NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis

1 Recommendations

1.1 Fedratinib is recommended as an option for treating disease-related splenomegaly or symptoms of primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis. It is recommended for adults, only if:

- they have had ruxolitinib, and
- momelotinib is unsuitable, and
- the company provides fedratinib according to the commercial arrangement.

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 healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

This evaluation reviews the evidence for fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (NICE technology appraisal guidance 756). It also reviews new data collected as part of the managed access agreement.

Most people with higher risk myelofibrosis have ruxolitinib (a JAK inhibitor). After stopping ruxolitinib, people can have best available therapy, which includes hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation

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therapy, erythropoietin, and red blood cell transfusions. Some people with moderate to severe anaemia also have momelotinib. The company asked for fedratinib to be considered only for use after ruxolitinib and when momelotinib is unsuitable. This does not include everyone who it is licensed for.

Evidence from a clinical trial suggests that fedratinib reduces spleen volume and symptoms more than best available therapy. But it is not clear if people having fedratinib live for longer than people having best available therapy.

Because of uncertainty in the long-term clinical evidence, the cost-effectiveness estimates are uncertain. But the most likely estimates are within the range that NICE considers an acceptable use of NHS resources. So, fedratinib is recommended.

2 Information about fedratinib

Marketing authorisation indication

2.1 Fedratinib (Inrebic, Bristol-Myers Squibb) is indicated 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 for fedratinib.

Price

2.3 The list price of fedratinib is £6,119.68 for a 120-capsule pack of 100-mg capsules (excluding VAT; BNF online, accessed August 2024)

2.4 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.

3 Committee discussion

The evaluation committee considered evidence submitted by Bristol-Myers Squibb, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

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 reduce their working hours or stop working completely because of fatigue. The patient experts explained that myelofibrosis is a debilitating chronic condition that has a major impact on quality of life, with significant negative social and economic impacts on people with the disease and their carers. The patient experts explained the fear of living with an incurable disease for most people. They explained that knowing there are limited treatment options adds to their worry. They would like a new treatment option that increases life expectancy and improves 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 carers.

Unmet need

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. Healthcare professionals 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. Most others have best available therapy (see section 3.3). The clinical experts explained that these treatments are largely supportive and do not significantly alter the course of the disease. They 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 that mean they have to stop treatment. The clinical and patient experts agreed that most best available therapies are supportive and have limited effectiveness. This means many people continue having suboptimal ruxolitinib treatment even if the disease does not respond or loses response, because there are no other effective treatment options. But disease symptoms will usually return for people having suboptimal ruxolitinib. When ruxolitinib is no longer suitable, there are no options other than best available therapy. The committee agreed that fedratinib may address the unmet needs of people with myelofibrosis.

Clinical management

Treatment options and positioning

3.3 There are limited treatment options available for myelofibrosis. Allogenic stem cell transplant is the only potentially curative treatment available, but it is unsuitable for many people with myelofibrosis. The clinical experts explained that most people with intermediate-2 or high-risk myelofibrosis will initially have ruxolitinib. Those with moderate to severe anaemia who have not had a JAK inhibitor or have had ruxolitinib can have momelotinib, as recommended in NICE's technology appraisal guidance on momelotinib. People who have previously had ruxolitinib or for whom ruxolitinib and momelotinib are unsuitable have best available therapy. This includes hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin, and red blood cell transfusions. The patient expert explained that treatments often lose effectiveness over time and that prognosis without ruxolitinib is poor. The

clinical experts said that even when ruxolitinib has lost effectiveness, it is often used as part of best available therapy because no other treatments are available. The committee noted that the company positioned fedratinib for use in intermediate-2 or high-risk disease after ruxolitinib and when momelotinib is unsuitable. The clinical experts clarified that this is an identifiable population in clinical practice. They considered this reflected an area of unmet need and was how clinicians would use fedratinib in clinical practice. Using fedratinib after ruxolitinib was also in line with the way it was used via the Cancer Drugs Fund (CDF), but was narrower than its marketing authorisation indication. People who have had ruxolitinib have few treatment options, with limited effectiveness. The committee agreed that people with myelofibrosis and healthcare professionals would welcome effective treatments that reduce the symptoms and improve the quality of life for people with myelofibrosis and their carers.

Comparators

3.4 The comparators in the NICE scope for people who have had ruxolitinib or for whom ruxolitinib is not appropriate (including people with low or intermediate-1 risk disease) were established clinical practice, also called best available therapy, and momelotinib (subject to NICE evaluation). The committee noted that the company included best available therapy as the only comparator in its submission. This included hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusions. The company stated that the NICE technology appraisal guidance on momelotinib was published in March 2024 and cannot be considered established NHS clinical practice. It explained that momelotinib was only recommended for people with moderate to severe anaemia, so it considered the overlap between the populations eligible for momelotinib and fedratinib was very small. The EAG explained that the main evidence for fedratinib came from FREEDOM-2, a phase 3 randomised, open-label, multicentre trial. It compared fedratinib with best available therapy. In FREEDOM-2, 67% of people having fedratinib and 61% of people having best available therapy

had a haemoglobin level of 100 g/l or less at baseline, which aligns with the National Cancer Institute definition of moderate to severe anaemia. So, the EAG did not consider the overlap between the populations eligible for fedratinib and momelotinib to be small. The clinical experts clarified that people with myelofibrosis could access momelotinib through a compassionate use programme before it was evaluated by NICE. The NHS England CDF lead pharmacist confirmed the number of people with myelofibrosis who had momelotinib per month, combining both first-line and second-line treatment (exact number is confidential and cannot be reported here). The clinical experts explained that myelofibrosis is a heterogeneous condition and people could have momelotinib at both first and second line. But they would prefer to use momelotinib for people with moderate to severe anaemia rather than people with other symptoms including people with a large spleen. The clinical experts considered that there was some overlap between the populations and they would consider momelotinib a relevant comparator for fedratinib. The committee was aware that at the clarification stage, the EAG asked the company to provide a comparison with momelotinib, but the company did not provide it. The committee considered there may be different reasons to choose momelotinib over fedratinib at second line, but there was an overlap between the eligible population for both treatments. It concluded that it would have liked to see a comparison with momelotinib, but it accepted the company's positioning of fedratinib for use when momelotinib is unsuitable.

Clinical effectiveness

Fedratinib data sources

3.5 The main clinical-effectiveness evidence for fedratinib came from the FREEDOM-2 trial (see section 3.4). FREEDOM-2 compared fedratinib 400 mg (n=134) with best available therapy (n=67) for people with intermediate-2 or high-risk myelofibrosis and splenomegaly. Following the recommendation in the NICE technology appraisal guidance on fedratinib

(from here, TA756), new evidence was collected as part of the managed access agreement. The current submission relies mainly on the FREEDOM-2 trial providing additional data for overall survival. Additionally, the Systemic Anti-Cancer Therapy (SACT) dataset collected data on people (n=54) with intermediate-2 or high-risk myelofibrosis and splenomegaly, symptoms or both.

Clinical effectiveness in the fedratinib study

3.6 Evidence from FREEDOM-2 showed that, compared with the best available therapy, fedratinib led to improvement in the primary outcomes. These included spleen and symptom response (spleen volume reduction of 35% or more) at 6 months. The spleen volume response rate was 36% for fedratinib and 6% for best available therapy. The symptom response rate was 34% for fedratinib and 17% for best available therapy. The median time to discontinuation was 51 weeks with fedratinib and 67 weeks for best available therapy. Median overall survival was not estimable for fedratinib (95% confidence interval [CI] 113 weeks to not estimable) and 125 weeks for best available therapy (95% CI 99 weeks to not estimable). The committee recalled that the long-term effectiveness was a key uncertainty in the original appraisal. The EAG noted that there was still considerable uncertainty in the long-term overall survival beyond 6 months (see section 3.8). The committee concluded that people having fedratinib have higher spleen volume and symptom response rates compared with best available therapy, but there was uncertainty around the extent to which overall survival benefit would continue beyond 6 months.

SACT data set

3.7 The SACT dataset collected data on 54 people who had fedratinib between November 2021 and October 2022. At the latest data cut-off, 27 (50%) people were having fedratinib and 27 (50%) had stopped fedratinib. The median treatment duration was 25 weeks, and the median overall survival was 67 weeks. The EAG considered that the baseline

characteristics in FREEDOM-2 and SACT were similar, but noted that the SACT dataset had a higher proportion of men (76%) than FREEDOM-2 (52%). The EAG also highlighted that the population in the SACT dataset was older (median age 72 years) than the population in the FREEDOM-2 trial (median age 69 years). The EAG highlighted that the median time to discontinuation and overall survival were shorter in SACT than FREEDOM-2 for fedratinib. The company explained that the SACT data was less certain than the FREEDOM-2 data because of diverse patient characteristics, comorbidities and treatment histories, which could affect time to treatment discontinuation and overall survival. The committee questioned whether the SACT and FREEDOM-2 populations were similar. The clinical experts noted that in the NHS, people who switch from ruxolitinib to fedratinib cannot switch back to ruxolitinib if fedratinib is ineffective. So people with myelofibrosis and healthcare professionals may wait longer to switch from suboptimal ruxolitinib to fedratinib. The NHS England CDF lead pharmacist confirmed that the commissioning criteria mean that people are not able to have ruxolitinib again if their disease does not respond to fedratinib. The clinical experts also added that people usually switch from ruxolitinib to fedratinib without any break in treatment because of the severity of their condition, but in FREEDOM-2, there was a 14-day ruxolitinib washout period before switching to fedratinib. So for both these reasons they considered the FREEDOM-2 population to be fitter than the SACT population. The committee discussed whether the data from SACT suggested outcomes were more pessimistic in the real world. The committee noted that the SACT population had more severe disease than the population in FREEDOM-2. The committee concluded that the SACT data was more generalisable to people who will have fedratinib in clinical practice in England.

Crossover

3.8 In FREEDOM-2, people in the best available therapy arm were allowed to cross over to have fedratinib at the end of cycle 6, or earlier on disease progression. The EAG noted that out of 67 people having best available

therapy, 46 (69%) crossed over to have fedratinib. It explained that most people (43; 93%) switched to fedratinib after 6 cycles, while only 3 (7%) switched on disease progression, which made it difficult to compare overall survival, time to treatment discontinuation or durability of response beyond 6 months from FREEDOM-2. The company clarified that it had explored formal methods for adjusting for treatment switching such as:

- rank-preserving structure failure time models with and without re-censoring
- iterative parameter estimation
- simplified 2-stage estimation
- complex 2-stage estimation with g-estimation
- inverse probability of censoring weighting.

The company thought that none of these methods were appropriate because of the violation of assumptions of each method, small sample size and contradictory results. The EAG agreed that none of the formal methods to adjust for treatment switching explored by the company were appropriate. When the Kaplan–Meier estimates for best available therapy were grouped based on whether people switched to fedratinib, those who switched had better survival outcomes than those who did not switch. Only 21 people who did not switch to fedratinib had uncertain survival rates. People with better prognosis were more likely to switch to fedratinib (see section 3.7). And observed time to treatment discontinuation and overall survival were similar between fedratinib and best available therapy in the model (see section 3.10). The committee thought that overall survival could not be determined because of the high rate of crossover before progression. It noted that the FREEDOM-2 data did not provide conclusive evidence on overall survival, leaving the survival benefit with fedratinib uncertain. It considered that the time to treatment discontinuation analysis was flawed because crossover to best available therapy was not considered an event and people were not censored at the point of crossover. This introduced bias that was

not accounted for in the results. The committee concluded that the survival benefit with fedratinib compared with best available therapy from FREEDOM-2 was too uncertain. It was aware that because of this uncertainty, the company assumed in its economic model that survival and time to treatment discontinuation were the same for both fedratinib and best available therapy. But it thought that if a more robust comparison could be made using data for best available therapy from an alternative source, it would have welcomed this analysis.

Economic model

Company's modelling approach

3.9 The company submitted an individual patient discrete event simulation model comparing fedratinib with best available therapy. The model included 4 health states: on fedratinib, on best available therapy, supportive care and death. People entered the model having either fedratinib or best available therapy. They were assigned a sampled time to treatment discontinuation based on log-logistic extrapolation and time to death from a Weibull extrapolation. The sampled time to treatment discontinuation and overall survival were correlated: people who were assigned a longer time on treatment had a longer time to death and vice versa. People who stopped treatment after fedratinib could transition to best available therapy or supportive care, but people who stopped treatment after best available therapy could only transition to supportive care. For people having best available therapy as a subsequent treatment, no time to treatment discontinuation was sampled. But subsequent best available therapy was determined based on the remaining time to death, which was assumed to split as 59.6% on best available therapy and 40.4% on supportive care. People who transitioned to supportive care remained in that health state until death. The EAG highlighted that the company's model differed from that in TA756 in 3 ways: duration of response was not sampled separately (instead the disease was assumed to respond until treatment was stopped); it

excluded acute myeloid leukaemia; and it used supportive care instead of palliative care. The EAG also identified errors in the company's model. It explained that the company model was based mainly on literature identified in TA756, with updated unit costs applied or published costs uplifted for inflation. The clinical experts agreed that the company's model structure appropriately captured all the relevant health states. The committee concluded that the model structure was appropriate for decision making.

Overall survival and time to treatment discontinuation extrapolation

3.10 Both time to treatment discontinuation and overall survival on fedratinib were longer in FREEDOM-2 than in SACT (see sections 3.6 and 3.7). The committee considered that the company model overestimated both time on treatment and overall survival in the population likely to have fedratinib in the NHS. It acknowledged that the SACT data represented a more heterogenous population than the FREEDOM-2 data. It noted diverse patient characteristics, comorbidities and treatment histories that could affect time to treatment discontinuation and overall survival. But, the committee recalled that the SACT data was more generalisable to people who will have fedratinib in clinical practice in England than the FREEDOM-2 data. It concluded that despite the uncertainties, using the SACT data was more appropriate than using the FREEDOM-2 data.

Composition of best available therapy after fedratinib

3.11 The company's model assumed that people with myelofibrosis whose disease did not respond to fedratinib or partially responded to fedratinib would not have any subsequent treatment with fedratinib. The EAG explained that the treatments included in best available therapy as a comparator for fedratinib and treatments included in best available therapy as a subsequent treatment after fedratinib differed. It noted that people were allowed to have ruxolitinib as part of best available therapy in the comparator arm, but were not allowed to have either ruxolitinib or fedratinib as part of best available therapy after fedratinib. TA756 noted

that in clinical practice, healthcare professionals would 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. So the EAG preferred to assume that the proportion of people having suboptimal fedratinib was the same (77.6%) as the proportion of people having ruxolitinib in the best available therapy arm of FREEDOM-2. The clinical experts explained that people whose disease does not respond to both ruxolitinib and fedratinib have a very short life expectancy (just a few weeks). They noted that in these people their disease is also unlikely to respond to other treatments included in best available therapy (see section 3.4). They considered that a significant proportion of people would continue to have suboptimal fedratinib. The committee agreed that the company's assumption of no suboptimal fedratinib was unrealistic. It concluded that the EAG's approach of allowing people to have suboptimal fedratinib was closer to reflecting how fedratinib will be used in clinical practice. But the exact proportion was uncertain because no data was available. The committee also noted that the company had not modelled a switch back to ruxolitinib, which clinical experts suggested might be desirable in clinical practice, but is not currently possible.

Transition to supportive care

3.12 The company's model assumed that people with myelofibrosis having fedratinib transition to supportive care instead of transitioning to best available therapy after fedratinib. The EAG noted that the company's model assumed everyone stopping best available therapy, including people having suboptimal ruxolitinib, would transition directly to supportive care rather than having any other form of best available therapy. In people having fedratinib, the proportion transitioning to supportive care was higher (66.7%) for people with myelofibrosis whose disease did not respond to fedratinib and lower (33.3%) for people with myelofibrosis whose disease responded to fedratinib initially and then stopped responding. The EAG explained that transitioning to supportive care was associated with a utility decrement, which was delayed for people having

fedratinib compared with people having best available therapy. It explained that this provided an indirect quality-adjusted life year (QALY) gain for people having fedratinib regardless of response status. The clinical experts reiterated that people whose disease does not respond to either ruxolitinib or fedratinib have only a few weeks to live, and will transition to supportive care, which has limited effectiveness. They explained that people who have both ruxolitinib and fedratinib have different disease trajectories compared with people who only have ruxolitinib. The committee recalled that the current NHS criteria for eligibility for treatment with fedratinib mean that people cannot transition back to ruxolitinib if their disease does not respond to fedratinib. The committee was aware that a large proportion of people have suboptimal ruxolitinib as part of best available therapy. When they stop suboptimal ruxolitinib they transition to supportive care, which is generally ineffective in most people (see section 3.2). The committee considered that the exact proportion of people having fedratinib who will transition to supportive care in clinical practice was uncertain. It would consider the scenario presented in its decision making.

Duration of suboptimal ruxolitinib within best available therapy

3.13 The company's model fitted parametric curves for time to treatment discontinuation to Kaplan–Meier curves that included time on treatment with fedratinib in people who crossed over from best available therapy to fedratinib (see section 3.8). The EAG explained that no censoring was considered at crossover because crossover to fedratinib was not considered a discontinuation event. It noted that most people having best available therapy who switched to fedratinib after 6 cycles may have done so because they chose to have fedratinib instead of best available therapy. The committee noted that in FREEDOM-2, people having best available therapy switched to fedratinib earlier than in the SACT dataset. This was also earlier than fedratinib is likely to be used in clinical practice. The committee considered whether the duration of treatment with best available therapy would have been similar if people had not had the option

to cross over to fedratinib. It noted that duration of treatment on best available therapy (as a comparator) may have been longer in FREEDOM-2 than in clinical practice. This was because healthcare professionals would be concerned that people having best available therapy would not be able to go back to ruxolitinib after fedratinib, so would delay switching to fedratinib for as long as possible. The committee noted this had a large effect on the cost-effectiveness results. It concluded that duration of suboptimal ruxolitinib treatment within best available therapy was uncertain and was not appropriately explored by the company.

Utility values

3.14 In the company's model, health-related quality of life was derived by a combination of disease-specific utility values based on Myelofibrosis 8 Dimension (MF-8D) values from FREEDOM-2, with an adjustment from literature for disutility associated with best supportive care, and an adjustment over time for declining utility with age in the general population based on the EQ-5D-3L. The committee noted that EQ-5D-5L utility values were collected in FREEDOM-2, but were not used to inform the model. The NICE reference case recommends using directly measured EQ-5D-3L data. The company considered the MF-8D the most appropriate because it was developed specifically for people with myelofibrosis and is more sensitive to changes in the quality of life of people with this condition than the EQ-5D. The EAG noted that utilities at the start of the model were set to match the baseline utility level from FREEDOM-2, which was pooled across treatment groups. This initial utility level was maintained for the first 4 weeks. After that, the utility value depended on how the disease responded to treatment and whether people were having fedratinib or best available therapy. The EAG explained that for people whose disease did not respond to treatment, their utility values differed depending on whether they were having fedratinib or best available therapy. But for people whose disease responded, their utility values were the same regardless of treatment. When people switched from fedratinib to best available therapy they were

assumed to have the same utility value (0.649) as people whose disease did not respond and who had best available therapy. When people transitioned to supportive care, their utility value reverted to the baseline levels from FREEDOM-2. Additionally, a utility decrement was applied for the whole 24-week period spent in supportive care. The clinical experts explained that because of the heterogeneity of the condition they would expect slightly higher utility values for people having fedratinib than for those having best available therapy because they would expect better JAK inhibition from fedratinib. The committee noted that even if a treatment does not reduce spleen volume by 35% (primary outcome measure), even a small reduction in symptoms can still improve quality of life. It also noted that the company model assumed no change in utility from baseline for people with no response to best available therapy, but applied an increase in utility of 0.052 from baseline for people with no response to fedratinib. It was aware that utilities had a large effect on the results. It acknowledged the benefits offered by fedratinib but considered that these were insufficient to be categorised as a response. The committee concluded that because of the lack of evidence, it was more appropriate to use equal utility values for no response with both fedratinib and best available therapy.

Costs

Ruxolitinib wastage

3.15 In FREEDOM-2, the mean daily dose of ruxolitinib for people having best available therapy was 24.1 mg. But the cost included in the company's model was for a dose higher than 24.1 mg. The company considers the mean cost included in the model to be confidential so it cannot be reported here. The committee noted that the company's model assumed that whenever a new dose was prescribed mid-cycle, the remaining pack of tablets was discarded and a new pack of was dispensed. Frequent dose adjustments in FREEDOM-2 resulted in an average of less than 2 packs (the company considers the exact number to be confidential so it

cannot be reported here) being prescribed per person per cycle across the first 6 cycles when a single pack would usually provide 1 cycle of treatment. The EAG explained that in clinical practice, the dosing of ruxolitinib depends on platelet count and haematology tests on day 1 of each cycle with additional testing on day 15 of cycles 1 to 3, whereas equivalent tests were only assumed approximately every 3 weeks in the model. The EAG acknowledged that there may be some wastage of ruxolitinib because of the mid-cycle change of dose to manage adverse events for some people. But this wastage was not as significant as modelled by the company. So the EAG preferred to use an average initial daily dose of 23.8 mg with 5% wastage for dose adjustment in its base case.

The company agreed that the wastage based on the mean dose of ruxolitinib FREEDOM-2 was high. It clarified that it had done an audit of ruxolitinib's use by 2 pharmacists, which estimated around 10% ruxolitinib wastage. It explained that people need more dose adjustments at the second line of treatment so it would expect wastage of around 5% to 10%. This audit data was not presented to the committee. The clinical experts explained that in clinical practice, people having ruxolitinib have blood test monitoring every 2 weeks. They explained that dose adjustment is only needed for severe cytopenia to maintain blood count. But most people do not need dose adjustment in the first 4 to 6 weeks of the treatment. They explained that ruxolitinib is usually prescribed for 1 cycle and the dose is adjusted for the second cycle, so they would expect wastage of less than 5% in the clinical practice. Including wastage for ruxolitinib had a large effect on the cost-effectiveness results. The committee acknowledged the uncertainty and concluded that it was appropriate to use 5% wastage in the base case, but that it would have liked to have seen a scenario analysis with 10% wastage for ruxolitinib.

Definition of spleen volume and symptom response

3.16 The company's model applied a combined definition of response in which either a spleen volume response of more than 35% or a symptom response of more than 50% was considered a response. The company also assumed equal utility gains for these based on clinical opinion, which suggested that both measures track each other. The EAG explained that this conflicted with the FREEDOM-2 results and the company regression analysis using separate definitions, where the utility gain associated with a symptom response was greater than that associated with a spleen volume response. The committee concluded that it would have liked to have seen results using individual definitions of response for spleen volume and symptoms to determine response rates and utility gain for people whose disease had responded to treatment.

Modelling red blood cell transfusion

3.17 The company used a lower red blood cell (RBC) transfusion rate for fedratinib than for best available therapy. It stated that RBC transfusions were only accounted for in routine management of myelofibrosis if people were having either JAK inhibitors (fedratinib or ruxolitinib), best available therapy (excluding ruxolitinib) or supportive care. It explained that adverse events such as thrombocytopenia needing RBC transfusions were excluded from the model because they were captured within routine management. The EAG disagreed with the company's approach because RBC transfusions were allowed in both the fedratinib and best available therapy arms of FREEDOM-2. But RBC transfusions in people having fedratinib were not accounted for in the company model. The EAG explained that evidence from FREEDOM-2 did not suggest that fedratinib lowered transfusion burden compared with best available therapy. So, it preferred to use an equal rate of RBC transfusions for the JAK inhibitors and best available therapy. The committee broadly agreed with the EAG's approach. It concluded that equal rate of RBC transfusions for JAK inhibitors and best available therapy was appropriate.

Severity

3.18 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The company and EAG estimates were below 0.85 for the proportional QALY shortfall and below 12 for the absolute QALY shortfall. So fedratinib did not meet the criteria for applying a severity weighting other than 1.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.19 The cost-effectiveness estimates used by the committee for decision making took into account all of the available confidential discounts, including those for comparators and subsequent treatments. The resulting cost-effectiveness estimates are confidential and cannot be reported here. The company's base-case results were below the range normally considered a cost-effective use of NHS resources. The EAG updated the company's model using its preferred assumptions. The EAG's base-case result for fedratinib compared with best available therapy was also below £30,000 per QALY gained, and was towards the lower end of the range normally considered a cost-effective use of NHS resources. The committee's preferred base case used the EAG's base case plus the SACT data, specifically:

- the EAG's corrected version of the model after clarification
- time to treatment discontinuation and overall survival from SACT (see section 3.10)
- use of suboptimal fedratinib being the same as the use of suboptimal ruxolitinib in best available therapy (see section 3.13)

- equal utility gains for people whose disease did not respond to fedratinib and best available therapy (see section 3.14)
- average initial dose distribution across the first 6 cycles in FREEDOM-2 with 5% wastage for ruxolitinib (see section 3.15)
- the RBC transfusion rates for fedratinib and best available therapy (see section 3.17)
- best available therapy comparator including all treatments used in FREEDOM-2 and not excluding hydroxyurea.

Acceptable ICER

3.20 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically in:

- long-term overall survival and time treatment discontinuation (see section 3.10)
- the modelling assumptions used by the company (see sections 3.9 to 3.17).

Taking into account the uncertainties, the committee concluded that an acceptable ICER would be towards the lower end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Equality

3.21 The committee noted that there is an unmet need for additional treatment options for older people who are ineligible for stem cell transplantation

and are at a disadvantage compared with younger people. Age is a protected characteristic under the Equality Act 2010. But because its recommendation does not restrict access to treatment for some people over others, the committee agreed this was not a potential equalities issue.

Uncaptured benefits

3.22 The committee considered whether there were any uncaptured benefits of fedratinib. It did not identify additional benefits not captured in the economic modelling. So, the committee concluded that all additional benefits of fedratinib had already been taken into account.

Conclusion

Recommendation

3.23 The committee took into account its preferred assumptions, the key uncertainties in the modelling and additional analyses. The range of ICERs that the committee considered to be plausible were towards the lower end of the range normally considered a cost-effective use of NHS resources. So, the committee recommended fedratinib for treating disease-related splenomegaly or symptoms of primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis in adults, only if:

- they have had ruxolitinib, and
- momelotinib is unsuitable.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local

authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

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 routine commissioning, 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. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England 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 a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has disease-related splenomegaly or symptoms in myelofibrosis and the healthcare professional responsible for their care thinks that fedratinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

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

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley

Chair, technology appraisal committee B

NICE project team

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

Harsimran Sarpal

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Project managers

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