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

1 Purpose of submission

1.1 The Category 2 submission requested a Section 85 (General Schedule), Authority Required (Telephone/Online) 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.

1.2 PBS listing was requested on the basis of a cost-effectiveness analysis versus 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.

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

Component	Description
Population	Adult patients with intermediate-2 and high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis who have had prior ruxolitinib treatment.
Intervention	Fedratinib 400 mg (4 × 100 mg capsules) administered orally once a day.
Comparator	Best available therapy, consisting of suboptimal ruxolitinib treatment (due to loss of response or intolerance), hydroxyurea, peginterferon alfa-2a, busulfan or prednisone.
Outcomes	Spleen volume; myelofibrosis-associated symptoms; quality of life.
Clinical claim	Fedratinib is superior in terms of efficacy and inferior in terms of safety compared to best available therapy.

Source: Table 1, p15 of the submission.

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.

3 Requested listing

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

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	$[redacted] (published) $[redacted] (effective)	1	120	5	Inrebic
Restriction Summary / Treatment of Concept:					
	Category / Program: ☒ GENERAL - General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required (immediate assessment)				
	Administrative Advice: *No increase in the maximum quantity or number of units may be authorised.*				
	Administrative Advice: *No increase in the maximum number of repeats may be authorised.*				
	Administrative Advice: *Special Pricing Arrangements apply.*				
	Administrative Advice: *Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (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: High-risk and intermediate-2 risk myelofibrosis				
	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 disease related symptoms that are resistant, refractory or intolerant to ~~ruxolitinib~~ *best available therapy*				
	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.*				

3.2 The submission requested a special pricing arrangement (SPA) apply to fedratinib, with a published dispensed price per maximum quantity (DPMQ) price of $[redacted] and an effective price of $[redacted] per pack of 120 capsules.

3.3 The proposed PBS listing for fedratinib is narrower than the approved TGA indication. The TGA indication includes patients who are JAK inhibitor naïve, does not restrict based on disease risk, and does not require patients to be resistant, refractory or intolerant to ruxolitinib. The ESC noted the fedratinib submission did not request a listing for patients with intermediate-1 disease, similar to the current PBS listing for ruxolitinib and momelotinib. This is further discussed in paragraph 4.10.

3.4 The proposed PBS listing required patients to have disease-related symptoms that are resistant, refractory or intolerant to ruxolitinib. This differed from the FREEDOM-2 trial, which included patients with previous ruxolitinib exposure who had relapsed, were refractory, or were intolerant to ruxolitinib. The Pre-Sub Committee Response (PSCR) noted the Sponsor is amenable to include clinical criteria "Patient must have disease related symptoms that are relapsed, refractory or intolerant to ruxolitinib" to align closer to the FREEDOM-2 trial.

3.5 The proposed PBS listing did not include a definition for the terms 'resistant', 'refractory' or 'intolerant'. The evaluation noted the following from the FREEDOM-2 trial:

- Refractory disease was defined as treatment with ruxolitinib for ≥3 months with inadequate efficacy response (<10% spleen volume reduction by MRI or <30% decrease from baseline in spleen size by palpation). There is likely to be substantial overlap between patients considered 'refractory' and 'resistant'.
- Intolerance was defined as treatment with ruxolitinib for ≥28 days that was complicated by the development of a red blood cell transfusion requirement of at least 2 units/month for 2 months, or Grade ≥3 adverse events of thrombocytopenia, anaemia, haematoma, and/or haemorrhage while on treatment with ruxolitinib.
- Patients with relapsed disease, defined as regrowth in spleen volume parameters following an initial response. Patients with relapsed disease are not specifically included in the proposed restriction.

The PSCR noted the Sponsor suggested consistency with ruxolitinib, with the decision to cease ruxolitinib treatment remain the decision of the clinician. The ESC considered this was appropriate, as the current myelofibrosis restriction wording restricts the population in line with current standard care.

3.6 The proposed PBS listing did not include evidentiary requirements relating to disease status. The PBS restriction for ruxolitinib requires prescribers to include details (date, unique identifying number/code or provider number) of the bone marrow biopsy report confirming the diagnosis of myelofibrosis; and a classification of risk of myelofibrosis according to either the Myelofibrosis International Prognostic Scoring

System (IPSS), Dynamic International Prognostic Scoring System (DIPSS), or the age-adjusted DIPSS. The FREEDOM-2 trial required patients to have intermediate-2 and high-risk disease based on the DIPSS. A number of other scoring systems are also used in clinical practice to estimate risk status (i.e., the MIPSS-70 and MIPSS-70-Plus for primary myelofibrosis and the MYSEC-PM for post-polycythaemia vera and post-essential thrombocythaemia myelofibrosis). Given the proposed listing is after treatment with ruxolitinib, patients would have had to satisfy the criteria for treatment with ruxolitinib, including a classification of risk based on IPSS or DIPSS, prior to being eligible for fedratinib.

3.7 Due to the risk of Wernicke's encephalopathy associated with fedratinib treatment (see paragraph 4.9), a prescribing instruction and/or caution regarding assessment and monitoring for thiamine deficiency prior to fedratinib initiation, and for thiamine prophylaxis during treatment with fedratinib was included.

3.8 The ESC considered it appropriate that the restriction should preclude the use of fedratinib in combination with other JAK inhibitors, similar to existing PBS requirements for ruxolitinib and momelotinib.

3.9 The ESC also considered it was appropriate to consider flow-on changes that enabled switching between ruxolitinib, momelotinib and fedratinib under limited circumstances, consistent with how momelotinib and ruxolitinib are listed (as of 1 April 2025), although it may be appropriate to consider the total number of JAK inhibitor treatment attempts that can be undertaken in a lifetime under the PBS for myelofibrosis (as ruxolitinib and momelotinib are limited to two treatment attempts for each).

3.10 Grandfathering provisions were not requested on the basis that the sponsor does not intend to initiate a patient access program for fedratinib prior to PBS listing.

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 cytopenias (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 Myelofibrosis is classified as primary myelofibrosis if it arises spontaneously, and secondary myelofibrosis if it occurs secondary to another disorder, such as polycythaemia vera or essential thrombocythaemia. While the underlying causes of

myelofibrosis are not completely understood, most patients have a mutation in the JAK2, CALR, or MPL genes. The reported incidence of primary myelofibrosis in Australia in 2020 was 263 cases, with a higher proportion of males (61%) compared to females (39%; AIHW, 2024). The disease predominantly affects middle-aged and older adults. The estimated median age at diagnosis for primary myelofibrosis between 2003 and 2014 was 72 years (Baade et al., 2019).

4.3 While patients with asymptomatic, lower risk disease may be managed with observation alone, patients with symptomatic and/or higher risk disease typically receive first-line treatment with ruxolitinib, a selective inhibitor of JAK1 and JAK2. Allogeneic haematopoietic stem cell transplantation (HSCT) may lead to long-term remission in patients with myelofibrosis, but is generally reserved for use in younger, fitter patients, due to the morbidity and mortality associated with the procedure.

4.4 A number of supportive treatments are used in the management of myelofibrosis, including blood transfusions (red blood cells and platelets), antifibrinolytic agents for bleeding that is refractory to transfusions, iron chelation therapy, antibiotic prophylaxis for recurrent infections, prophylactic vaccinations, and haematopoietic growth factor support (erythropoiesis-stimulating agents and granulocyte colony-stimulating factor).

4.5 The submission positioned fedratinib as an option for patients with intermediate-2 and high-risk myelofibrosis who are considered unsuitable for allogeneic HSCT, and who experience persistent symptoms despite treatment with ruxolitinib, or are intolerant to ruxolitinib. Alternative second or later line therapies included in the submission's treatment algorithm include ruxolitinib with or without other treatments, hydroxyurea, peginterferon alfa-2a, busulfan and prednisone.

4.6 A resubmission for ruxolitinib, for the treatment of adult patients with polycythaemia vera who are resistant to, or intolerant of hydroxyurea, was recommended at the March 2025 PBAC meeting (p32, PBAC Web Outcomes, March 2025 PBAC meeting). Use of ruxolitinib to treat polycythaemia vera may impact the treatment options available to patients if they subsequently develop post-polycythaemia vera myelofibrosis.

4.7 Fedratinib is an oral kinase inhibitor with activity against wild-type and mutationally activated JAK2 and FMS-like tyrosine kinase 3 (FLT3). Fedratinib is a selective inhibitor of JAKs, with higher activity against JAK2 compared to other JAK family members (JAK1, JAK3 and TYK2). Abnormal activation of JAK2 is associated with myeloproliferative neoplasms, including myelofibrosis and polycythaemia vera.

4.8 The recommended dose of fedratinib for patients with a baseline platelet count $\geq 50 \times 10^9$/L is 400 mg (4 × 100 mg capsules) administered orally once a day. The product information states that fedratinib has not been studied in patients with a baseline platelet count $<50 \times 10^9$/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.

4.9 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.

4.10 The updated NCCN guidelines (Version 1.2025; February 2025) recommend the use of ruxolitinib, momelotinib or fedratinib in first-line myelofibrosis. The ESC noted fedratinib did not seek a PBS listing for intermediate-1 risk myelofibrosis and may create an inequity or limitation on reimbursed access to treatment based on available evidence. The ESC noted the clinical data supporting the efficacy of fedratinib versus placebo in first-line myelofibrosis (JAKARTA clinical trial) has been available for a number of years and was disappointed that the evidence presented was limited to the second-line setting and did not allow an assessment of a broader PBS population in line with ruxolitinib current PBS population, that would be expected to lead to equity of access and alignment with clinical guidelines. The ESC expressed a view that given there was robust evidence for fedratinib in a first-line setting that a broader listing may be simpler for prescribers and patients.

4.11 The Pre-PBAC Response acknowledged the views of ESC and submitted two options for the PBAC consideration: 1) a line agnostic broad listing for fedratinib, based on a non-inferiority claim and cost-minimisation analysis to ruxolitinib and 2) consistent with the original submission, a second-line listing based on a cost utility analysis versus best available therapy. The PBAC considered the evidence provided for a first-line listing would require a fulsome a full evaluation of the clinical, economic and financial implications.

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

5 Comparator

5.1 The submission nominated best available therapy, comprised of suboptimal treatment with ruxolitinib for the majority of patients, along with other treatments such as hydroxyurea, interferon alfa, prednisone, or busulfan for a small proportion of patients, as the main comparator.

5.2 The main arguments provided in support of this nomination were:

- Ruxolitinib is a selective JAK1/JAK2 inhibitor that represents the current standard of care for patients with intermediate-2 and high-risk primary myelofibrosis. The PBS restriction for ruxolitinib allows treatment to continue despite loss of response to ruxolitinib.

- Best available therapy was the comparator in the FREEDOM-2 trial, with 70.1% of patients receiving treatment with ruxolitinib monotherapy, and 7.5% receiving treatment with ruxolitinib in combination with hydroxyurea.

5.3 Momelotinib, a selective JAK1/JAK2 inhibitor that also inhibits activin A receptor type 1 (ACVR1), was recommended at the November 2024 PBAC meeting for the treatment of intermediate or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis in patients with moderate to severe anaemia and who are JAK inhibitor naïve or have been treated with ruxolitinib. The recommendation for listing was based on the PBAC's assessment that the cost-effectiveness of momelotinib would be acceptable if it were cost-minimised against ruxolitinib (Paragraph 7.1, momelotinib Public Summary Document [PSD], November 2024 PBAC meeting). While the submission acknowledged that momelotinib was considered at the November 2024 PBAC meeting, momelotinib was not nominated as a near market comparator in the submission. Although there are differences between the requested populations for fedratinib and momelotinib (the proposed fedratinib restriction excludes patients with intermediate-1 myelofibrosis and patients who are treatment naïve and does not limit treatment based on the presence of moderate to severe anaemia), momelotinib may be a relevant comparator for some patients (i.e., the subgroup of patients with intermediate-2 and high-risk myelofibrosis who have moderate to severe anaemia).

5.4 The PSCR stated the patient group treated with fedratinib or momelotinib are mutually exclusive for majority of patients and only a very small proportion of patients will overlap. The ESC noted that approximately 67% of patients in the fedratinib arm and 61% of patients in the BAT arm of the FREEDOM-2 trial had a haemoglobin ≤ 100 g/dL at baseline. The ESC considered this suggested that a relatively large number of patients in the proposed PBS population may meet the PBS eligibility criteria for both treatments.

5.5 The evaluation and ESC considered best available therapy is an appropriate comparator. However, the ESC also considered that while the momelotinib and fedratinib populations are different, they are not mutually exclusive where they overlap (such as by line of therapy and anaemia status/haemoglobin level).

5.6 The ESC further noted updated NCCN guidelines (Version 1.2025; February 2025) stratify treatment for patients with higher risk myelofibrosis according to platelet count (≥ 50 or < 50 × 10^9/L) as well as the presence of anaemia (previously based on platelet count alone). Momelotinib and clinical trial participation are listed as the preferred treatment options for patients with anaemia and ongoing symptomatic splenomegaly and/or constitutional symptoms. The ESC further noted that while the NCCN guidelines provide comparative evidence recommendations for first-line JAK inhibitor use in patients with a platelet count ≥50 × 109/L (Category 1 for fedratinib; Category 2B for momelotinib), no specific recommendations are made in the

subsequent-line treatment setting (the guidelines recommend the use of a JAK inhibitor that has not previously been used).

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 comments

6.2 The PBAC noted and welcomed the input from individuals (8), health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The PBAC noted the comments from individuals described the impact of myelofibrosis on their quality of life, including the heavy mental burden associated with the disease and the uncertain future it creates. The comments also noted limited treatment options available to treat myelofibrosis, with the available options stop being effective after prolonged use. Input from health professionals who had experience in treating patients with the condition noted fedratinib may be described as advantageous due to its efficacy in patients where ruxolitinib fails, or as an alternative to ruxolitinib where it cannot be used due to side-effects or toxicity. The input also noted the toxicity of fedratinib.

6.3 The Leukaemia Foundation stated ruxolitinib is the current standard of care for the treatment of myelofibrosis. The input noted that ruxolitinib has shown efficacy in reducing spleen volume and increase 5-year overall survival rates. However, the prognosis for patients that stop responding to ruxolitinib is poor and due to limited treatment options, patient with relapsed or refractory disease often remain on suboptimal ruxolitinib therapy. The Leukaemia Foundation stated more treatment options are vital to improve overall survival rates for people suffering from this disease.

6.4 The Myeloproliferative Neoplasms (MPN) Alliance Australia described the impact of myelofibrosis on a patient's quality of life, stating an enlarged spleen can be very painful, uncomfortable and impacts on ability to eat properly and sleep. The input further described full-time employment to be challenging due to symptom burden and need for ongoing regular medical care. The MPN Alliance noted ruxolitinib as the standard of care, with momelotinib and fedratinib as second-line therapy options. It further stated without further treatment options many myelofibrosis patients are likely to experience clinical deterioration.

6.5 Rare Cancers Australia noted the emotional, mental burden and reduced quality of life associated with myelofibrosis.

Clinical trials

6.6 The submission was based on one head-to-head trial comparing fedratinib to best available therapy (predominantly ruxolitinib) in adults with intermediate-2 and high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis and who were refractory, relapsed or intolerant to ruxolitinib (FREEDOM-2).

6.7 Details of the trial presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
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.	Clinical Study Report, August 2023
	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.	Lancet Haematology 2024; 11(10):e729-e740
	Harrison CN, Mesa R, Talpaz M, et al. Efficacy and safety of fedratinib in patients with myelofibrosis previously treated with ruxolitinib: Results from the Phase 3 randomized FREEDOM2 study.	Blood 2023; 142:3204 (conference abstract)

Source: Table 25, p49 of the submission.

6.8 The key features of the FREEDOM-2 trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
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	Post hoc analyses of IPD based on spleen and/or symptom response

Source: Table 26, p51 of the submission.
Abbreviations: ET, essential thrombocythaemia; IPD, individual patient data; MFSAF, Myelofibrosis Symptom Assessment Form; PV, polycythaemia vera; TSS, total symptom score.

6.9 The FREEDOM-2 trial had an overall high risk of bias. While the primary endpoint of spleen volume response (proportion of patients with ≥35% reduction in spleen volume) was objectively assessed, the open-label design has the potential to introduce bias in other areas, as knowledge of treatment assignment may affect disease management decisions, and assessment of other outcomes (e.g. self-reported Myelofibrosis Symptom Assessment Form (MFSAF) total symptom score, quality of life measures, adverse events).

6.10 The applicability of the FREEDOM-2 trial to the target PBS population is unclear, as the proposed restriction does not define relapsed/refractory disease or intolerance,

whereas the treatment eligibility criteria from the trial were based on specific definitions of relapsed/refractory disease (ruxolitinib use for ≥3 months with an inadequate spleen volume reduction of <10% by MRI or <30% by palpation; or regrowth to these parameters following initial response; no symptom criteria for eligibility) or intolerance (ruxolitinib use for ≥28 days with concomitant red blood cell transfusions or severe thrombocytopenia, anaemia, haematoma and/or haemorrhage).

6.11 Additionally, the November 2024 PBAC recommendation of momelotinib as a treatment option for myelofibrosis (PSD November 2024 PBAC meeting) also has the potential to shift the target patient population as momelotinib may capture more patients with haematological risk factors.

6.12 Most patients in FREEDOM-2 were reported to be refractory/relapsed after ruxolitinib treatment (82.8% fedratinib arm, 82.1% best available therapy arm). In addition, 22% to 40% of patients were reported to be intolerant to ruxolitinib either based on RBC transfusion requirement (31.3% fedratinib, 22.4% best available therapy) or Grade ≥3 specified adverse events (39.6% fedratinib, 40.3% best available therapy). The extent of the overlap between these subgroups is unclear. The FREEDOM-2 clinical study report described the stratification of patients at randomisation, whereby patients recorded as both refractory/relapsed and intolerant were stratified as refractory/relapsed.

6.13 Participants in the FREEDOM-2 trial were randomised to treatment with either fedratinib or best available therapy for 24 weeks (divided into 6 × 28 day cycles for administrative purposes). Best available therapy included any investigator-selected treatment such as approved JAK inhibitors, chemotherapy, anagrelide, corticosteroid, haematopoietic growth factor, immunomodulating agents, androgens or interferon, and could also include 'no treatment' and symptom-directed treatment. The majority of patients in the best available therapy arm were treated with ruxolitinib (77.6%), followed by hydroxyurea with or without other medications (17.9%), with 28.4% of patients receiving red blood cell transfusions during the trial.

6.14 Patients in the best available therapy arm could switch to fedratinib treatment after the Cycle 6 response assessment or earlier in the event of a confirmed progression of splenomegaly (by MRI/CT scan), with 64.2% of patients in the best available therapy arm crossing over to fedratinib after the randomised phase and 4.5% prior to the Cycle 6 response assessment. During the randomised period, 28.4% of patients in the fedratinib arm discontinued their study treatment, compared to 16.4% of patients in the best available therapy arm. The submission argued that the open-label design of the FREEDOM-2 trial may have resulted in patients randomised to the best available therapy arm having increased compliance for the first 6 cycles of treatment so they could crossover to fedratinib at the end of Cycle 6 assessments. The submission did not appear to consider other explanations for the observed treatment patterns. For example, in the absence of other treatment options patients may remain on their existing therapies particularly if they are demonstrating some clinical benefit. In

addition, given the majority of patients in the best available therapy arm crossed over to fedratinib treatment after Week 24, the results of the longer term outcomes are of limited benefit in assessing the comparative efficacy of fedratinib and best available therapy.

6.15 Subjects were allowed to continue study treatment beyond the initial 24 week period until unacceptable toxicity, lack of therapeutic effect, progression of disease or withdrawal of consent. Patients discontinuing treatment were followed for survival, subsequent therapies, new malignancy and progression of myelofibrosis to acute myeloid leukaemia every 3 months until death, loss to follow-up, withdrawal of consent, or study closure. The follow-up period of FREEDOM-2 is ongoing with anticipated completion in June 2025. The submission provided data from a clinical study report with a data cut-off date of 27 December 2022 and utility data from a later data cut-off of May 2023.

Comparative effectiveness

6.16 Results for the primary endpoint and key secondary spleen response outcomes at Week 24 (end of Cycle 6) from FREEDOM-2 are summarised in Table 4.

Table 4: Results of primary and key secondary spleen response 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)**

Source: Table 39, p67 of the submission.
Abbreviations: BAT, best available therapy; CI, confidence interval; ITT, intent-to-treat.
Note: The FREEDOM-2 clinical study report noted differences between the information provided to the interactive response technology (during screening) and the electronic case report form (derived from last non-missing data prior to or on randomisation date) regarding assignment of a patient to pre-defined strata. There were minor differences in the results based on the stratification method chosen, however these differences did not materially alter the outcome of the analyses. The results presented in the commentary are based on the stratified analysis using data reported in the electronic case report form.
Bold indicates statistically significant results.

6.17 Fedratinib was associated with a statistically significantly greater proportion of responders compared to best available therapy for the primary and key secondary spleen response outcomes. Spleen volume response was also measured at the end of Cycle 3 (12 weeks), with 58 (43.3%) patients in the fedratinib arm and 4 (6.0%) patients in the best available therapy arm achieving splenic response (≥35% reduction) by the end of Cycle 3 (difference in proportion 36.8%, 95% CI 26.9, 46.8).

6.18 Prespecified subgroup analyses of the primary outcome (proportion of patients with ≥35% spleen volume reduction) were generally consistent with the ITT population, with higher proportions of fedratinib-treated patients achieving spleen volume reduction of ≥35% than patients treated with best available therapy across all subgroups. There was a trend towards increased differences in spleen response (favouring fedratinib) in the subgroup with lower baseline platelet counts between 50 and 100×10^9/L compared to the subgroup with higher baseline platelets ≥100×10^9/L, and in ruxolitinib intolerant patients compared to ruxolitinib refractory/relapsed

patients. However, small patient numbers in these subgroups may limit the generalisability of these results. In addition, there was an overlap in baseline patient characteristics between ruxolitinib refractory/relapsed and ruxolitinib intolerance, with patients reporting both characteristics classified as refractory/relapsed. Tests for treatment effect interaction were not reported.

6.19 Durability of spleen response through the follow-up period (December 2022 data cut-off) was based on a median follow-up of 36.1 weeks for fedratinib and 18.7 weeks for the best available therapy arm, with a median durability of spleen response by MRI/CT scan of 86.3 weeks (95% CI 63.0, 126.4) in the fedratinib arm (not estimable in the best available therapy arm). Given the majority of patients in the best available therapy arm crossed over to fedratinib treatment after 24 weeks, the results of the longer term outcomes are of limited benefit in assessing the comparative efficacy of fedratinib and best available therapy.

6.20 Results of the key secondary outcome from FREEDOM-2, proportion of patients with at least a 50% reduction in total symptom scores, measured using the MFSAF, are summarised in Table 5.

Table 5: Proportion of patients with at least 50% reduction in MFSAF total symptom scores, FREEDOM-2, ITT population with non-zero baseline total symptom score

Outcome at week 24	Fedratinib N = 126	BAT N = 65	Difference in proportion (95% CI)
≥50% reduction in TSS, n (%)	43 (34.1%)	11 (16.9%)	**17.1 (4.8, 29.4)**

Source: Table 40, p68 of the submission.
Abbreviations: BAT, best available therapy; ITT, intent-to-treat; MFSAF, Myelofibrosis Symptom Assessment Form; TSS, total symptom score.
Note: stratified analysis based on data reported in the electronic case report form.
Note: There were 3 patients in the fedratinib arm and no patients in the BAT arm with a total symptom score of zero. The remaining 5 patients in the fedratinib arm and 2 patients in the BAT arm did not have baseline MFSAF scores.
Note: The MFSAF (version 4) 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, bone or muscle pain, and fatigue. Each symptom is scored from 0 to 10, with the total symptom score (0 to 70) the sum of the scores for the 7 symptoms, and higher scores corresponding to more severe symptoms.
Bold indicates statistically significant results.

6.21 A statistically significantly greater proportion of patients treated with fedratinib achieved at least a 50% reduction in MFSAF total symptom scores compared to patients in the best available therapy arm. Durability of symptom response through the follow-up period was based on a median follow-up of 11.5 weeks for fedratinib and 8.1 weeks for best available therapy, with a median duration of symptom response of 12.1 weeks (95% CI 8.1, 16.1) in the fedratinib arm and 10.1 weeks (95% CI 4.1, 16.7) in the best available therapy arm. The ESC noted the majority of patients in the best available therapy arm crossed over to fedratinib treatment after Week 24, the results of the longer term outcomes are of limited benefit in assessing the comparative efficacy of fedratinib and best available therapy.

6.22 The FREEDOM-2 clinical study report noted that concordance between spleen volume response and symptom response at the end of Cycle 6 was 69.6% overall (62.7% in the fedratinib arm and 83.1% in the best available therapy arm). At the end of Cycle 6,

21/126 fedratinib treated patients (16.7%) achieved both spleen and symptom response compared to 2/65 (3.1%) best available therapy-treated patients. There were 68 (54.0%) patients in the fedratinib arm who achieved either spleen or symptom response compared to 13 (20.0%) in the best available therapy arm.

6.23 Anaemia response, defined as ≥20 g/L increase in haemoglobin level in transfusion-independent subjects or transfusion-dependent subjects who become transfusion-independent, was reported in the FREEDOM-2 trial as an exploratory outcome. Anaemia response was recorded in 19.8% of patients in the fedratinib arm and 22.6% of patients in the best available therapy arm. Across the entire treatment period, the mean red blood cell transfusion rate per 28 days (number of units of transfusions that occurred from first dose of study medication to last dose of study medication +30 days/on treatment period (days) × 28 days) was 1.935 (SD 2.090) in the fedratinib arm and 1.408 (1.209) in the best available therapy arm. However, results for the best available therapy arm only included data prior to treatment crossover to fedratinib.

6.24 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), based on the HRQoL evaluable population (all subjects who had an evaluable assessment of a given health-related quality of life measure at baseline and at least one evaluable assessment post-baseline). The ESC noted 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.

6.25 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.

6.26 Over the entire treatment period (to December 2022 data cut-off) there were 43 (32.1%) deaths in the fedratinib arm and 18 (26.9%) deaths in the best available therapy arm. Based on a median follow-up time of 64.5 weeks for the fedratinib arm and 63.7 weeks for the best available therapy arm, median overall survival was not estimable in the fedratinib arm (95% CI 112.6, not estimable) and 124.6 weeks (95% CI 98.9, not estimable) in the best available therapy arm. The submission noted that overall survival was similar in both treatment arms but favoured the best available therapy arm for the first two years. Interpretation of comparative efficacy for survival outcomes after 24 weeks is limited by the crossover of patients in the best available therapy arm to fedratinib treatment.

Comparative harms

6.27 Adverse events during the randomised phase of the FREEDOM-2 trial are summarised in Table 6.

Table 6: 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.

6.28 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 41.8%, nausea 36.6%, constipation 20.9%, vomiting 15.7%), anaemia (38.8%) and thrombocytopenia (26.9%). The 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. The ESC considered the assumption to be reasonable,

considering majority of patients were on ruxolitinib. In the best available therapy arm, the most frequently reported adverse events were anaemia (34.3%), asthenia (22.4%), thrombocytopenia (16.4%), nausea (14.9%) and fatigue (11.9%).

6.29 Gastrointestinal adverse events of nausea, diarrhoea or vomiting occurred more frequently in fedratinib-treated patients, with 87 (64.9%) patients in the fedratinib arm reporting at least one gastrointestinal adverse event across the entire treatment period (to December 2022 data cut-off) compared to 14 (20.9%) patients in the best available therapy arm. A breakdown of gastrointestinal adverse events by treatment and cycle indicated a greater incidence of nausea, vomiting or diarrhoea events in earlier treatment cycles in the fedratinib arm, with a brief increase in incidence in the best available therapy arm in Cycle 6, likely indicative of patients crossing over to fedratinib treatment (see Table 8.5.2-1, FREEDOM-2 clinical study report). It is unclear whether the incidence of gastrointestinal adverse events in the trial would be representative of clinical practice given the fedratinib product information states that appropriate prophylactic anti-emetic therapy should be considered during fedratinib treatment and recommends prompt treatment of diarrhoea with anti-diarrhoeal medications at the first onset of symptoms. In the trial, only 50% of patients in the fedratinib arm received concomitant anti-emetic therapy and 33% received anti-diarrhoeal medicines. The ESC considered, based on the available safety data, that anti-emetic therapy, anti-diarrhoeal and thiamine supplementation (and monitoring) were likely relevant costs associated with fedratinib treatment that should be considered in the economic analysis.

6.30 During the first 6 treatment cycles, more patients in the fedratinib arm reported adverse events leading to dose reduction, dose interruption or permanent treatment discontinuation (30.6%, 31.3% and 9.7%, respectively), compared to the best available therapy arm (10.4%, 6.0% and 6.0%, respectively).

6.31 Adverse events of special interest including encephalopathy/Wernicke's encephalopathy (or suspected cases associated with thiamine levels below normal range), thiamine levels below normal range, progression to AML, Grade 3 or 4 anaemia and Grade 3 or 4 thrombocytopenia were investigated during the FREEDOM-2 trial. During the first 6 treatment cycles, 65.7% of fedratinib-treated patients experienced an adverse event of special interest, compared to 40.3% of patients in the best available therapy arm. There were no patients in either treatment arm who experienced transformation to acute myeloid leukaemia. Encephalopathy-related events were reported 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.

6.32 The overall incidence of Grade 3 or 4 thrombocytopenia was higher in the fedratinib arm (20.1%) than the best available therapy arm (6.0%), as was the incidence of Grade 3 or 4 anaemia (27.6% versus 19.4%). The incidence of Grade 3 or 4 renal and urinary disorders (including acute kidney injury, chronic kidney disease, renal failure and renal impairment reported for more than 1 patient in the fedratinib arm) was higher in the fedratinib arm (12.7%) compared to the best available therapy arm (1.5%). 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 (8.2%) compared to the best available therapy arm (0%).

6.33 The most recent 6 month Periodic Benefit-Risk Evaluation Report (covering the period 16 February 2024 to 15 August 2024) noted the following important identified risks: anaemia, thrombocytopenia/bleeding, encephalopathy (including Wernicke's encephalopathy), and gastrointestinal toxicities (diarrhoea, nausea, vomiting). Important potential risks include pancreatitis, severe hepatotoxicity and severe infections including viral reactivation. Missing information includes use in patients with severe hepatic impairment, and long term safety, including secondary malignancies. During the current reporting period, there was one new validated safety signal of uveitis that was evaluated and closed. Eleven cases of uveitis were reported among 251 patients treated in three fedratinib trials (FREEDOM, FREEDOM-2 and a Japanese Phase 1/2 single arm study FEDR-MF-003), with the highest incidence (19.4%) reported in the Japanese study, and a trend for increasing incidence with increased duration of therapy. The PBRER advised that all patients should be counselled on the risks of developing uveitis before starting fedratinib therapy.

Benefits/harms

6.34 On the basis of direct evidence presented in the submission, for every 100 patients treated with fedratinib in comparison with best available therapy over a median duration of exposure of 23.9 weeks:

- Approximately 30 additional patients would have at least a 35% reduction in spleen volume.
- Approximately 17 additional patients would have at least a 50% reduction in total symptom scores.
- Approximately 39 additional patients would experience diarrhoea.
- Approximately 22 additional patients would experience nausea and approximately 11 additional patients would experience vomiting.
- Approximately 10 additional patients would experience symptoms related to encephalopathy (disturbance of brain function)

- Approximately 1 additional patient would experience Wernicke's encephalopathy.

Clinical claim

6.35 The submission described fedratinib as superior in terms of effectiveness and inferior in terms of safety compared to best available therapy. The evaluation considered the efficacy claim was adequately supported, but that some issues required further consideration (discussed in the paragraphs below). The ESC considered the efficacy claim was adequately supported in terms of spleen volume reduction but considered the available data did not strongly suggest there was a clear benefit in terms of quality of life.

6.36 The evaluation and ESC noted the following issues:

- While there is evidence to support improvements in treatment response with fedratinib compared to best available therapy (based on spleen volume reduction and/or total symptom scores), there is insufficient evidence to support an improvement in quality of life or survival outcomes. The PSCR argued the MFSAF tool was designed to provide a specific myelofibrosis evidence based symptom and quality of life assessment tool, and assessed symptoms and quality of life in patients with myelofibrosis, with greater numbers of fedratinib-treated patients in the FREEDOM-2 trial achieving at least 50% reduction in total symptom scores compared to patients treated with best available therapy. The ESC noted the results of the FREEDOM-2 trial did not demonstrate a benefit for fedratinib over best available therapy in other measures of quality of life (e.g. EORTC QLQ-C30 or EQ-5D-5L) or in survival outcomes and considered a quality of life benefit had not been clearly established and was not well supported.
- There is a lack of long-term comparative efficacy and safety data for fedratinib compared to best available therapy. The PSCR argued cross over at week 24 is common practice in JAK inhibitor trials, and additional real-world evidence supports the efficacy and safety of fedratinib in patients with intermeditate-2 and high-risk myelofibrosis. The PSCR referenced a retrospective study from the UK, Germany and Canada (Passamonti et al 2025[1]) which reviewed medical records of 196 eligible patients and reported findings consistent with the FREEDOM-2 trial, which demonstrated both decreases in spleen volume and myelofibrosis-related symptom burden for patients treated with fedratinib after ruxolitinib exposure, with an overall median treatment duration of 11.5 months and mean follow up of 14 months. While the study provided some evidence to support symptom and

[1] Passamonti F et al. Real-world treatment patterns and health outcomes for patients with myelofibrosis treated with fedratinib. Future Oncology 2025; 5:579-591

spleen volume reduction with fedratinib treatment, the overall median treatment duration reported in the study was only 0.7 months longer than in the FREEDOM-2 trial. The ESC considered therefore that the additional data did not provide useful additional information for assessing the longer-term and there remained a lack of long-term comparative efficacy and safety of data for fedratinib.

6.37 The FREEDOM-2 trial population may not be representative of the proposed PBS population given differences between the trial eligibility criteria and clinical criteria in the proposed fedratinib restriction. The recent PBAC recommendation of momelotinib as a treatment option for myelofibrosis also has the potential to shift the target patient population and may relegate fedratinib to a third-line therapy in some patients. In addition, the ESC reiterated its view that given there is clinical trial data available for fedratinib in the first-line setting, that an assessment of the evidence and potential for a line-agnostic listing (or additional listing in the first-line setting) may be simpler for prescribers and patients (paragraph 4.10 refers).

6.38 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.39 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.40 The submission presented a stepped economic evaluation of fedratinib compared to best available therapy in myelofibrosis patients who were relapsed, refractory or intolerant to ruxolitinib. The economic evaluation was based on a direct randomised trial (FREEDOM-2) with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

6.41 Key components of the economic evaluation are summarised in Table 7.

Table 7: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	Patients with response; treatment years; quality adjusted life years
Time horizon	10 years
Methods used to generate results	Cohort-level area under the curve model
Treatments	Second-line fedratinib followed by subsequent treatment with either third-line therapies (including hydroxyurea, peginterferon alfa-2a and busulfan) or supportive care versus best available therapy (primarily ruxolitinib) followed by supportive care.
Health states	4 health states including responders on second-line treatment, non-responders on second-line treatment; subsequent treatment and death
Cycle length	4-weeks (with half-cycle correction)
Circumstances of use	Treatment persistence and adherence to second-line fedratinib were based on the fedratinib treatment arm of the FREEDOM-2 trial. Treatment persistence to best available therapy was based on counterfactual assumptions using data from the fedratinib treatment arm adjusted for response rates at 24 weeks in the best available therapy arm of the FREEDOM-2 trial. Treatment adherence was assumed to be perfect in the best available therapy arm. It was assumed that patients previously treated with fedratinib who switch to subsequent treatment would spend 36% of their remaining survival time using third-line therapies and 64% of time using

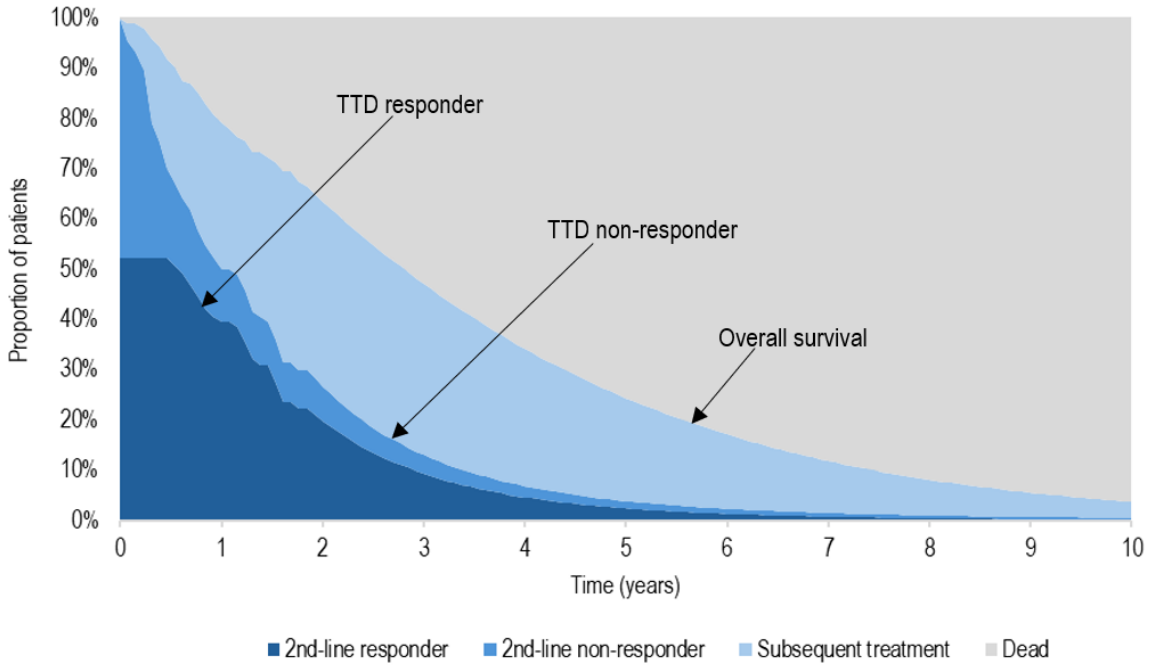
Component	Description
	supportive care. It was assumed that only 15% of patients receiving third-line therapies would be treated with hydroxyurea, peginterferon alfa-2a and busulfan and no patients would be treated with ruxolitinib. It was assumed that patients previously treated with best available therapy would only receive supportive care as subsequent treatment.
Transition probability	Treatment response rates were based on a post hoc analysis of individual patient data from the FREEDOM-2 trial with response defined as ≥35% reduction in spleen volume or ≥50% reduction in symptom scores (MFSAF instrument) at 24 weeks. Response rates were retrospectively applied to patients from the start of the model with separate time to treatment discontinuation curves estimated for treatment responders and non-responders. Time to treatment discontinuation curves for treatment responders and non-responders were derived using data from the fedratinib treatment arm of the FREEDOM-2 trial extrapolated using a log-normal function. Best available therapy was assumed to have the same time to treatment discontinuation curves as fedratinib. An overall survival curve was derived using data from the combined arms of the FREEDOM-2 trial extrapolated using a Weibull function. General population mortality was added after 96 weeks based on Australian life tables. Time to treatment discontinuation curves were used to estimate probabilities of remaining in the response/non-response health states over time. The overall survival curve was used to estimate the probability of death (which was assumed to be independent of health state). The proportion of patients in the subsequent treatment state was calculated as 1 minus the proportion of patients in the response, non-response and dead health states in any given cycle.
Utility values	Second-line responder (0.816) and non-responder (0.701) health state utility values were estimated based on a post hoc analysis of the FREEDOM-2 trial using the condition-specific Myelofibrosis 8 Dimensions (MF-8D) utility instrument. The third-line treatment utility in the fedratinib arm was based on the assumption that patients had the same utility as second-line non-responders (0.701). The supportive care utility (0.59) was based on EQ-5D-3L utility values reported in a cross-sectional study of breast, prostate and colorectal cancer patients receiving palliative care in Finland between 2009 and 2011 (Färkkilä 2014). The disutilities associated with severe adverse events were based on various published sources and additional assumptions.
Costs	The cost of fedratinib was based on the proposed effective price and the recommended dosing regimen in the product information. The submission adjusted costs based on the median dose intensity reported in the fedratinib treatment arm of the FREEDOM-2 trial. The cost of ruxolitinib was estimated based on an assumed effective price consisting of a 30% rebate on the published AEMP as well as the assumption of flat pricing across ruxolitinib dose strengths. Third-line treatment costs in the fedratinib arm were estimated assuming that 15% of patients would receive treatment with hydroxyurea, peginterferon alfa-2a and busulfan. No treatment costs were estimated for supportive care. The costs of severe adverse events were based on the assumption that all patients would be hospitalised. The cost of each hospitalisation was based on public and private hospital price weights for AR-DRG items weighted by complexity level (based on separations in the public hospital system) and setting (based on lenalidomide use on the PBS for myelodysplastic disease in the private/public hospital setting in 2023-2024). The costs of thiamine monitoring and supplementation in the fedratinib treatment arm were based

Component	Description
	on the recommendations in the product information, with unit costs based on MBS/PBS items. The costs associated with prophylaxis and treatment of gastrointestinal events were not included in the submission. Health resource use for disease management (emergency room visits, pathology testing, hospital nights, outpatient visits, specialist visits, and blood transfusions) was based on various published sources that were referenced in the ruxolitinib June 2015 NICE submission (TA386) as well as additional assumptions. Health resources were costed based on various MBS, NHCDC and NBA items. Terminal care costs were estimated based on the median cost of care in the last 6 months of life for elderly patients who died from cancer, based on a retrospective analysis of data from Australian veterans (Langton 2016).
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel 365

Source: Section 3, pp104-150 of the submission.
Abbreviations: AR-DRG, Australian Refined Diagnosis Related Group; MBS, Medicare Benefits Schedule; MFSAF, Myelofibrosis Symptom Assessment Form; NBA, National Blood Authority; NHCDC, National Hospital Cost Data Collection; PBS, Pharmaceutical Benefits Scheme; QALY, quality-adjusted life year.

6.42 The submission presented a cohort-level area under the curve model (the model structure is illustrated in Figure 1). The submission did not adequately justify the computational methods used for the economic analysis.

Figure 1: Model structural overview



Source: Constructed during the evaluation based on the fedratinib arm in 'Attachment 11 – Fedratinib economic model' spreadsheet provided with the submission.
Abbreviations: TTD, time to treatment discontinuation

6.43 Modelled patients are retrospectively assigned to the response or non-response health states based on a response assessment at 24 weeks. The retrospective application of response assumed that response rates do not change over time and all

responders must remain alive and on therapy for the first 24 weeks. After 24 weeks responders may remain on therapy with response, discontinue treatment or die. Patients assigned to the non-response state can discontinue treatment or die at any timepoint. Patients who discontinue therapy remain in the subsequent treatment state until death.

6.44 Key drivers of the economic model are summarised in Table 8.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Treatment discontinuation	The proportions of treatment responders/non-responders who discontinued therapy over time were based on the assumptions that treatment response states could not change over time and treatment responders could not die or discontinue treatment in the first 24 weeks of therapy. The submission claimed this was appropriate to ensure that the modelled proportion of responders at 24 weeks matched the data from the FREEDOM-2 trial. The submission used these assumptions to derive post hoc time to treatment discontinuation curves for treatment responders/non-responders based on the fedratinib treatment arm of the FREEDOM-2 trial. The submission claimed that it was appropriate to use the same curves for the best available therapy arm as the ability of patients to cross-over to fedratinib after disease progression or the end of the randomised period of the FREEDOM-2 trial (24 weeks) may have created an incentive to remain on therapy for longer than would be expected in clinical practice. The submission did not adequately justify the counterfactual assumptions used to model the best available therapy arm which resulted in a significantly larger proportion of patients discontinuing treatment over the first 24 weeks of the model than occurred in the FREEDOM-2 trial (50.4% versus 16.4%). The submission did not appear to consider other explanations for the observed treatment patterns in the trial. For example, in the absence of other treatment options patients may remain on existing therapies, particularly if they are demonstrating some clinical benefit as suggested by improved quality of life in both treatment responders and non-responders in the FREEDOM-2 trial. Treatment with fedratinib was associated with an inferior safety profile compared to best available therapy and therefore the circumstances of use from the fedratinib arm are unlikely to be generalisable to the best available therapy arm.	High, direction unclear
Third-line therapy	It was assumed that patients previously treated with fedratinib would spend 36% of their remaining survival time using third-line therapies and 64% of time using supportive care. The submission claimed that these proportions were consistent with the proportion of time the modelled best available therapy arm spent in the second-line treatment states (1.1552 / 3.3497 life years; 34.5%) compared to the subsequent treatment state (2.1945 / 3.3497 life years; 65.5%). The relevance of these proportions to the likely time spent using third-line therapies after fedratinib was unclear. This approach assumed that these proportions remain constant regardless of prior therapy (treatment duration, line of therapy, type of therapy), which may not be reasonable. It was assumed that only 15% of patients receiving third-line therapies would be treated with hydroxyurea, peginterferon alfa-2a or busulfan and no patients would receive treatment with ruxolitinib. This assumption was not adequately justified and was inconsistent with data from the FREEDOM-2 trial which indicated that ruxolitinib was the active therapy most frequently used after fedratinib (82%). The ESC considered the assumption was not appropriate and did not align with the PBS listing where the sponsor assumed in the fedratinib arm patients can access third-line	High, favours fedratinib

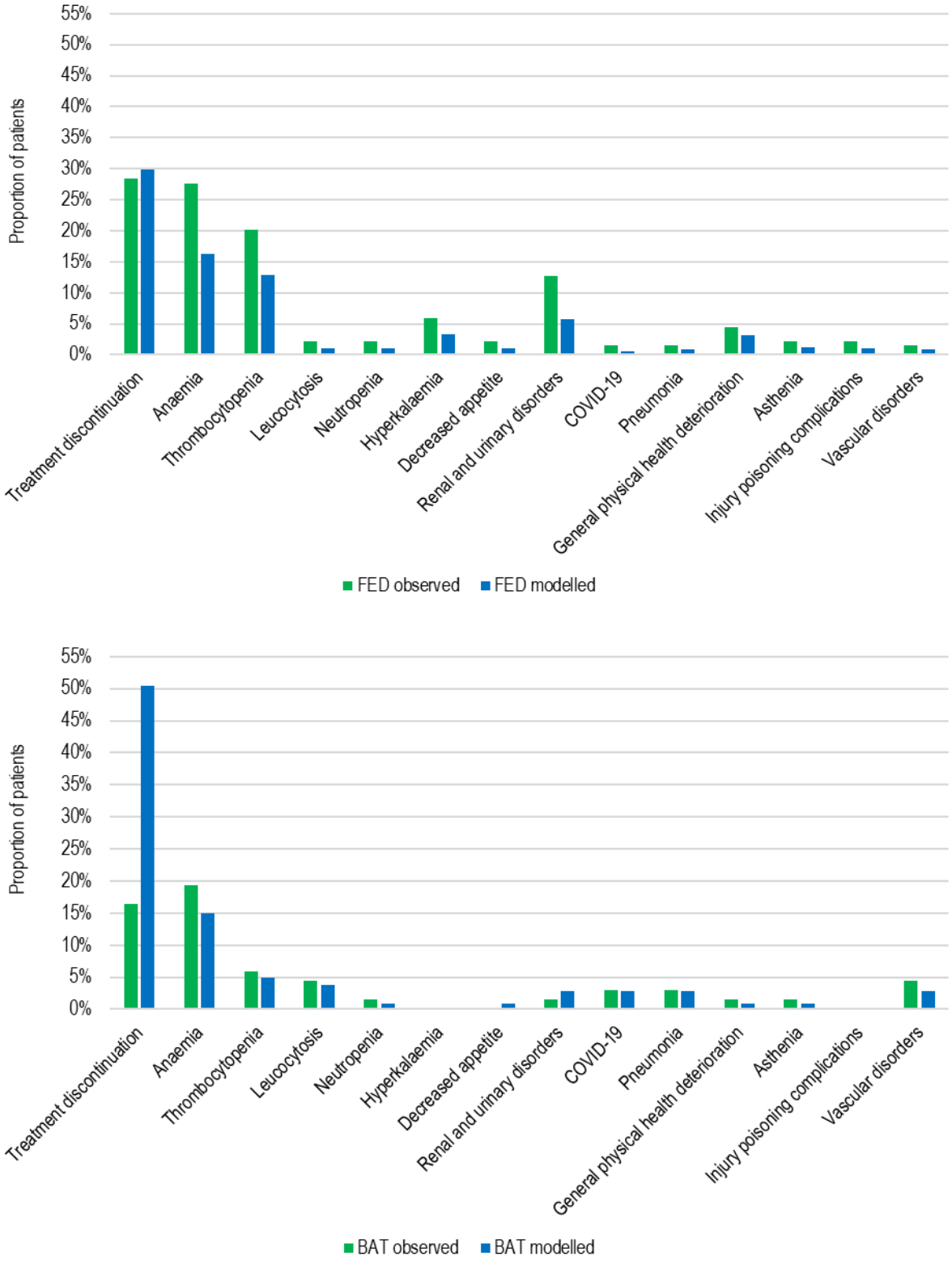
Description	Method/Value	Impact
	treatment, but patients in the best available therapy arm only receive supportive care. It was assumed that all patients receiving third-line therapies would have the same utility as second-line non-responders. The assumption was not appropriate given substantial differences in the therapies received in the second-line (77-100% treated with JAK inhibitors) and third-line settings (only 15% of patients treated with hydroxyurea, peginterferon alfa-2a or busulfan).	
Adverse events	Adverse events in each modelled arm were based on the exposure-adjusted incidence of severe adverse events that occurred in more than 2% of patients in either arm during the first 24 weeks of the FREEDOM-2 trial. The selection of severe adverse events used in the model was inconsistent, with some estimates based on individual events (e.g. anaemia), while other estimates were based on broad groups of events (e.g. renal and urinary disorders). In particular, the submission did not include the broad category of severe gastrointestinal disorders, which had a higher incidence in the fedratinib arm compared to best available therapy (incidence 8.2% versus 0% during the 24-week randomised period; exposure-adjusted incidence 11.58 versus 2.57 per 100 patient-years during the randomised and extension periods). The use of an exposure-adjusted incidence rate may not be appropriate as it does not account for patients experiencing multiple events of the same type, which was likely to have occurred in the trial and would also be expected to occur in clinical practice. The disutilities associated with adverse events were based on various published sources, and estimated costs were based on the 2024-2025 National Weighted Activity Unit (NWAU) calculator. The submission did not adequately justify the mapping of disutilities and costs to specific events. The private hospital costs estimated using the NWAU calculator did not appear to be representative of the full costs of care. The submission did not estimate any costs associated with prophylaxis or treatment of non-severe gastrointestinal events. This was not appropriate given that gastrointestinal events were frequently associated with fedratinib in the FREEDOM-2 trial, with a substantial proportion of patients receiving concomitant antiemetics and antinauseants (50%, primarily ondansetron) as well as antipropulsive therapies (33.6%, primarily loperamide). Additionally, the product information for fedratinib also recommends the use prophylactic antiemetic therapy (with 5-HT3 antagonists) as well as prompt treatment of diarrhoea at the first onset of symptoms.	Moderate, favours fedratinib
Hospital overnight stays	The estimated number of hospital nights for myelofibrosis patients who were not using a JAK inhibitor was estimated based on a retrospective audit of 93 myelofibrosis patients from two UK cancer networks between September 2004 and August 2010 (prior to the introduction of ruxolitinib). Reductions in hospital nights associated with using a JAK inhibitor were based on the JUMP study, a Phase 3 single arm expanded access study of 1,144 patients using ruxolitinib for the management of myelofibrosis. The cost of each individual hospital night was estimated as a separate hospitalisation episode based on AR-DRG items X63A/B (sequalae of treatment). This was inappropriate as it does not account for the average length of stay for these items, which include multiple days in hospital (5.1 days for X63A and 1.7 days for X63B). An example of the consequences of this approach can be seen in patients not using a JAK inhibitor, with the original NICE submission noting that patients	High, favours fedratinib

Description	Method/Value	Impact
	spent on average 7.98 nights in hospital per year while the current submission estimated costs based on patients spending 21 days in hospital per year.	
Ruxolitinib drug cost	The submission noted the current PBS listing of ruxolitinib for myelofibrosis is subject to a special pricing arrangement. The submission estimated an effective price assuming a 30% rebate on the published AEMP for ruxolitinib. The submission assumed that all ruxolitinib dose strengths had the same cost and patients would only require 1 pack per cycle. While the published price appears the same across ruxolitinib dose strengths, the dispensed quantity varies between dose strengths, with 2 packs of the 5 mg dose dispensed for the same price as 1 pack of the 10 mg, 15 mg and 20 mg dose strengths. Additionally, a small number of patients may require 2 packs per cycle to achieve the maximum recommended dose of 25 mg twice daily.	High, favours fedratinib

Source: Constructed during the evaluation.
Abbreviations: AR-DRG, Australian Refined Diagnosis Related Group; JAK, Janus kinase; NICE, National Institute for Health and Care Excellence; NWAU, National Weighted Activity Unit; PBS, Pharmaceutical Benefits Scheme.

6.45 A comparison of treatment discontinuations and severe adverse events reported in the first 24 weeks of the FREEDOM-2 trial compared to the first 24 weeks of the model is presented in Figure 2.

Figure 2: Observed versus modelled treatment discontinuations and severe adverse events over 24 weeks



Source: Constructed during the evaluation using 'Attachment 11 – Fedratinib economic model' spreadsheet provided with the submission.
Abbreviations: BAT, best available therapy; FED, fedratinib.

6.46 Treatment discontinuations in the fedratinib treatment arm were broadly consistent between the trial and modelled data, however the model appeared to substantially underestimate the incidence of adverse events associated with fedratinib treatment during the first 24 weeks.

6.47 The evaluation and ESC considered it was not appropriate to consider the treatment discontinuations in the best available therapy arm to be approximately 3 times higher in the model compared to reported estimates from the FREEDOM-2 trial. The PSCR argued the rationale for not using the TTD curves for BAT in the base case was that patients in the BAT arm had a strong incentive to remain on BAT until they were eligible for crossover, which would likely not reflect clinical practice. The ESC noted the PSCR arguments, however considered the values applied in the model were not supported by the available evidence and were inherently uncertain. The model also appeared to slightly underestimate the incidence of adverse events associated with best available therapy during the first 24 weeks.

6.48 The results of the stepped economic evaluation are summarised in Table 9.

Table 9: Stepped economic evaluation of fedratinib compared to best available therapy

Type of resource item	Fedratinib	Best available therapy	Increment
Step 1: Modelled estimate based on a 144-week time horizon (2.77 years); no discounting; JAK inhibitor drug costs only; health state utility values only			
Costs	$[redacted]	$33,233	$[redacted]
Patients with response	0.5224	0.1940	0.3284
Treatment years	1.2515	0.9412	0.3103
QALYs	1.4751	1.3474	0.1278
Incremental cost per additional responder			$[redacted] [1]
Incremental cost per additional year on treatment			$[redacted] [2]
Incremental cost per QALY gained			$[redacted] [3]
Step 2: Include standard therapy, thiamine monitoring and supplementation, disease management and terminal care costs			
Costs	$[redacted]	$123,903	$[redacted]
QALYs	1.4751	1.3474	0.1278
Incremental cost per QALY gained			$[redacted] [1]
Step 3: Include adverse event costs and disutility values			
Costs	$[redacted]	$126,968	$[redacted]
QALYs	1.4626	1.3415	0.1211
Incremental cost per QALY gained			$[redacted] [2]
Step 4: Extrapolate modelled results to 10 years			
Costs	$[redacted]	$206,392	$[redacted]
QALYs	2.3125	2.1367	0.1758
Incremental cost per QALY gained			$[redacted] [1]
Step 5: Apply discounting to costs and outcomes			
Costs	$[redacted]	$187,252	$[redacted]
QALYs	2.1057	1.9438	0.1620
Incremental cost per QALY gained			**$**[redacted] [1]

Source: Table 75, p137 of the submission.

Abbreviations: JAK, Janus kinase; QALY, quality-adjusted life year.

Note: Some estimates could not be matched between the submission and the Excel model, but differences were minimal.

The redacted values correspond to the following ranges:

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

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

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

6.49 Based on the economic model, treatment with fedratinib was associated with an incremental cost per QALY gained of $55,000 to < $75,000 compared to best available therapy in myelofibrosis patients who were relapsed, refractory or intolerant to ruxolitinib. The ESC noted the corrected costings for ruxolitinib treatment and hospital overnight stays resulted in a substantial increase of the incremental costs associated with fedratinib treatment. The PSCR acknowledged a revised model base case that accounted only for these two issues (based on assumed effective prices) was $155,000 to < $255,000 per QALY gained.

6.50 The evaluation and ESC considered the cost-effectiveness estimate should not be considered reliable due to the disconnect between observed and modelled discontinuation patterns, poorly justified assumptions regarding third-line therapy, inadequate modelling of adverse events, as well as inappropriate treatment and disease management costs.

6.51 The results of key sensitivity analyses presented in the submission and conducted during the evaluation are summarised in Table 10.

Table 10: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALYs	ICER	Change from base case ICER
Base case	**$[redacted]**	**0.1620**	**$[redacted] 1**	**-**
Discount rate (base case: 5% for benefits and costs)				
3.5% discount rate	$[redacted]	0.1658	$[redacted] 1	-[redacted]%
0% discount rate	$[redacted]	0.1758	$[redacted] 1	-[redacted]%
Time horizon (base case: 10 years)				
5 years	$[redacted]	0.1476	$[redacted] 2	+[redacted]%
15 years	$[redacted]	0.1629	$[redacted] 1	-[redacted]%
Circumstances of use (base case: patients previously treated with fedratinib would spend 36% of remaining time using third-line treatment and the rest of the time using supportive care; during third-line treatment only 15% of patients would be treated with hydroxyurea, peginterferon alfa-2a and busulfan and no patients would be treated with ruxolitinib; all patients previously treated with BAT use supportive care)				
Increase time spent using third-line treatment by 50%	$[redacted]	0.2157	$[redacted] 1	-[redacted]%
Decrease time spent using third-line treatment by 50%	$[redacted]	0.1082	$[redacted] 3	+[redacted]%
Assume 82% of patients using third-line treatment switch back to ruxolitinib, consistent with trial data	$[redacted]	0.1620	$[redacted] 4	+[redacted]%
Time to treatment discontinuation (base case: separate KM estimates for responders and non-responders in the fedratinib arm of the FREEDOM-2 applied to both treatment arms to 96 weeks with log-normal extrapolation)				
Use KM estimates of TTD in the FREEDOM-2 overall population independent of response and treatment arm (log-logistic extrapolation) adjusted for retrospective response assumptions	$[redacted]	0.1279	$[redacted] 1	-[redacted]%
Use KM estimates dependent on response for individual treatment arms (BAT estimates based on BAT treatment arm; fedratinib responders: log-normal, BAT responders: log-normal, fedratinib non-responders: log-logistic, BAT non-responders: exponential)	$[redacted]	0.1046	$[redacted] 5	-[redacted]%
Adverse events (base case: exposure adjusted incidence rate of severe adverse events in each treatment arm for the FREEDOM-2 trial)				
Increase exposure adjusted incidence rates by 50%	$[redacted]	0.1574	$[redacted] 2	+[redacted]%
Decrease exposure adjusted incidence rates by 50%	$[redacted]	0.1665	$[redacted] 1	-[redacted]%
Utility values (base case: second-line utility values for response/non-response based on a post hoc analysis of the FREEDOM-2 trial using the MF-8D instrument; third-line utility values following fedratinib assumed to be the same as non-responders; supportive care utility values based on Färkkilä 2014; adverse event disutility based on various published sources)				
Increase baseline utility by 10%	$[redacted]	0.2213	$[redacted] 6	-[redacted]%
Decrease baseline utility by 10%	$[redacted]	0.1026	$[redacted] 7	+[redacted]%
Assume third-line utility values the same as supportive care[a]	$[redacted]	0.0978	$[redacted] 7	+[redacted]%
Increase supportive care utility by 10%	$[redacted]	0.1080	$[redacted] 3	+[redacted]%
Decrease supportive care utility by 10%	$[redacted]	0.2159	$[redacted] 1	-[redacted]%
Double adverse event disutility values	$[redacted]	0.1529	$[redacted] 2	+[redacted]%
Halve adverse event disutility values	$[redacted]	0.1665	$[redacted] 1	-[redacted]%
Costs (base case: based on various sources)				
Assume variable ruxolitinib doses consistent with FREEDOM-2 trial (5 mg twice daily: 32.69%, 10-20 mg twice daily: 63.46%; 25mg twice daily: 3.85%) (effective DPMQ cost $2,984.58 per cycle)	$[redacted]	0.1620	$[redacted] 3	+[redacted]%

Analyses	Incremental cost	Incremental QALYs	ICER	Change from base case ICER
Base case	**$[redacted]**	**0.1620**	**$[redacted]** [1]	**-**
Double adverse event costs	$[redacted]	0.1620	$[redacted] [2]	+[redacted]%
Halve adverse event costs	$[redacted]	0.1620	$[redacted] [1]	-[redacted]%
Correction of hospital overnight stays ($1,527.03 per unit)	$[redacted]	0.1620	$[redacted] [8]	+[redacted]%
Multivariate sensitivity analyses				
Scenario 1 (same transition probabilities as base case, allow ruxolitinib switching after fedratinib, assume variable ruxolitinib dosing, correction of hospital overnight stays)	$[redacted]	0.1620	$[redacted] [9]	+[redacted]%
Scenario 2 (same transition probabilities as base case, assume third-line utility the same as supportive care utility, assume variable ruxolitinib dosing, correction of hospital overnight stays)	$[redacted]	0.0978	$[redacted] [9]	+[redacted]%
Scenario 3 (TTD estimates dependent on response for individual treatment arms, allow ruxolitinib switching after fedratinib, assume variable ruxolitinib dosing, correction of hospital overnight stays)	$[redacted]	0.1046	$[redacted] [9]	+[redacted]%
Scenario 4 (TTD estimates dependent on response for individual treatment arms, assume third-line utility the same as supportive care utility, assume variable ruxolitinib dosing, correction of hospital overnight stays)	$[redacted]	0.0415	$[redacted] [9]	+[redacted]%

Source: Table 82, p146 of the submission; 'Attachment 11 – Fedratinib economic model' spreadsheet provided with the submission.
Abbreviations: BAT, best available therapy; DPMQ, dispensed price for maximum quantity; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; QALY, quality-adjusted life year; TTD, time to treatment discontinuation.
[a] Baseline 0.641; second-line responders 0.810; second-line non-responders 0.693.
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*
[2] *$75,000 to < $95,000*
[3] *$95,000 to < $115,000*
[4] *$155,000 to < $255,000*
[5] *$25,000 to < $35,000*
[6] *$45,000 to < $55,000*
[7] *$115,000 to < $135,000*
[8] *$135,000 to < $155,000*
[9] *$255,000 to < $355,000*

6.52 The results of the sensitivity analyses indicate that the model is most sensitive to assumptions regarding third-line treatment (including the potential for fedratinib patients to switch back to ruxolitinib), time to treatment discontinuation, utility values for baseline, third-line therapy and supportive care, ruxolitinib dosing and the correction of costs associated with a hospital overnight stay.

6.53 The ESC noted that while the structure of the economic model may be reasonable, multiple key inputs were uncertain and likely favour fedratinib, and the ICER was sensitive to these inputs. The ESC considered key inputs remained of significant concern, including the disparity between treatment discontinuations in the BAT arm of the clinical trials (16.4% at 24 weeks) and modelled value (50.4% at 24 weeks), use of subsequent line therapies and adverse events. The ESC noted multivariate sensitivity analysis scenario 3 considered TTD estimates dependent on response for individual treatment arms, allowed ruxolitinib treatment in third line therapy, and

included the changes to ruxolitinib costs/dosing and hospital overnight stay costs, and considered this to be the most reliable scenario for the economic model, with a resultant ICER of $255,000 to < $355,000 (based on assumed effective prices).

6.54 Given the uncertainties with the choice of inputs not derived from the clinical trials, as well as other inputs into the model (as noted above), the ESC considered it may be difficult to adequately address these uncertainties without further revisions to the inputs.

Drug cost/patient

6.55 Table 11 presents a comparison of drug costs for fedratinib and ruxolitinib included in the economic model and financial estimates.

Table 11: Drug cost per patient for fedratinib and ruxolitinib

	Cost per 28 days (effective DPMQ adjusted for pack size and dose intensity)	
	Economic model	Financial estimates
Fedratinib 100 mg dose strength	$[redacted][a]	$[redacted][a]
Ruxolitinib 5 mg dose strength	$2,984.58	$1,743.80[b,c]
Ruxolitinib 10 mg dose strength	$2,984.58[b]	$2,984.58
Ruxolitinib 15 mg dose strength	$2,984.58[b]	$2,984.58[b]
Ruxolitinib 20 mg dose strength	$2,984.58[b]	$2,984.58[b]

Source: Constructed during the evaluation, updated based on values accepted in the PSCR (pg 2)
Abbreviations: AEMP, approved ex-manufacture price; DPMQ, dispensed price for maximum quantity.
[a] Each script assumed to provide 30 days of treatment which was adjusted to a 28-day equivalent with a median dose intensity of 96.7%.
[b] Estimated effective price for ruxolitinib based on assumption of a 30% rebate to the published AEMP.
[c] Each script assumed to provide 56 days of treatment which was adjusted to a 28-day equivalent.

Estimated PBS usage & financial implications

6.56 This submission was not considered by DUSC.

6.57 The submission used a market share approach to estimate the utilisation and financial impact of listing fedratinib on the PBS, for the treatment of patients with intermediate-2 and high-risk myelofibrosis, who are relapsed, refractory, or intolerant to treatment with ruxolitinib. The market share approach presented in the submission was not appropriate as it did not account for market expansion in eligible patients receiving non-JAK inhibitor therapies (such as hydroxyurea, peginterferon alfa-2a, busulfan), or the claimed increased duration of JAK inhibitor therapy associated with fedratinib.

6.58 Table 12 presents the key inputs used to derive the financial estimates.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible population		
Ruxolitinib scripts	Ruxolitinib PBS continuing treatment scripts for intermediate-1, intermediate-2 and high risk MF, dispensed from July 2023 to June 2024; with an estimated annual growth rate of 7.24% based on ruxolitinib scripts between 2020 and 2023.	The evaluation considered this appeared reasonable.
Proportion of patients with intermediate-2 or high risk MF	78.43%; based on ruxolitinib script data (informed by the DHS authority approvals database) reported in the 2018 DUSC ruxolitinib utilisation report. The assumed proportion of ruxolitinib intermediate-2 or high risk MF scripts was derived from the reported number of ruxolitinib MF scripts in the second year of ruxolitinib listing (7,557÷ [2078 + 7557]).	The evaluation considered that in the absence of more recent data, this may be a reasonable estimate.
Proportion of patients with loss of ruxolitinib response or who are intolerant to ruxolitinib	51%; based on the proportion of patients who had discontinued ruxolitinib treatment at 3 years in the COMFORT-1 trial, which compared treatment with ruxolitinib versus placebo in patients with intermediate-2 or high-risk myelofibrosis (Verstovsek et al., 2015).	The 3-year discontinuation rate in the COMFORT-1 trial is not a reasonable proxy for the proportion of patients who will be eligible for fedratinib treatment (based on the proposed PBS restriction). Reported reasons for treatment discontinuation in the COMFORT-1 trial included disease progression (23.1%), death (19.2%) adverse events (19.2%), withdrawal of consent (15.4%), non-compliance with medications (1.3%), non-compliance with study (1.3%), and other (23.1%).
Treatment utilisation		
Uptake rate for fedratinib [redacted]%	[redacted]%; based on the average uptake rates estimated in a sponsor-commissioned survey of 11 haematologists conducted in September to October 2024. Respondents were asked to indicate the proportion of intermediate-2/high risk MF patients currently receiving ruxolitinib and experiencing suboptimal efficacy or intolerances that they would switch to fedratinib if it was available on the PBS.	A wide range of uptake estimates were reported across the surveyed haematologists (33% to 100%). The uptake estimates did not consider the PBS listing of momelotinib (1 April 2025). The assumption of constant uptake over the initial 6 years of listing may not be reasonable.
Fedratinib treatment adherence	0.967; based on the median dose intensity reported for the fedratinib arm of the FREEDOM-2 trial.	The median dose intensity reported for fedratinib in the FREEDOM-2 trial may not reflect treatment patterns in clinical practice. Additionally, 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 script equivalence - ruxolitinib 5 mg scripts	1.81; based on the assumption that the maximum quantity of 112 ruxolitinib 5 mg tablets provides 56 days of treatment, and each pack of 120 fedratinib 100 mg capsules provides 31 days of treatment (after adjustment for treatment adherence of 0.967 reported in the FREEDOM-2 trial; 30 days ÷ 0.967 = 31.0).	The market share approach adopted in the submission did not account for eligible patients who have discontinued ruxolitinib treatment, which will underestimate the cost of fedratinib to the PBS.

Parameter	Value applied and source	Comment
Fedratinib script equivalence - ruxolitinib 10 mg, 15 mg and 20 mg scripts	0.90; based on the assumption that each pack of 56 ruxolitinib 10 mg, 15 mg and 20 mg tablets provides 28 days of treatment, and each pack of 120 fedratinib 100 mg capsules provides 31 days of treatment.	The script equivalence did not account for differences in treatment persistence between ruxolitinib and fedratinib. The submission argued that the availability of fedratinib would allow patients to remain on JAK inhibitor therapy for longer, which will result in additional cost to the PBS. The script equivalence for ruxolitinib 5 mg was based on the assumption that all patients would receive the maximum quantity of 2 packs per dispensing, however, some patients may only be prescribed 1 pack per script. The assumed equivalence does not account for patients receiving the maximum ruxolitinib dose of 25 mg twice daily, who would require 2 scripts to make the required dose.

Source: Section 4, pp151-168 of the submission; Section 4 financial implications Excel workbook, Attachment 12 of the submission.
Abbreviations: DUSC, Drug Utilisation Sub Committee; JAK, Janus kinase; MF, myelofibrosis; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme.

6.59 Table 13 presents the estimated use and financial implications of listing fedratinib on the PBS.

Table 13: Estimated use and financial implications

	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] 3	$[redacted] 3	$[redacted] 2	$[redacted] 2	$[redacted] 2	$[redacted] 2
Net financial implications						
Net cost to PBS/RPBS	$[redacted] 4	$[redacted] 4	$[redacted] 4	$[redacted] 4	$[redacted] 4	$[redacted] 4
Net cost to MBS[a]	$[redacted] 4	$[redacted] 4	$[redacted] 4	$[redacted] 4	$[redacted] 4	$[redacted] 4
Net cost to PBS/RPBS/MBS	**$**[redacted] 4	**$**[redacted] 4	**$**[redacted] 4	**$**[redacted] 4	**$**[redacted] 4	**$**[redacted] 4

Source: Section 4 financial implications Excel workbook, Attachment 12 of the submission.
Abbreviations: MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.
[a] The submission assumed 1 thiamine level test (MBS item 66605, quantitation of vitamins; 80% of the Schedule fee; $24.48) per patient per treatment course (with patient numbers derived from script numbers based on the mean fedratinib treatment duration of 52.5 weeks reported in the FREEDOM-2 trial).
The redacted values correspond to the following ranges:
[1] *5,000 to < 10,000*
[2] *$20 million to < $30 million*
[3] *$10 million to < $20 million*
[4] *$0 to < $10 million*

6.60 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 $10 million to < $20 million over the first 6 years of listing.

6.61 The estimated cost of fedratinib to the PBS/RPBS/MBS was considered uncertain due to the following reasons:

- The market share approach adopted in the submission did not account for eligible patients who have discontinued ruxolitinib treatment, which will underestimate the cost of fedratinib to the PBS.
- The script equivalence applied in the submission did not account for differences in treatment persistence between ruxolitinib and fedratinib. The submission argued that the availability of fedratinib would allow patients to remain on JAK inhibitor therapy for longer, which will result in additional cost to the PBS.
- The proportion of ruxolitinib-treated patients who will be eligible for fedratinib is considered uncertain. The 3-year discontinuation rate in the COMFORT-1 trial was not a reasonable proxy for the proportion of patients in the PBS population with prior ruxolitinib exposure who are eligible for fedratinib.
- The median relative dose intensity reported for fedratinib in the FREEDOM-2 trial may not reflect treatment adherence for fedratinib in clinical practice. Additionally, 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 uptake estimates did not account for the PBS listing of momelotinib (PBS listed 1 April 2025).
- The submission assumed that fedratinib would only substitute for ruxolitinib. However, some patients who are eligible for fedratinib may be receiving other therapies, such as hydroxyurea, peginterferon alfa-2a, busulfan and prednisone; or receiving treatment with other therapies in combination with ruxolitinib.
- The assumed script equivalence did not account for patients receiving the maximum ruxolitinib dose of 25 mg twice daily, who would require 2 ruxolitinib scripts to make the required dose.
- The submission assumed that all patients dispensed ruxolitinib 5 mg would receive the maximum quantity of 2 packs per dispensing, however some patients may only be prescribed 1 pack per script.
- 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., antiemetics or anti-diarrhoeal medications).
- The assumption of one thiamine level test per patient per course was inconsistent with the economic model, which assumed that all patients would receive thiamine level testing every 6 months. The product information for fedratinib states that all patients should have their thiamine level checked prior to initiating fedratinib, and subsequently as clinically indicated.

6.62 The PSCR argued the market share approach to be appropriate and argued that fedratinib would substitute suboptimal treatment with ruxolitinib in greater than 90% of patients. The PSCR also acknowledged uncertainty associated with the estimated proportion of patients who are resistant, refractory or intolerant to ruxolitinib, but noted that this uncertainty was explored in a sensitivity analysis presented in the submission.

6.63 The ESC agreed with the evaluation and was concerned the market share approach does not account for non-JAK inhibitor therapies and considered sensitivity analyses conducted in isolation (without correction of other issues) were of limited additional value. The ESC further agreed with the evaluation and considered the estimates include assumptions about the proportion of patients who are resistant, refractory or intolerant to ruxolitinib to be uncertain and further noted that as momelotinib is now listed on the PBS, additional market uncertainty exists where the eligible populations overlap.

Quality Use of Medicines

6.64 The 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. No additional activities to support the quality use of medicines were proposed in the submission.

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

7 PBAC Outcome

7.1 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. While the Committee considered there was a clinical place for fedratinib as an alternative or additional treatment option to or after ruxolitinib (and to a lesser extent momelotinib), the PBAC considered the incremental cost effectiveness ratio (ICER) to be unacceptably high and the listing would likely not be cost effective at the requested price. The PBAC also considered the submission base case economic model was based on optimistic or incorrectly determined inputs and assumptions and noted the sensitivity of the ICER to these parameters when more realistic inputs were used.

7.2 The primary reason for this outcome was due to the economic analysis provided in the submission.

7.3 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 (paragraph 4.10 refers) and expressed a preference for such an approach. Overall, the Committee considered the approach of a line agnostic listing on a cost minimisation basis with ruxolitinib may be reasonable. However, the PBAC considered that as the evidence for fedratinib in a first-line setting and an economic evaluation for such a listing had not been evaluated (noting a cost minimisation proposal was made in the Pre-PBAC Response), it was appropriate for a new submission to be made to allow for a fulsome evaluation of the evidence if such a listing were sought. The PBAC's advice that follows is based on the particulars of the submission made by the Sponsor, which sought a listing in a second-line setting following intolerance to, or inadequate/lost response to ruxolitinib.

7.4 The PBAC considered 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, noting 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. PBAC noted the input from the MPN Alliance that included patient stories and noted without further treatment options many patients with the disease are likely to experience clinical deterioration.

7.5 The PBAC 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.

7.6 The PBAC noted the listing requested in the submission was for second (or later) line only, following intolerance or lack of/loss of response to ruxolitinib and considered that whilst its preference was for a line agnostic listing, the restrictions for fedratinib should consider the following, irrespective of the line of therapy proposed in any re-submission:

- inclusion of both an initial and continuing treatment phase, similar to the current PBS restriction structure for ruxolitinib and momelotinib;
- include a criterion that the treatment must be sole PBS subsidised JAK inhibitor for the condition;
- include 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); and

- include a caution that thiamine levels must be monitored whilst on treatment, as per the approved TGA boxed warning.

7.7 The PBAC considered 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.

7.8 The PBAC noted the clinical evidence for fedratinib was based on the FREEDOM-2 trial (n=201), which was a head-to-head trial comparing fedratinib to best available therapy (predominantly ruxolitinib) in adults with intermediate-2 and high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis and who were refractory, relapsed or intolerant to ruxolitinib. The PBAC noted there was a statistically significantly greater proportion of responders for fedratinib compared to best available therapy for the primary and key secondary spleen response outcomes (splenic response rate difference in proportion 19.9%, 95% CI 10.0 - 29.7), but noted there was insufficient evidence to support an improvement in quality of life or survival outcomes. The PBAC agreed with ESC that the claimed quality of life benefit was not clearly established or well supported, but 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.

7.9 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, and reiterated this should be reflected in the PBS listing (paragraph 7.6 refers). The PBAC also noted the submission made a claim of inferior comparative safety and considered the evidence supported such a conclusion.

7.10 The PBAC noted the submission presented a modelled cost utility analysis based on the results of the FREEDOM-2 trial. The PBAC agreed with the evaluation and ESC that while the structure of the model may be reasonable, it included incorrectly determined ruxolitinib drug and overnight hospital stay costs, treatment discontinuation assumptions in the BAT arm that were inconsistent with the trials, and unrealistic third-line therapy assumptions (Table 8 refers). The Committee noted the Sponsor had agreed to evaluation-proposed changes to two of these (ruxolitinib and hospital costs), with a resultant base case ICER of $155,000 to < $255,000 per quality adjusted life year (QALY) gained (based on an assumed effective price of ruxolitinib). The PBAC considered there was uncertainty in the translation of the clinical trial results due to the substantial differences in the modelled treatment discontinuation compared to what was observed in the clinical trial and did not consider it appropriate to assume only patients treated with fedratinib would receive third-line active treatment. The PBAC agreed with the ESC that the inadequate modelling of adverse

events, as well as inappropriate treatment and disease management costs further increased the uncertainty in the modelled results.

7.11 The PBAC agreed with the ESC and considered multivariate sensitivity analysis 3, equating to an ICER of $255,000 to < $355,000 per QALY gained, to be the most reliable basis for assessing the cost-effectiveness of fedratinib compared to best available therapy in for the proposed listing. The Committee noted the Pre-PBAC Response disagreed with the ESC but provided no further alternative approaches, and considered that based on the available information, the listing of fedratinib would be unacceptably cost effective at the requested price, and that if a re-submission pursued a second-line listing, a substantial price reduction would be required for the listing to be cost effective.

7.12 The PBAC noted the submission used a market share approach to estimate the utilisation and financial impact of listing fedratinib on the PBS. The PBAC considered the 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. It also failed to include the claimed increased duration of JAK inhibitor therapy associated with fedratinib and includes uncertain assumptions about the proportion of patients who are resistant, refractory or intolerant to ruxolitinib. The PBAC considered that if a re-submission requested listing in a second-line setting, the financial estimates would require revision consistent with the issues outlined in paragraph 6.61.

7.13 The PBAC considered a resubmission for fedratinib should address the following issues:

- If a first-line or line agnostic listing is sought (noting the PBAC's preference for this option), a new submission based primarily on the 1st 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 do not respond/lose response to ruxolitinib);
- If a second-line listing is sought:
  - Revised PBS population to include a line-agnostic PBS listing as outlined in paragraph 7.6;
  - Revised economic analysis determining a cost-effective price on a comparable basis to ruxolitinib as outlined in paragraphs 7.10 to 7.12; and
  - Revision of the financial estimates as outlined in paragraph 7.12

The resubmission may be lodged at any future standard due date for PBAC submission using the standard re-entry pathway.

7.14 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 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.

9 Sponsor's Comment

The sponsor had no comment.