAKARTA (92.8%) and FREEDOM-2 (86.9%), weighted by assumed 10%/90% split of first/second line use.	The mean relative dose intensity reported for fedratinib in the FREEDOM-2 and JAKARTA trials, and the relative treatment adherence for ruxolitinib and fedratinib implied by the market share approach may not reflect the relative treatment adherence for ruxolitinib and fedratinib in clinical practice.
Fedratinib scripts/year equivalence - ruxolitinib 5 mg	1.63; Ruxolitinib 5 mg × 112 tablets/twice daily dosing = 56 days of treatment (6.52 scripts/year); while fedratinib 100 mg × 120 capsules/4 tablets once daily and relative dose intensity of 0.8749 provides 34.3 days of treatment (10.65 scripts/year).	The script equivalence for ruxolitinib 5 mg was based on the assumption that all patients receiving the 5 mg twice daily dose would receive the maximum quantity of 2 packs per dispensing, and all patients receiving the 25 mg twice daily dose would receive 1 pack per dispensing. The proportions of patients receiving 1 or 2 packs per dispensing in clinical practice is unclear. The resubmission's calculations of script equivalence effectively assume that ruxolitinib is utilised at full adherence. It was not reasonable to apply a relative dose intensity to fedratinib and not ruxolitinib.
Fedratinib scripts/year equivalence - ruxolitinib 10 mg, 15 mg and 20 mg scripts	0.82; Ruxolitinib 10 mg, 15 mg and 20 mg scripts × 56 tablets/twice daily dosing = 28 days of treatment (13.04 scripts/year); while fedratinib 100 mg scripts × 120 capsules/4 tablets once daily and relative dose intensity of 0.8749 provides 34.3 days of treatment (10.65 scripts/year).	
Fedratinib scripts/year equivalence - ruxolitinib 25 mg scripts	0.41 for each 20 mg and 5 mg script; Ruxolitinib 20 mg and 5 mg scripts (assumed 1 pack) × 56 tablets/twice daily dosing = 28 days of treatment (13.04 scripts/year); while fedratinib 100 mg scripts × 120 capsules/4 tablets once daily and relative dose intensity of 0.8749 provides 34.3 days of treatment (10.65 scripts/year), divided by 2 to represent the single fedratinib script replacing 2 ruxolitinib scripts (5.33 scripts/year).	
Proportion of ruxolitinib 5 mg and 20 mg dose strengths used as 25 mg twice daily	5 mg: 21.1%; 20 mg: 13.8%; based on utilisation in DUSC 2018 ruxolitinib report. All remaining 5 mg scripts used as 10 mg daily dose; all remaining 20 mg scripts used as 40 mg daily dose with script equivalence calculated as above.	The approach taken to estimate equivalent fedratinib scripts to the 25 mg twice daily ruxolitinib dose was reasonable. However, it is unclear whether DUSC utilisation data by dose from 2018 is representative of current utilisation of ruxolitinib.

Source: Section 4, pp86-88 of the resubmission; Section 4 financial implications Excel workbook

Abbreviations: DUSC, Drug Utilisation Sub Committee; JAK, Janus kinase; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; RDI, relative dose intensity.

6.66 Table 17 presents the estimated use and financial implications of listing fedratinib on the PBS.

Table 17: Estimation of number of treated patients and prescriptions

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Fedratinib scripts dispensed	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of fedratinib						
Cost to PBS/RPBS less copayments	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Estimated financial implications for ruxolitinib						
Cost to PBS/RPBS less copayments	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]
Net financial implications						
Net cost to PBS/RPBS	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]
Net cost to MBS[a]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to PBS/RPBS/MBS	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]
Previous submission (May 2025)						
Net cost to PBS/RPBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]

Source: Section 4 financial implications Excel workbook, Attachment 12 of the submission.
Abbreviations: MBS, Medicare Benefits Schedule
[a] The submission assumed 2 thiamine level test (MBS item 66605, quantitation of vitamins; 80% of the Schedule fee; $24.48) per patient per year, applied to one in every 6 scripts of fedratinib.
The redacted values correspond to the following ranges:
[1] 5,000 to < 10,000
[2] $20 million to < $30 million
[3] $0 to < $10 million

6.67 The estimated net cost to the PBS/RPBS was $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, a total cost of $0 to < $10 million over the first 6 years of listing.

6.68 The key drivers of the lower financial impact for fedratinib compared to the May 2025 submission were:

- The reduced size of the fedratinib market share though reduced annual market growth (6.37% compared to 7.24% in the May 2025 submission), a broader population with a lower uptake rate ([redacted]% across all lines of therapy in intermediate-1, intermediate-2 or high risk populations, compared to 72.23% in second-line intermediate-2 or high risk populations in the May 2025 submission).
- Changes to script substitution rates through lower estimates of fedratinib dose intensity (87.49% compared to 96.7% in the May 2025 submission, with full adherence assumed for ruxolitinib in both cases) and substitution of 2 ruxolitinib scripts for 1 fedratinib script for the ruxolitinib 25 mg twice daily dose (compared to 1 for 1 script substitution in the May 2025 submission), which resulted in increased numbers of offset scripts and associated cost offsets for ruxolitinib.

6.69 The financial estimates for fedratinib were considered uncertain for the following reasons:

- The mean relative dose intensity reported for fedratinib in the FREEDOM-2 (86.9%) and JAKARTA trials (92.8%), and the relative treatment adherence for ruxolitinib and fedratinib implied by the market share approach (100% for ruxolitinib/87.49% for fedratinib) may not reflect the relative treatment adherence for ruxolitinib and fedratinib in clinical practice. The PSCR acknowledged that while no adjustment was applied for ruxolitinib in the financial estimates, this was accounted for in the economic analysis and resultant cost minimised price of fedratinib.
- The annual market growth rate (6.37%) may be underestimated. DUSC previously considered an average annual growth rate of 9.1%, applied in the November 2024 momelotinib submission, to be an underestimate (Table 13, momelotinib PSD, November 2024 PBAC meeting).
- Uncertainty around the [redacted]% uptake rate for fedratinib which was based on clinical input that was not provided. Further, the assumption of constant uptake over the initial 6 years of listing may not be reasonable. The PSCR acknowledged the uptake of fedratinib in practice was uncertain. The ESC also considered the uptake assumption to be uncertain, but noted that in the absence of alternative sources to inform the likely uptake of fedratinib in practice, [redacted]% was likely reasonable.
- There may be additional costs to the PBS due to costs associated with the prophylaxis and treatment of gastrointestinal adverse events associated with fedratinib treatment (e.g., anti-emetics and anti-diarrhoeal medications) and thiamine supplementation for some patients, that were not included in the resubmission's estimates.

6.70 The resubmission presented the results of sensitivity analyses varying the annual market growth rate and assumed fedratinib uptake. Additional sensitivity analyses were conducted during the evaluation, given uncertainties associated with the derivation of the cost-minimised price of fedratinib noted in paragraph 6.60 above, and the lack of evidence to support the implied relative treatment adherence for ruxolitinib and fedratinib based on the market share approach (100% for ruxolitinib/87.49% for fedratinib). The financial estimates were sensitive to changes in the estimated uptake of fedratinib, as well as alternative approaches to deriving the cost-minimised price of fedratinib, assuming no difference in adherence between fedratinib and ruxolitinib.

Quality Use of Medicines

6.71 No additional activities to support the quality use of medicines were proposed in the resubmission. The original submission noted that the current Risk Management Plan for fedratinib contains five important identified risks (anaemia; thrombocytopenia/bleeding; encephalopathy, including Wernicke's encephalopathy;

gastrointestinal toxicities; and low thiamine levels). The submission argued that the routine risk minimisation measures included in the Product Information and Consumer Medicines Information are sufficient to minimise the potential risks associated with fedratinib.

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

7 PBAC Outcome

7.1 The PBAC recommended the PBS listing of fedratinib for the treatment of patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis who are JAK inhibitor naïve or post ruxolitinib or another JAK inhibitor; and intermediate-1 risk myelofibrosis patients with severe disease-related symptoms that are resistant, refractory or intolerant to available therapy (second line treatment). The PBAC's recommendation for listing was based on, among other matters, its assessment that fedratinib would be cost-effective if it cost no more than ruxolitinib.

7.2 The PBAC maintained its view that there is a clinical place for fedratinib as an alternative or additional treatment option to or after ruxolitinib (and to a lesser extent momelotinib). The PBAC reiterated its view that there was a moderate need for a new JAK inhibitor in this disease area and noted the evidence suggested fedratinib could be effective in patients who had lost response to ruxolitinib over time. The PBAC noted the consumer support for an additional treatment option and reiterated the impact of the disease on individual quality of life, limited treatment options available to treat myelofibrosis and the need for additional options when current options stop being effective after prolonged use. The PBAC noted the input from the MPN Alliance and Rare Cancers Australia included patient stories which described the lived experience with myelofibrosis and the potential benefits of having fedratinib available for this condition on the PBS.

7.3 The PBAC recalled from its previous consideration of fedratinib that it noted the National Comprehensive Cancer Network (NCCN guidelines (Version 1.2025; February 2025) recommend the use of ruxolitinib, momelotinib and fedratinib as first-line treatment options in myelofibrosis. The Committee further noted the guidelines made no specific recommendations for subsequent-line treatment setting, recommending the use of a JAK inhibitor that has not previously been used. (paragraph 7.5, fedratinib PSD, May 2025 PBAC meeting).

7.4 The PBAC accepted the resubmission's nomination of ruxolitinib as the main comparator for JAK inhibitor naïve patients. The PBAC considered there was likely to be limited overlap in the populations who would be considered for fedratinib and momelotinib, as momelotinib is restricted to patients with baseline haemoglobin of less than 100 g per litre and has demonstrated benefits in terms of reducing anaemia and as such would generally be a preferred treatment in those patients. This was also consistent with recently updated treatment guidelines and as such the PBAC considered ruxolitinib to be the appropriate main comparator for JAK inhibitor naïve

patients. The PBAC maintained its view that the submission's nomination of best available therapy (BAT) was appropriate for the requested listing for patients with intermediate-2 and high risk myelofibrosis who have had prior ruxolitinib treatment.

7.5 The PBAC noted the resubmission was based on an indirect treatment comparison (ITC) of one placebo-controlled fedratinib trial (JAKARTA) and two ruxolitinib trials (one placebo-controlled trial (COMFORT-I) and one BAT-controlled trial (COMFORT-II)) in adults with intermediate-2 or high risk myelofibrosis who had not received prior treatment with a JAK inhibitor. The PBAC noted there was no randomised controlled trial evidence for the intermediate-1 population, which was limited to single-arm data (fedratinib: JAKARTA 2, FREEDOM; ruxolitinib: JUMP, ROBUST, Barosi 2012).

7.6 The PBAC noted the JAKARTA trial was difficult to analyse given sponsor and protocol changes and the lack of long-term data, with no overall survival or progression free survival comparisons available given early termination of the trial (see paragraphs 6.11 and 6.13). The PBAC noted the consistent results across the ITCs comparing JAKARTA with the COMFORT 1 and COMFORT-II trials (the Bucher ITCs and the MAICs) for both the ITT population and the subgroup of patients with platelets ≥100 × 10^9/L, and that in the COMFORT-II comparisons, there were higher proportions of fedratinib treated patients with spleen volume response compared to ruxolitinib (see Table 8). The PBAC noted the evaluation and ESC concerns regarding the differences in common reference arms, inclusion criteria, and outcome definitions between the trials, however, the committee was satisfied that non-inferiority of fedratinib compared to ruxolitinib was reasonable based on the MAICs as measured by a reduction in spleen volume. The PBAC noted there were limited data available to compare fedratinib to ruxolitinib in the intermediate-1 risk subgroups. However, together with the evidence considered at the May 2025 PBAC meeting (paragraph 7.8, fedratinib PSD, May 2025 PBAC meeting) and noting that there is a lack of long-term comparative efficacy data for fedratinib in this setting, the PBAC considered that on balance the clinical claim of non-inferior comparative effectiveness was reasonable.

7.7 The PBAC recalled it had considered the safety profile of fedratinib raised concerns, particularly given the observed rate of encephalopathy, including Wernicke's (or suspected cases associated with thiamine levels below normal range). The Committee noted the TGA registration includes a box warning and states that all patients should receive prophylaxis with oral thiamine whilst on treatment with fedratinib, and reiterated this should be reflected in the PBS listing (refer to paragraph 7.6, fedratinib PSD, May 2025 PBAC meeting). It was noted the pre-PBAC response acknowledged the ESC's concerns regarding the non-inferior safety claim in the resubmission and accepted a claim of inferior comparative safety. The PBAC agreed with the revised claim of inferior comparative safety.

7.8 The PBAC noted the resubmission presented a cost-minimisation approach (CMA) to calculate the proposed effective price for fedratinib compared to ruxolitinib for patients with intermediate-1, intermediate-2 or high risk myelofibrosis across all lines of therapy. The equi-effective doses in the resubmission were estimated as fedratinib

349.96 mg per day and ruxolitinib 27.1 mg per day. The PBAC noted the fedratinib dose was based on the recommended 400 mg daily dose, multiplied by the trial-based mean relative dose intensity (RDI) during the total treatment period in the first line setting (JAKARTA trial; 92.8%, equivalent to 371.2 mg/day), and the second line setting (FREEDOM-2 trial; 86.9%, equivalent to 347.6 mg/day), weighted by an assumed 10%/90% utilisation in first and second line, respectively. The PBAC noted the impact of the RDI on the fedratinib dose (see Table 14), however, it was accepted that the use of the mean trial doses with the proposed first and second-line split was acceptable. The PBAC noted there were no mean doses or relative dose intensities reported in the ruxolitinib trial publications and that the resubmission relied on ruxolitinib dosing from a DUSC utilisation report from 2018. The PBAC recalled it had previously acknowledged the 2018 DUSC review was considered too old to be relied on and it had accepted a steady state ruxolitinib dose of 26.2 mg/day when determining the CMA for momelotinib (paragraphs 6.80 and 7.18, momelotinib PSD, November 2024 PBAC meeting).

7.9 The PBAC therefore considered the following equi-effective doses appropriate: fedratinib mean daily dose of 349.96 mg/day is equivalent to ruxolitinib mean daily dose of 26.2 mg/day.

7.10 The PBAC noted that the CMA proposed in the resubmission included additional daily costs for adverse events for fedratinib treatment, including treatment of diarrhoea, thiamine monitoring, and thiamine supplementation. The PBAC considered this was appropriate. The PBAC noted prophylactic anti-emetic therapy was not included. The Committee noted 5-HT3 receptor anti-emetic therapy (such as ondansetron) is not PBS listed for this indication and given this would be a private cost it was appropriate to exclude it from the adverse event costs in the CMA.

7.11 The PBAC noted the resubmission's approach to calculating the cost per day for the average ruxolitinib dose was estimated by using the cost per mg for each pack size of ruxolitinib to calculate a weighted price by ruxolitinib PBS prescribing by dose (Table 12). The PBAC noted alternative approaches proposed in the evaluation resulted in more conservative calculations (Table 14). Consistent with the approach taken for momelotinib, the PBAC considered the price of fedratinib should be determined using a weighted average cost by the distribution of actual daily doses of ruxolitinib, using the equi-effective doses from paragraph 7.9 and additional daily costs for AEs described in paragraph 7.10.

7.12 The PBAC considered the market share approach to be an appropriate way to estimate the utilisation and financial implications of a line agnostic PBS/RPBS listing for fedratinib for the treatment of patients with intermediate/high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis. The PBAC considered the annual market growth rate of 9.1%, consistent with the approach taken for momelotinib, was reasonable. The PBAC considered the uptake assumption to be uncertain, but noted that in the absence of alternative sources to inform the uptake of fedratinib in practice, [redacted]%

was likely reasonable. Additionally, the PBAC noted the mean RDI reported for fedratinib in the FREEDOM-2 and JAKARTA trials, and the relative treatment adherence for ruxolitinib and fedratinib implied by the market share approach may not reflect the relative treatment adherence for ruxolitinib and fedratinib in clinical practice. The PBAC noted the ESC's advice that RDI was implied for ruxolitinib by the dose distribution inputs to the CMA and therefore it may be reasonable not to make further adjustment to ruxolitinib treatment adherence in the financial estimates. The PBAC noted that the estimates do not account for the increased costs of managing AEs, which are included in the CMA calculation that will lower the fedratinib price relative to ruxolitinib. The estimates also do not include growth in the market due to eligible patients who have discontinued ruxolitinib treatment. However, overall, the PBAC considered the estimates to generally be reliable, once updated to reflect confidential pricing.

7.13 The PBAC recommended the General Schedule (Section 85), Authority Required (Telephone/Online) listing for initial treatment and an Authority Required (Streamlined) listing for continuing treatment for intermediate-1 or high-risk and intermediate-2 primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who are JAK inhibitor naïve or post ruxolitinib or another JAK inhibitor. The PBAC considered the amendments to the restrictions for fedratinib in the resubmission were appropriate. The PBAC recommended the following for the listing:

- inclusion of both an initial and continuing treatment phase, similar to the current PBS restriction structure for ruxolitinib and momelotinib
- inclusion of a criterion that the treatment must be sole PBS subsidised JAK inhibitor for the condition
- inclusion of prescribing instructions to document the details of the patients' medical records for the bone marrow biopsy report, confirming diagnosis of myelofibrosis and risk classification based on IPSS, DIPSS or age-adjusted DIPSS (consistent with the listings of ruxolitinib and momelotinib)
- inclusion of a caution that thiamine levels must be monitored whilst on treatment, as per the approved TGA boxed warning, on all treatment phases
- inclusion of an administrative note limiting use to twice in a lifetime for fedratinib in the initial treatment phase, consistent with the listings of ruxolitinib and momelotinib
- inclusion of "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." are appropriate so that JAK inhibitor experienced patients have the option of

switching treatment without needing to satisfy the disease-related symptoms requirement, consistent with the listings of ruxolitinib and momelotinib

- inclusion of administrative advice to both the initial and continuing treatment phases to not allow an increase to the maximum quantity or number of units or the maximum number of repeats authorised.
- listing be age agnostic to align with the current PBS listings of ruxolitinib and momelotinib for this indication

7.14 The PBAC recalled its recommendations from its July 2025 meeting on oncology and haematology medicines as part of the review of PBS items for prescribing by nurse practitioners and endorsed midwives. The PBAC had recommended amendment of most of the identified General Schedule oncology and haematology medicines to allow nurse practitioners to continue existing therapy where patient care is being shared with a medical practitioner. The PBAC confirmed for this fedratinib recommendation that prescribing by nurse practitioners for continuing therapy was appropriate. The PBAC recommended that nurse practitioners also be added as an eligible prescriber type for ruxolitinib and momelotinib for continuing therapy only, as would apply to fedratinib. The PBAC considered that the complexity of diagnosing myelofibrosis and forming appropriate therapeutic management strategies were high enough that initiating treatment and independent prescribing of fedratinib would be outside the scope of practice of nurse practitioners.

7.15 The PBAC recommended that fedratinib should not be treated as interchangeable on an individual patient basis with any other drugs.

7.16 The PBAC recommended the Early Supply Rule should not apply.

7.17 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because fedratinib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, 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.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

<u>High-risk and intermediate-2 risk myelofibrosis</u>

Initial treatment

Category / Program: GENERAL - General Schedule (Code GE)						
MEDICINAL PRODUCT medicinal product pack		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
FEDRATINIB						
Fedratinib 100 mg capsule, 120		NEW 1 MP	1	120	5	Inrebic
Restriction Summary [new1] / Treatment of Concept: [new1A]: Authority Required (telephone/online PBS Authorities system)						
Prescribing rule level		**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.				
		Administrative Advice: No increase in the maximum number of repeats may be authorised.				
		Administrative Advice: Special Pricing Arrangements apply.				
		Administrative Advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (OPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) OR the Age-Adjusted DIPSS (aaDIPSS).				
	33364	**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.				
	25796	**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 888 333.				
10846		**Indication:** High-risk and intermediate-2 risk myelofibrosis				
		Treatment Phase: Initial treatment				
29192		**Clinical criteria:**				
29191		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				
33362		**Clinical criteria:**				
33361		The treatment must be the sole PBS-subsidised JAK inhibitor therapy for this condition				
33363		**Prescribing Instructions:** Details of the following must be documented in the patient's medical records: (c) the bone marrow biopsy report confirming diagnosis of myelofibrosis (date, unique identifying number/code or provider number); and (d) a classification of risk of myelofibrosis according to either the IPSS, DIPSS, or the Age-Adjusted DIPSS				

New CI1	**Caution:** Thiamine levels should be assessed as per the approved Therapeutic Goods Administration (TGA) Product Information (PI) prior to receiving treatment and should be closely monitored throughout the treatment period.

Continuing treatment

Category / Program: GENERAL - General Schedule (Code GE)						
MEDICINAL PRODUCT medicinal product pack		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
FEDRATINIB						
Fedratinib 100 mg capsule, 120		NEW 2 MP, NP	1	120	5	Inrebic
Restriction Summary [new2] / Treatment of Concept: [new2A]: Authority Required – streamlined [new code]						
Prescribing rule level		**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.				
		Administrative Advice: No increase in the maximum number of repeats may be authorised.				
		Administrative Advice: Special Pricing Arrangements apply.				
		Administrative Advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (OPSS) 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				
		Treatment criteria				
		Must be treated by a medical practitioner; or				
		Must be treated by a nurse practitioner where both of the following are occurring: (i) patient care is being shared with a medical practitioner, (ii) the prescription continues existing therapy with this medicine				

Intermediate-1 risk myelofibrosis

Initial treatment

Category / Program: GENERAL – General Schedule (Code GE)						
MEDICINAL PRODUCT medicinal product pack		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
FEDRATINIB						
Fedratinib 100 mg capsule, 120		NEW 3 MP	1	120	5	Inrebic
Restriction Summary [new3] / Treatment of Concept: [new3A]: Authority required (telephone/online PBS Authorities system)						
Prescribing rule level		**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.				
		Administrative Advice: No increase in the maximum number of repeats may be authorised.				
		Administrative Advice: Special Pricing Arrangements apply.				
		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: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (OPSS) 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 888 333.				
		Indication: Intermediate-1 risk myelofibrosis				
		Treatment Phase: Initial treatment				
		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				
		OR				
		Patient must have intolerance to prior treatment with a JAK inhibitor 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: (e) the bone marrow biopsy report confirming diagnosis of myelofibrosis (date, unique identifying number/code or provider number); and (f) a classification of risk of myelofibrosis according to either the IPSS, DIPSS, or the Age-Adjusted DIPSS
	Caution: Thiamine levels should be assessed as per the approved Therapeutic Goods Administration (TGA) Product Information (PI) prior to receiving treatment and should be closely monitored throughout the treatment period.

Continuing treatment

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
FEDRATINIB					
Fedratinib 100 mg capsule, 120	NEW 4 MP, NP	1	120	5	Inrebic

Restriction Summary [new4] / Treatment of Concept: [new4A]: Authority Required – streamlined [new code]		
Prescribing rule level		**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Administrative Advice: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (OPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) OR the Age-Adjusted DIPSS (aaDIPSS).
		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
		Treatment criteria
		Must be treated by a medical practitioner; or
		Must be treated by a nurse practitioner where both of the following are occurring: (i) patient care is being shared with a medical practitioner, (ii) the prescription continues existing therapy with this medicine
		Caution: Thiamine levels should be assessed as per the approved Therapeutic Goods Administration (TGA) Product Information (PI) prior to receiving treatment and should be closely monitored throughout the treatment period.

Flow-ons to momelotinib:

8.2 Add new prescriber type in momelotinib (to allow nurse practitioner prescribing in continued therapy):

- 14743Y/ momelotinib 100mg tablet, 30 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)
- 14744B/ momelotinib 150mg tablet, 30 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)
- 14770J/ momelotinib 200mg tablet, 30 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)

Prescriber type:
☒Medical Practitioners ☒ *Nurse practitioners*

8.3 Add new concept in momelotinib (to allow nurse practitioner prescribing in continued therapy):

- 14743Y/ momelotinib 100mg tablet, 30 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)
- 14744B/ momelotinib 150mg tablet, 30 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)
- 14770J/ momelotinib 200mg tablet, 30 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)

	Treatment criteria
	Must be treated by a medical practitioner; or
	Must be treated by a nurse practitioner where both of the following are occurring: (i) patient care is being shared with a medical practitioner, (ii) the prescription continues existing therapy with this medicine

Flow-ons to ruxolitinib:

8.4 Add new prescriber type in ruxolitinib (to allow nurse practitioner prescribing in continued therapy):

- 10616R/ ruxolitinib 5mg tablet, 56 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)
- 10927D/ ruxolitinib 10mg tablet, 56 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)
- 10615Q/ ruxolitinib 15mg tablet, 56 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)

- 10617T/ ruxolitinib 20mg tablet, 56 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)

Prescriber type:
☒Medical Practitioners ☒ *Nurse practitioners*

8.5 Add new concept in ruxolitinib (to allow nurse practitioner prescribing in continued therapy):

- 10616R/ ruxolitinib 5mg tablet, 56 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)
- 10927D/ ruxolitinib 10mg tablet, 56 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)
- 10615Q/ ruxolitinib 15mg tablet, 56 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)
- 10617T/ ruxolitinib 20mg tablet, 56 (Continuing treatment- Intermediate-1 risk myelofibrosis/High risk and intermediate-2 risk myelofibrosis)

	Treatment criteria
	Must be treated by a medical practitioner; or
	Must be treated by a nurse practitioner where both of the following are occurring: (i) patient care is being shared with a medical practitioner, (ii) the prescription continues existing therapy with this medicine

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

The sponsor had no comment.