NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using fedratinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: June 2021

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using fedratinib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 28 July 2021

Second appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Fedratinib is not recommended, within its marketing authorisation, for treating disease-related splenomegaly or symptoms of primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis in adults who have not had a Janus kinase (JAK) inhibitor or who have had ruxolitinib.

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 narrower than the marketing authorisation for fedratinib.

Clinical trial evidence in this population 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 only been compared indirectly with best available therapy using evidence from other trials. There is further uncertainty because of some differences between the trial populations in the indirect comparison.

Also, it is not clear how much longer people having fedratinib live compared with best available therapy, and which treatments would be used after fedratinib. These uncertainties have a large effect on the cost-effectiveness results.

Fedratinib does not meet NICE's criteria to be considered a life extending treatment at the end of life. Also, the cost-effectiveness estimates for fedratinib compared with best available therapy are higher than what NICE normally considers an acceptable use of NHS resources. It is unlikely that collecting more data in the Cancer Drugs Fund would resolve the uncertainties in the evidence. So, fedratinib is not recommended for routine use or through 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, company submission). The company has a commercial arrangement, which would have applied if the technology had been recommended.

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), 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 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 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 who have 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. 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 resistant to ruxolitinib, or who were intolerant to ruxolitinib, after at least 14 days 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 the end of the study. 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 there was regression to the mean effects. This is where 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%). 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, which were 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. After stopping fedratinib, the company assumed that people would have best available therapy without ruxolitinib. 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. It concluded 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 best

available therapy. 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. The committee considered that fedratinib was likely to extend overall survival. 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 JAKARTA-2 evidence, but noted that the models for time to fedratinib discontinuation were not one of the main drivers of the cost-effectiveness results.

Most people are likely to keep having fedratinib after losing disease response, although the proportion who will do so is uncertain

3.13 The company assumed that people having fedratinib would stop having it after disease relapse, and 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 the 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. The committee discussed what proportion of people would keep having fedratinib after disease relapse. It considered a scenario presented by the company in which 35% of people permanently stopped having fedratinib and 65% continued. This was based on the discontinuation rate in JAKARTA-2 after the end of cycle 6. The committee concluded that most people with relapsed or refractory disease would continue having fedratinib, similar to how people

keep having ruxolitinib because there are no other treatment options. However, the proportion of people who would continue having fedratinib was uncertain and would likely be between the estimates of the company scenario (65%) and ERG (89%).

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 original model, the company used the same AML transformation rate for both fedratinib and best available therapy arms. However, in its updated model 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, as in the company's original submission, the same AML transformation rate should be used for fedratinib and best available therapy. This is 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.

Ruxolitinib costs are uncertain, but are not one of the main drivers of the cost-effectiveness results

3.15 Ruxolitinib dose depends on platelet count. People with a platelet count of less than 100 x 10^9/litre have a lower dose of ruxolitinib, which costs less. Without individual patient data from the best available therapy arm of SIMPLIFY-2, the proportion of people with a lower platelet count was

uncertain. The company estimated the proportion of people with a lower platelet count in SIMPLIFY-2 by applying a normal distribution to the mean platelet count and standard deviation, which had been published. This method estimated that 39% of people would have a platelet count of less than 100 x 10^9/litre and so have a lower ruxolitinib dose. The ERG noted that assuming a normal distribution for the SIMPLIFY-2 population resulted in many people having a platelet count of less than 0, which was not plausible. It considered a log-normal distribution to be more appropriate. Using that assumption, 49% of people would have the lower platelet count and lower ruxolitinib dose. The ERG also noted that the company base case included an additional 5% drug wastage for ruxolitinib. It 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. The committee noted the uncertainty around the ruxolitinib costs, but concluded that this was not one of the main drivers of the cost-effectiveness results.

End of life

Fedratinib does not meet the end of life criteria

3.16 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) was optimistic. Selecting a more conservative exponential model resulted in a mean life expectancy of less than 24 months. The company also noted supporting evidence suggesting that people who have had ruxolitinib have poor survival outcomes. The ERG base case assumed no survival difference (see section 3.17), so people having best available therapy had the same life expectancy as people having fedratinib (34.9 months). The committee considered 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). The committee concluded that it had not seen sufficiently robust evidence to conclude that fedratinib met the criteria for end of life treatments.

Cost-effectiveness estimates

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

3.17 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 which treatment people switched to after stopping fedratinib (see section 3.13). In the company's base case, fedratinib was assumed to extend overall survival, and people switched to best available therapy without ruxolitinib after stopping fedratinib. The ERG presented 2 base cases in which it assumed that fedratinib had no overall survival benefit compared with best available therapy, and that most people either continued suboptimal fedratinib (base case 1) or had retreatment with ruxolitinib (base case 2) after disease relapse on fedratinib. The ERG

base cases also included several other of the ERG's preferred assumptions, that is:

- including best available therapy drug costs for people not having a JAK inhibitor after fedratinib
- excluding gender from the utility regression model
- removing ruxolitinib wastage (see section 3.15)
- using the same dose intensity for all people having fedratinib (suboptimal or not)
- applying the same AML transformation rate between arms from COMFORT-2 (see section 3.14)
- basing the fedratinib adverse event rates in the model from the intention-to-treat population from JAKARTA-2, rather than the intermediate-2 or high-risk subgroup.

There was considerable uncertainty about the extent of fedratinib's survival benefit over best available therapy, and which treatment people would have after stopping fedratinib. The committee also noted several other remaining uncertainties in the modelling, specifically:

- the overly complex model structure (see section 3.9)
- the inconsistent approach to modelling fedratinib and best available therapy
- the inconsistent use of evidence sources for best available therapy (see section 3.10)
- the most appropriate model of time to treatment discontinuation for fedratinib (see section 3.12), and
- the ruxolitinib treatment costs (see section 3.15).

The committee would have preferred to see a cost-effectiveness model that used a consistent modelling approach for fedratinib and best available therapy, and consistently used evidence sources for best available therapy. This would increase confidence that any survival benefit for fedratinib predicted by the model would not be from the modelling

approach itself. The committee considered that the most plausible ICER was likely to be between the company and ERG base cases. However, it noted that both the company and ERG ICERs were above the upper end of the range normally considered a cost-effective use of NHS resources when the end of life criteria are not met (£30,000 per quality-adjusted life year [QALY] gained).

Other factors

3.18 The company considered fedratinib to be an innovative treatment. However, 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.

3.19 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.

Conclusion

Fedratinib is not recommended for routine use in the NHS

3.20 The committee noted there was uncertainty around the clinical evidence for fedratinib (see section 3.6) but acknowledged the challenges of data collection for rare diseases. It noted considerable uncertainty around the company's modelling approach, particularly about the extent of fedratinib's survival benefit and which treatment people switched to after stopping fedratinib. These uncertainties had a large effect on the cost-effectiveness results. The ICERs for fedratinib compared with best available therapy in both the company and ERG base cases were higher than what is normally considered an acceptable use of NHS resources. Therefore, fedratinib is not recommended for routine use in the NHS.

Cancer Drugs Fund

Fedratinib is not recommended for use 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 while FREEDOM-2 would likely resolve some of the modelling uncertainties, it may not robustly resolve the uncertainty around a fedratinib survival benefit because crossover is allowed at 6 months (or earlier with disease progression). The committee also recalled that a simpler model structure may have been more robust for decision making (see section 3.9), and that fedratinib had not shown the plausible potential to be cost effective in any of the ERG or company scenarios (see section 3.17). The committee concluded that fedratinib did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
June 2021

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.

Catie Parker
Technical lead

Charlie Hewitt
Technical adviser

Louise Jafferally
Project manager

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