

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis

Technology appraisal guidance
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1 Recommendations

- 1.1 Fedratinib is recommended for use within the Cancer Drugs Fund as an option for treating disease-related splenomegaly or symptoms of primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis in adults. It is recommended only if:
- they have previously had ruxolitinib and
 - the conditions in the [managed access agreement](#) for fedratinib are followed.
- 1.2 This recommendation is not intended to affect treatment with fedratinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Most people with higher-risk myelofibrosis have ruxolitinib, and continue having it even if their disease does not fully respond, or stops responding. After ruxolitinib is stopped, people can have best available therapy, which includes chemotherapy, radiation therapy, splenectomy or red blood cell transfusion. The company proposes that fedratinib would only be used after ruxolitinib, which is more restrictive than its marketing authorisation.

Clinical trial evidence for people who have stopped ruxolitinib suggests that fedratinib improves myelofibrosis symptoms and reduces spleen size. However, this evidence is uncertain because fedratinib was not compared with best available therapy and some people did not finish the trial. Fedratinib has been compared indirectly with best available therapy using evidence from other studies. There is further uncertainty because of some differences between the trial populations in the indirect comparison.

Also, it is unclear how much longer people having fedratinib live compared with best available therapy, and this has a large effect on the cost-effectiveness results. There is also uncertainty around how many people would continue having fedratinib if their disease does not fully respond, or stops responding.

Fedratinib does not meet NICE's criteria to be considered a life-extending treatment at the end of life based on the evidence currently available. The cost-effectiveness estimates for fedratinib compared with best available therapy are uncertain because of limitations in the data. Because some of these estimates are higher than what NICE normally considers an acceptable use of NHS resources, fedratinib cannot be recommended for routine use in the NHS. Collecting more data on overall survival and treatment duration will reduce the uncertainty in the evidence. Therefore, fedratinib is recommended for use in the Cancer Drugs Fund.

2 Information about fedratinib

Marketing authorisation indication

- 2.1 Fedratinib (Inrebic, Celgene) has a marketing authorisation for 'the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naive or have been treated with ruxolitinib'.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The list price of fedratinib is £6,120 for a 120-capsule pack of 100 mg capsules (excluding VAT; BNF online accessed September 2021). The company has a [commercial arrangement](#). This makes fedratinib available to the NHS with a discount. The size of the discount is commercial in confidence. It's the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The [appraisal committee](#) considered evidence submitted by Celgene, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee recognised that there were remaining areas of uncertainty associated with the analyses presented, and took these into account in its decision making. It discussed the following key issues, which were outstanding after the technical engagement stage:

- Whether there was an overall survival benefit for fedratinib over best available therapy (see ERG critique of company technical engagement response, issue 7, page 16).
- Which was the most appropriate model of time to treatment discontinuation for fedratinib (see ERG critique of company addendum submission, page 6).
- Whether the company's subsequent treatment assumption for people having fedratinib was appropriate (see ERG critique of company technical engagement response, issue 6, page 15).
- Whether the company's approach to estimating ruxolitinib costs was appropriate (see ERG critique of company technical engagement response, issue 9, page 20).
- How the transformation rate to acute myeloid leukaemia (AML) should be modelled for people having fedratinib (see ERG critique of company addendum submission, page 9).
- Whether fedratinib meets the criteria for end of life treatments (see ERG critique of company technical engagement response, issue 11, page 22).

Treatment pathway, population and comparator

People with myelofibrosis often experience severe symptoms

- 3.1 Myelofibrosis is a rare haematological disorder that often causes an enlarged spleen (splenomegaly) and constitutional symptoms, and

shortens life. The patient experts explained that people with myelofibrosis experience debilitating fatigue, pain from splenomegaly, severe itching, night sweats, bone pain, and mental health problems including depression. Many people with myelofibrosis must reduce working hours or stop working completely because of fatigue. The patient experts added that the combined symptom burden can be very intense, and people can become dependent on carers. They also noted that people with myelofibrosis may be unable to exercise and that lack of exercise could contribute to other health issues. Around 75% of people with myelofibrosis reported experiencing depression or low mood. The patient experts explained the fear of living with a disease that is incurable for most people. They explained that knowing there are limited treatment options adds to their worry. They would like a new treatment option to increase life expectancy and improve quality of life. The committee concluded that people with myelofibrosis often have a high symptom burden. Improving survival and the symptoms associated with myelofibrosis, particularly fatigue and itching, would greatly benefit the wellbeing of people with myelofibrosis and their families.

People with myelofibrosis would welcome a new treatment option, particularly when ruxolitinib is no longer suitable

3.2 Myelofibrosis has 4 different risk categories according to the Dynamic International Prognostic Scoring System (DIPSS): low, intermediate-1, intermediate-2 and high risk. Clinicians can use these risk scores to guide treatment. People without symptoms or who have low-risk disease may have their myelofibrosis observed without active treatment. Most people with intermediate-2 or high-risk disease have ruxolitinib, which was recommended in [NICE's technology appraisal guidance on ruxolitinib for treating disease-related splenomegaly or symptoms in adults with primary or secondary myelofibrosis](#) (from now, TA386). The rest have best available therapy, which comprises several treatment options including hydroxycarbamide, androgens, radiation therapy, and red blood cell transfusion. The clinical experts explained that peoples' experiences with ruxolitinib varied. Ruxolitinib may work well at first, but many people experience disease relapse. People having ruxolitinib often have side effects which can mean they have to stop treatment. The clinical and patient experts also explained that best available therapy has limited

effectiveness. This means that many people continue having suboptimal ruxolitinib treatment even if the disease does not respond or subsequently loses response, because there are no other effective treatment options. However, disease symptoms will usually return for people having suboptimal ruxolitinib. When ruxolitinib is no longer suitable there are no other options other than best available therapy. The committee agreed that patients and clinicians would welcome a new treatment option for myelofibrosis, particularly when ruxolitinib is no longer suitable.

The company's positioning of fedratinib for people with intermediate-2 or high-risk myelofibrosis who have had ruxolitinib is appropriate

3.3 Fedratinib's marketing authorisation covers people with primary or secondary myelofibrosis (regardless of risk category) who have either not had a Janus kinase (JAK) inhibitor, or had ruxolitinib. However, the company positioned fedratinib in people with intermediate-2 or high-risk disease who have had ruxolitinib. The company considered this positioning reflected an area of unmet need and was how clinicians would use fedratinib in clinical practice. People who have had ruxolitinib have few treatment options (see [section 3.2](#)). So, the committee concluded that it was appropriate to appraise fedratinib for intermediate-2 or high-risk myelofibrosis after ruxolitinib.

The company's mixed comparator is acceptable, but the evidence for best available therapy in the model should reflect the proportion of people assumed to have ruxolitinib

3.4 The comparator in the NICE scope for people who had previous treatment with ruxolitinib, or when ruxolitinib was not appropriate, was established clinical practice, also called best available therapy. This included hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion. In the company's economic model (see [section 3.9](#)), around 89% of people having best available therapy were assumed to have ruxolitinib. The ERG considered that the company should have split the

population in its model into 2 subgroups: people who would have continued having suboptimal ruxolitinib, and people who would have stopped having ruxolitinib altogether. This was supported by the feedback from clinical experts. The clinical experts commented that most people whose disease is relapsed or refractory to ruxolitinib would keep having it, but people for whom ruxolitinib is poorly tolerated would usually stop having it. The ERG noted that the 2 subgroups would have different comparators. The comparator for the first group would be ruxolitinib, and the comparator for the second group would be best available therapy without ruxolitinib. The ERG considered that separating the population in this way would have helped to interpret the results. However, the company stated that it was not possible to split the trial population into the groups suggested by the ERG. The company also noted that there were no internationally recognised criteria for defining these groups, and they could therefore overlap. The comparator included a mix of people having ruxolitinib and people having best available therapy without ruxolitinib. The committee agreed that this mixed comparator was acceptable, but noted that the evidence used for best available therapy in the model should reflect the proportion of people assumed to have ruxolitinib (see [section 3.10](#)).

Clinical evidence

JAKARTA-2 is generalisable to people in the NHS with myelofibrosis who would have fedratinib

3.5 The evidence for fedratinib came from JAKARTA-2, a single-arm, open-label, phase 2 study. The study included 97 adults with intermediate or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis that was deemed resistant to ruxolitinib after at least 14 days of treatment, or who were intolerant to ruxolitinib after any duration of treatment. Of these people, 81 had intermediate-2 or high-risk disease, corresponding to where the company positioned fedratinib (see [section 3.3](#)). The dose of fedratinib used in the study was 400 mg per day for 6 consecutive 28-day cycles (24 weeks). The daily dose could be increased to up to 600 mg within the first 6 cycles if there was a reduction in spleen size by palpation of

less than 50% at the end of cycles 2 and 4. The primary outcome was spleen response, defined as the proportion of people with a spleen volume reduction of 35% or more from baseline at the end of cycle 6. Secondary outcomes included: symptom response (the proportion of people with a reduction in total symptom score of 50% or more from baseline to the end of cycle 6), the proportion of people with a reduction in palpable spleen length of 50% or more from baseline to the end of cycle 6, spleen response at the end of cycle 3 (12 weeks), percentage change in spleen volume from baseline to the end of cycles 3 and 6, and safety. The clinical experts noted that the inclusion criteria for JAKARTA-2 were quite unrestricted, and that the study would be generalisable to the NHS in England. The committee concluded that JAKARTA-2 was generalisable to people in the NHS with myelofibrosis who would have fedratinib.

Fedratinib is clinically effective, but the lack of comparator data makes assessing comparative effectiveness challenging

3.6 In November 2013, the Food and Drug Administration (FDA) in the US put a clinical hold on fedratinib because of 8 suspected cases of Wernicke's encephalopathy. During the clinical hold, people stopped having fedratinib while the suspected cases of Wernicke's encephalopathy were investigated. The clinical hold meant that 13 people in JAKARTA-2 stopped having fedratinib before they reached cycle 6 because of the study being stopped early. Also, during the marketing authorisation process, the Committee for Medicinal Products for Human Use (CHMP) requested additional analyses of JAKARTA-2 because of uncertainty around the additional benefits from increasing the fedratinib daily dose above 400 mg. The company therefore submitted analyses that counted disease response with a daily dose of more than 400 mg as not responding. This CHMP definition of response was used in the company and ERG analyses in the model. In the JAKARTA-2 intention-to-treat population, 23% of people had a spleen response while having a maximum daily dose of 400 mg. The proportion of people who had a symptom response in the intention-to-treat population while having a maximum daily dose of 400 mg was 21%. The ERG noted that the absence of a control arm in JAKARTA-2 meant that it was possible that there was regression to the mean effects. This is when extreme values

return to average over time. The committee acknowledged the difficulty of collecting data for rare diseases. It concluded that fedratinib is clinically effective, but that the disruption to the trial and lack of comparative data made the assessment of comparative effectiveness challenging.

Fedratinib has manageable adverse events

3.7 The company noted that the adverse event rates from JAKARTA-2 were generally low. The most common non-haematological adverse events for people having fedratinib were gastrointestinal disorders including diarrhoea (62%), nausea (56%), and vomiting (41%). The most common grade 3 or 4 adverse events were haematological and included anaemia (38%) and thrombocytopenia (22%). Treatment-emergent adverse events that meant fedratinib was stopped were seen in 20% of people. Across all fedratinib studies there were 8 suspected cases of Wernicke's encephalopathy, 1 of which had a clear diagnosis. It was found to be a consequence of gastrointestinal adverse events in people who were undernourished. Wernicke's encephalopathy can be managed by monitoring thiamine levels and supplementing as needed. The clinical experts noted that they follow the summary of product characteristics for monitoring thiamine levels and making dose adjustments. The company confirmed that there have been no additional instances of Wernicke's encephalopathy since the end of the FDA's clinical hold. The committee concluded that fedratinib has a manageable adverse event profile.

Indirect treatment comparison

The indirect treatment comparison suggests fedratinib improves response compared with best available therapy, but there are uncertainties

3.8 In the absence of direct head-to-head evidence comparing the efficacy of fedratinib with best available therapy, the company did a matching-adjusted indirect comparison (MAIC) for spleen or symptom response (see [section 3.5](#) for definitions of these outcomes). The company used

evidence from the intermediate-2 or high-risk group from JAKARTA-2 (n=81) for fedratinib and evidence from the SIMPLIFY-2 trial (n=52) for best available therapy. SIMPLIFY-2 was a randomised trial comparing momelotinib with best available therapy in people whose myelofibrosis had a suboptimal response to ruxolitinib, or who had haematological toxic effects with ruxolitinib. The company's base-case MAIC was adjusted for DIPSS risk category (see [section 3.2](#)) and Eastern Cooperative Oncology Group (ECOG) performance status. The company chose these variables based on clinical input that they were prognostic, and that there was a meaningful imbalance between JAKARTA-2 and the best available therapy arm from SIMPLIFY-2. The results of the MAIC suggested that fedratinib improves response compared with best available therapy, but the exact values are confidential and cannot be reported here. The ERG commented that ignoring variables because they were balanced individually may not achieve balance between the study populations overall. It noted that people in SIMPLIFY-2 could be currently having ruxolitinib (which was not the case in JAKARTA-2), and that this difference could not be adjusted for in the MAIC. Differences in how symptom response was assessed between JAKARTA-2 and SIMPLIFY-2 and the absence of a washout period in SIMPLIFY-2 may also have favoured fedratinib. The committee agreed that the MAIC suggests fedratinib improves response compared with best available therapy, but there was considerable uncertainty around these results.

The company's cost-effectiveness model

The company's model is similar to that from TA386, but a simpler model structure may have been more robust for decision making

- 3.9 The company submitted an individual patient discrete event simulation model comparing fedratinib with best available therapy. This was similar to the approach used in TA386. The company considered this design to be more flexible and transparent compared with a Markov cohort approach. The model had 5 health states (on fedratinib, on best available therapy, on best available therapy after fedratinib, supportive care, and death). People entered the model having either fedratinib or best available therapy. They were then categorised into response or non-

response groups at 24 weeks based on the outputs of the company's MAIC (see [section 3.8](#)). People having fedratinib stopped treatment according to models of time to treatment discontinuation fitted to the data from JAKARTA-2. The company modelled time to treatment discontinuation from the start of the model, using separate extrapolations according to whether there was a response at week 24. For people having fedratinib, the company estimated survival from the point of stopping fedratinib, using models fitted to the survival data after stopping treatment from JAKARTA-2. Like time to treatment discontinuation, this was split by response at week 24. People having best available therapy at the start of the model stopped treatment according to a model of time to treatment discontinuation fitted to data from the Haematological Malignancy Research Network (HMRN; see [section 3.10](#)). Unlike the fedratinib arm, the company used a single extrapolation of time to treatment discontinuation from the start of the model regardless of response at week 24. The company estimated overall survival for people having best available therapy using data from Schain et al. 2019 (see [section 3.10](#)). Like time to treatment discontinuation for best available therapy, the company fitted a single overall survival curve from the start of the model regardless of response at week 24. The ERG had several concerns with the company's model. It questioned the value of separating the population by response at week 24, given the small sample size of JAKARTA-2. It also noted that the company had used several different evidence sources for people having best available therapy (see [section 3.10](#)), and that there were important differences between these sources in terms of the patient populations and treatments. The ERG was also concerned that the company had used a different modelling approach for the fedratinib arm compared with the best available therapy arm. The committee shared the ERG's reservations with the model, noting that it was overly complex given the limitations of the clinical evidence for fedratinib (see [section 3.6](#)). In response to consultation, the company provided additional justification for the model structure. It noted that the issues identified with the model structure could only be overcome by additional data collection. Also, the different modelling approaches for the 2 treatment arms reflected that the treatment pathways would be different. The company acknowledged that some complexity arose from splitting people in the model into those whose disease did or did not respond to

fedratinib for the survival and time to treatment discontinuation models. But it stated that survival and time to treatment discontinuation models could also be applied to the overall population having fedratinib in the model (not split by disease response). This gave similar results to the company's base case. The company further noted that a simpler model could have created separate issues. The ERG's view of the model remained unchanged after consultation. At its second meeting, the committee noted that the company had made few changes to the model presented at the first committee meeting. It reiterated its conclusion from the first committee meeting that a simpler model structure may have been more robust for decision making.

Using different sources of evidence to model best available therapy increases uncertainty

3.10 The company used a range of evidence sources for best available therapy in its model. For its base case, the company used the data from SIMPLIFY-2 for the spleen or symptom response MAIC (see [section 3.8](#)), for the adverse event frequency for best available therapy as a comparator, and for the composition of best available therapy. Although overall survival data for people having best available therapy was available from SIMPLIFY-2, the company did not use that in its base case. Instead, it used evidence from people who had stopped having ruxolitinib from Schain et al. 2019 (n=71). This was a retrospective observational study of people with myelofibrosis in Sweden and Norway, which the company considered best represented the people likely to have fedratinib in the NHS. The ERG noted that Schain included more people with primary myelofibrosis than JAKARTA-2, and the population was also older on average. Therefore, the ERG expected people in Schain to have a worse prognosis than those in JAKARTA-2. The ERG had additional concerns with comparing survival data from an observational study (Schain) with a clinical trial (JAKARTA-2). It also considered that SIMPLIFY-2 was a more appropriate source of evidence for best available therapy to align costs and outcomes in the model. This was because nobody in Schain had ruxolitinib, and so it did not reflect the composition of best available therapy from SIMPLIFY-2 (in which around 89% of people had ruxolitinib). The company used evidence from people who stopped having ruxolitinib (n=39) in COMFORT-2 for the adverse event

frequency for people having best available therapy after fedratinib. COMFORT-2 was a randomised phase 3 trial comparing ruxolitinib with best available therapy in people with myelofibrosis. The company also used the data from the best available therapy arm of COMFORT-2 (n=73) to model the rate of transformation to AML for people having fedratinib and for people having best available therapy (see [section 3.14](#)). Finally, the company used evidence from the HMRN to inform the model of time to treatment discontinuation for people having best available therapy. The HMRN measured treatment outcomes in people with primary or secondary myelofibrosis in the Yorkshire and the Humber and Yorkshire Coast Cancer Networks between September 2004 and August 2017. The ERG was concerned that the populations in SIMPLIFY-2, COMFORT-2, Schain, and the HMRN were different in terms of age, risk score, and the types of best available therapy options that people were having. It was also concerned that the company did not use evidence sources consistently in its model. The committee agreed that using different sources of evidence to model best available therapy was inappropriate and increased uncertainty. The comparator in the company's model was comprised mainly of people having ruxolitinib (see [section 3.4](#)), and the evidence used for best available therapy should reflect this.

Fedratinib is likely to extend survival, but the extent of the survival benefit is highly uncertain

- 3.11 To model survival after stopping treatment for people having fedratinib, the company fitted parametric models to the JAKARTA-2 intermediate-2 or high-risk subgroup survival data after stopping treatment, split by response status at week 24. Based on clinical expert advice, the company considered a Weibull distribution to be the most plausible distribution for people whose disease did respond and those whose disease did not respond. The company also noted that the Weibull distribution provided a conservative survival estimate for fedratinib. For best available therapy, the company fitted a Weibull distribution to the overall survival data from Schain for people who stopped having ruxolitinib. The company's base-case model predicted a mean overall survival benefit for fedratinib of 6.2 months based on the naive comparison of overall survival from JAKARTA-2 and Schain. However, the ERG had concerns with using the overall survival data from Schain (see

section 3.10). It considered that the observed survival benefit could be because the company had used different modelling approaches for the 2 treatment arms. The ERG requested that the company do an exploratory MAIC for overall survival using evidence from JAKARTA-2 and SIMPLIFY-2. It noted that after matching based on DIPSS risk category, the overall survival for people having fedratinib was similar to that for people having best available therapy. The ERG also noted that after adjusting for other prognostic factors such as platelet count and transfusion dependence in the MAIC, people having fedratinib had a shorter overall survival than those having best available therapy. The company considered that the overall survival data from SIMPLIFY-2 was not reliable because of discrepancies in the data reported. It also noted that overall survival was not a pre-specified outcome in SIMPLIFY-2, and that people could switch from best available therapy to momelotinib after 24 weeks. The company highlighted that there was evidence to suggest that spleen response is linked to overall survival. As such, fedratinib could be expected to have an overall survival benefit based on the results of the company's MAIC for spleen or symptom response (see section 3.8). The clinical experts agreed, stating that there is real-world and clinical trial evidence linking spleen response to overall survival. They considered that it was implausible that fedratinib would have no overall survival benefit over best available therapy. At its first meeting, the committee considered that fedratinib was likely to extend overall survival, but the extent of this overall survival benefit was highly uncertain. In response to consultation, the company highlighted 4 studies that quantified the association between spleen response and improved survival. The ERG noted that the company did not use spleen response as a surrogate for survival in its base-case model. The ERG reiterated that when survival was compared with the same evidence source the company used in its response MAIC (SIMPLIFY-2, see section 3.8), there did not appear to be a survival benefit for fedratinib. The committee was concerned that the population in Schain, where people had stopped ruxolitinib treatment, did not reflect the modelled best available therapy arm, where most people continued ruxolitinib treatment. It considered that it had not seen sufficient evidence to change its conclusion from the first meeting. It felt that fedratinib was likely to extend overall survival compared with best available therapy. However, it concluded that based on the evidence presented, the extent

of this overall survival benefit was highly uncertain.

The fedratinib extrapolations for time to treatment discontinuation are uncertain, but are not a main driver of the cost-effectiveness results

3.12 The company fitted several parametric models to the time to treatment discontinuation data from JAKARTA-2 and identified the exponential curve for disease response and the log-normal curve for disease non-response as the most appropriate. The ERG noted that the choice of distribution was very uncertain because of the small sample size and short follow up, and was confounded by the clinical hold and CHMP response definition for JAKARTA-2 (see [section 3.6](#)). The ERG added that other distributions were also equally plausible, and provided a scenario analysis assuming a Gompertz distribution for both disease response and non-response. The committee understood the limitations with the JAKARTA-2 evidence, but noted that the models for time to fedratinib discontinuation were not among the main drivers of the cost-effectiveness results.

The proportion of people staying on ruxolitinib in the model after their disease stops responding (89%) should also apply to fedratinib, for consistency

3.13 In its model presented at the first committee meeting, the company assumed that people having fedratinib would stop having it after their disease stops responding. They would then have best available therapy (without ruxolitinib) or supportive care, or both, until death. In contrast, the company assumed that most people (89%) starting best available therapy in the model were having ruxolitinib, in a population that had already had ruxolitinib (see [section 3.4](#)). The ERG considered that in NHS clinical practice, most people whose disease was relapsed or refractory to fedratinib would keep having it, or would switch back to ruxolitinib. It presented scenarios assuming the same proportion of people (89%) would keep having fedratinib or switch back to ruxolitinib as were having ruxolitinib in the best available therapy arm. The clinical experts noted that the treatment assumptions after fedratinib were hard to comment on

because fedratinib is not used in current clinical practice. They agreed that most people were likely to continue having fedratinib even if their disease had not responded adequately, consistent with how ruxolitinib is used in practice. The clinical lead for the Cancer Drugs Fund noted that it was unlikely that NHS England would commission ruxolitinib after fedratinib, given that people switched to fedratinib because of insufficient disease response or intolerance to ruxolitinib. At its first meeting, the committee considered that most people with relapsed or refractory disease would continue having fedratinib, similar to how people currently keep having ruxolitinib because there are no other treatment options. In response to consultation, the company updated its model base case with the assumption that 65% of people whose disease responded to fedratinib would continue having fedratinib after their disease stops responding. This was calculated based on the discontinuation rate in JAKARTA-2 up to the end of cycle 6. The ERG noted that the company's updated assumption for fedratinib was inconsistent with the best available therapy arm, in which 89% of people continued ruxolitinib treatment until supportive care or death. The company commented on the proportion of time spent on a JAK inhibitor in each arm, but the values are confidential and cannot be reported here. The ERG presented 2 further scenarios. The scenarios assumed that 65% or 89%, respectively, of all people starting fedratinib would keep having it after their disease stops responding. This was regardless of whether their disease initially responded at 24 weeks. The committee understood that in practice clinicians would likely be reluctant to stop fedratinib even if the disease does not fully respond, or stops responding. This was because there would be no other treatment options. The committee concluded that it was appropriate to assume that 89% of all people starting fedratinib would continue fedratinib after their disease stops responding. This was consistent with the proportion who were assumed to continue ruxolitinib in the best available therapy arm.

People having fedratinib should be assumed to have the same AML transformation rate as people having best available therapy

3.14 Myelofibrosis can transform into AML. The company modelled AML as an adverse event, with an associated cost and quality-of-life impact. In its model presented at the first committee meeting, the company used

evidence from the JAKARTA-2 intermediate-2 or high-risk subgroup to inform the AML transformation for people having fedratinib. For people having best available therapy, the company used evidence from COMFORT-2 (see [section 3.10](#)). The ERG commented that the same AML transformation rate should be used for fedratinib and best available therapy, because it is unclear whether fedratinib treatment affects AML transformation. The ERG added that it was more appropriate to use evidence from COMFORT-2 to inform the AML transformation rate for both fedratinib and best available therapy arms. This was because COMFORT-2 had a longer follow up than JAKARTA-2. The committee considered that there was insufficient evidence to tell whether fedratinib affects the rate of AML transformation. It concluded that it was appropriate to assume the same AML transformation rate for fedratinib as for people having best available therapy. In response to consultation, the company updated its base case to assume the same AML transformation rate for both arms, consistent with the committee preference.

Ruxolitinib costs

It is appropriate to use the platelet count distribution from JAKARTA-2 to estimate the cost of ruxolitinib

3.15 Ruxolitinib dose depends on platelet count. People with a platelet count of less than 100×10^9 /litre have a lower dose of ruxolitinib, which costs less. In its model, the company based the proportion of people having the lower ruxolitinib dose in the best available therapy arm on the platelet count distribution from JAKARTA-2. The ERG noted that mean platelet count in JAKARTA-2 was higher than that reported in SIMPLIFY-2, from which the company used the data for best available therapy in the indirect treatment comparison for response (see [section 3.8](#)). The ERG considered that the cost of ruxolitinib had therefore been overestimated by the company. The company noted that although the proportion of people with a platelet count of less than 100×10^9 /litre was not reported from SIMPLIFY-2, around 27% of patients were having a 5 mg dose 2 times per day or less. This was lower than the proportion based on the platelet count distribution from JAKARTA-2, suggesting that the cost of

ruxolitinib had been underestimated in the model rather than overestimated. In response to consultation, the company provided baseline characteristics from a global chart review to support its argument that people having best available therapy have poor survival outcomes (see [section 3.17](#)). These baseline characteristics included the proportion of people with a platelet count of less than 100×10^9 /litre. The ERG noted that this proportion was higher than in JAKARTA-2, and considered that it was more likely to resemble the distribution in SIMPLIFY-2 than JAKARTA-2 did. So, the ERG used the figure from the global chart review in its updated base case for the second committee meeting. The company reiterated that it considered that the cost of ruxolitinib had been underestimated in the model, and that basing the platelet count distribution on the global chart review would further underestimate its cost. The company also noted that using the global chart review to inform the proportion of people having the lower ruxolitinib dose would mean that costs and outcomes in the model would not be aligned, because this data was available from SIMPLIFY-2. The committee understood that there was uncertainty as to which platelet count distribution should be used in the model. It noted the company's concerns with using the global chart review to inform ruxolitinib costs. It concluded that, on balance, the platelet count distribution from JAKARTA-2 was appropriate to use to estimate the cost of ruxolitinib.

It is appropriate to consider scenarios with and without drug wastage for ruxolitinib

3.16 The company base-case model included an additional 5% drug wastage for ruxolitinib, in line with the ERG preference in TA386. The ERG considered this inappropriate because in TA386 the clinical experts advised that assuming no drug wastage for ruxolitinib reflected its use in clinical practice. As such, the ERG preferred to exclude ruxolitinib wastage from the model. In response to consultation, the company did not update its base case. The company indicated that informal discussions with clinicians supported that drug wastage would happen for ruxolitinib in clinical practice. The ERG speculated that there could be less ruxolitinib wastage in the second-line setting because more people would have the 5 mg dose. It also reiterated that the cost of ruxolitinib could already be overestimated in the model (see [section 3.15](#)). The

committee was aware that including drug wastage for ruxolitinib had a large effect on the cost-effectiveness results in some scenarios. It acknowledged the uncertainty, and concluded that it was appropriate to consider scenarios with and without drug wastage for ruxolitinib.

End of life

Fedratinib does not meet the end of life criteria based on the evidence currently available

3.17 The committee considered the advice about life-extending treatments for people with a short life expectancy in [NICE's guide to the methods of technology appraisal](#). The clinical experts explained that life expectancy for people who stop ruxolitinib is around 12 to 18 months. They noted that most people in JAKARTA-2 had died within 2 to 3 years of stopping fedratinib, even though most had retreatment with ruxolitinib. The committee was aware that median overall survival after stopping ruxolitinib was 16 months or less in COMFORT-2, Schain and based on the HMRN data. However, it noted that the company base-case model predicted that people having best available therapy had a mean life expectancy of 28.7 months. The company explained that the Weibull distribution it had used to extrapolate overall survival for people having best available therapy (see [section 3.11](#)) gave an optimistic survival prediction. Selecting a more conservative exponential model resulted in a mean life expectancy of less than 24 months. The ERG base case assumed no survival difference (see [section 3.11](#)), so people having best available therapy had the same life expectancy as people having fedratinib (34.9 months). At its first meeting, the committee concluded that there was considerable uncertainty about whether people having best available therapy would have a life expectancy of less than 24 months. There was also uncertainty about the extent of fedratinib's survival benefit over best available therapy (see [section 3.11](#)). In response to consultation, the company noted that the high-risk disease group in TA386 met the end of life criteria. Because 42% of the modelled population were high risk, the company indicated that these people should therefore meet the end of life criteria for consistency with TA386. The company added that because the Kaplan–Meier data from Schain

was immature, the median survival was more appropriate than the mean survival to inform the life expectancy criterion. The company also provided baseline characteristics for a global chart review that it considered showed poor survival outcomes for people having best available therapy (including ruxolitinib). The company believed that these baseline characteristics were similar to JAKARTA-2. The ERG noted that the survival estimates discussed at the first committee meeting (from COMFORT-2, Schain and the HMRN data) were from people who had stopped ruxolitinib treatment, but in the best available therapy arm in the model 89% of people were having ruxolitinib. The ERG also considered that there was a lack of detail on the global chart review, and that it was unclear how similar the population was to JAKARTA-2. At its second meeting, the committee discussed the survival estimates from clinicians that the company had used to select its survival model for people having best available therapy. It understood that the company had originally asked clinicians for their estimates of survival for when people had stopped having ruxolitinib, rather than for when most people were having suboptimal ruxolitinib. There was also some variability around the clinician responses. The committee noted that the 2 distributions selected as clinically plausible by the company (Weibull and exponential) lay on either side of the clinician estimates, and it would have preferred to see a scenario with a survival model fitted directly through these estimates. Because this would lie above the exponential distribution (which gave a mean survival of 23.3 months), the committee considered that it was likely that this scenario would give a mean survival of more than 24 months. The committee also noted that because the cost-effectiveness results are calculated based on mean (rather than median) values, it is important to consider the mean survival results when assessing if the end of life criteria were met. The committee considered that it had not seen robust enough evidence to conclude that fedratinib met either of the criteria to be considered a life-extending treatment at the end of life based on the evidence currently available.

Cost-effectiveness estimates

The most likely cost-effectiveness estimates are higher than those normally considered an acceptable use of NHS resources

3.18 The committee considered the deterministic incremental cost-effectiveness ratios (ICERs) for fedratinib compared with best available therapy. Because of a confidential commercial arrangement for ruxolitinib, the exact cost-effectiveness results cannot be reported here. The committee noted that the 2 main drivers of the cost-effectiveness results were whether or not fedratinib was assumed to extend overall survival (see [section 3.11](#)) and what proportion of people would continue having fedratinib after their disease stops responding (see [section 3.13](#)). In the company's base case, fedratinib was assumed to extend overall survival by 6.2 months, and 65% of people whose disease initially responded to fedratinib continued having it. The ERG presented 2 base cases in which it assumed that fedratinib had no overall survival benefit compared with best available therapy and 89% of all people starting fedratinib continue having fedratinib after their disease stops responding. Ruxolitinib wastage was included in ERG base case 1, and excluded in ERG base case 2. The ERG base cases also included several other of the ERG's preferred assumptions, that is:

- excluding gender from the utility regression model
- using the same dose intensity for all people having fedratinib (suboptimal or not)
- basing the fedratinib adverse event rates in the model on the intention-to-treat population from JAKARTA-2, rather than the intermediate-2 or high-risk subgroup.

The committee considered analyses including the following assumptions:

- with and without a survival benefit (see [section 3.11](#))
- the cost of ruxolitinib based on the platelet count distribution from JAKARTA-2 (see [section 3.15](#))

- both with and without drug wastage for ruxolitinib (see [section 3.16](#))
- 89% of all people starting fedratinib would keep having it after their disease does not fully respond or stops responding (see [section 3.13](#))
- including the other ERG-preferred assumptions, outlined above.

The analyses accounting for a survival benefit for fedratinib resulted in ICERs less than £30,000 per quality-adjusted life year (QALY) gained, but the analyses without a survival benefit resulted in ICERs greater than this. The committee considered that the most plausible ICER was likely to be between the scenarios with and without a survival benefit for fedratinib applied. However, this ICER would likely be above £30,000 per QALY gained, the upper end of the range normally considered a cost-effective use of NHS resources when the end of life criteria are not met. The committee concluded that fedratinib could not be recommended for routine use in the NHS.

Other factors

- 3.19 The company considered fedratinib to be an innovative treatment but did not provide evidence of significant and substantial health-related benefits that were not included in the QALY calculations. The committee concluded that there were no additional gains in health-related quality of life associated with fedratinib over those already included in the QALY calculations.
- 3.20 An equalities issue was raised that myelofibrosis often affects older people. However, issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal.

Cancer Drugs Fund

Fedratinib is recommended in the Cancer Drugs Fund

- 3.21 Having concluded that fedratinib could not be recommended for routine use, the committee then considered if it could be recommended within the Cancer Drugs Fund. The committee discussed the arrangements for

the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting [NICE's Cancer Drugs Fund methods guide \(addendum\)](#). The committee considered whether the remaining uncertainties in the company's modelling could be addressed through collecting more data. It was aware that FREEDOM-2, a randomised controlled trial directly comparing fedratinib with best available therapy in people with myelofibrosis previously treated with ruxolitinib, is currently ongoing. The company expressed an interest in fedratinib being considered for funding through the Cancer Drugs Fund. The committee considered that FREEDOM-2 would likely resolve some of the modelling uncertainties. These included the extent of a fedratinib survival benefit compared with best available therapy and the ruxolitinib treatment costs (how many people have the lower dose of ruxolitinib in the setting of best available therapy). Using fedratinib in the NHS would also allow data to be collected using the Systemic Anti-Cancer (SACT) dataset. This would provide data on overall survival and treatment duration for people having fedratinib in clinical practice. The committee recalled that fedratinib had shown plausible potential to be cost effective when assuming the size of survival benefit from the company's base case (see [section 3.18](#)). The committee concluded that fedratinib met the criteria for inclusion in the Cancer Drugs Fund for treating disease-related splenomegaly or symptoms of primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis in adults who have previously had ruxolitinib.

4 Implementation

- 4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has disease-related splenomegaly or symptoms of primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis, previous treatment with ruxolitinib and the doctor responsible for their care thinks that fedratinib is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in [NHS England's Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#).
- 4.2 [Chapter 2 of Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for use in the Cancer Drugs Fund, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Drugs that are recommended for use in the Cancer Drugs Fund will be funded in line with the terms of their managed access agreement, after the period of interim funding. The [NHS England and NHS Improvement Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales,

whichever is the later.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Charlie Hewitt

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