NICE National Institute for Health and Care Excellence

NICE guidance

Momelotinib for treating myelofibrosis-related splenomegaly or symptoms

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Momelotinib is recommended as an option for treating myelofibrosis-related splenomegaly or symptoms in adults with moderate to severe anaemia who have not had a JAK inhibitor or have had ruxolitinib, only if:

- they have intermediate-2 or high-risk myelofibrosis, and
- the company provides momelotinib according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with momelotinib 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

Usual treatment for splenomegaly or symptoms of intermediate-2 or high-risk myelofibrosis in adults with moderate to severe anaemia who have not had a JAK inhibitor is ruxolitinib. For people who have had ruxolitinib, usual treatment is best available therapy.

For this evaluation, the company asked for momelotinib to be considered only for people with intermediate-2 or high-risk myelofibrosis. This does not include everyone who it is licensed for.

Momelotinib works in a similar way to ruxolitinib and would be offered to the same population. Clinical trial evidence shows that momelotinib is likely to work as well as ruxolitinib for people who have not had a JAK inhibitor. A cost comparison suggests momelotinib has similar costs to ruxolitinib in this population.

Clinical trial evidence suggests that momelotinib is likely to work as well as best available therapy for people who have had ruxolitinib. The cost-effectiveness estimates for momelotinib in this population are within the range that NICE considers an acceptable use of NHS resources.

So, momelotinib is recommended for adults with intermediate-2 or high-risk myelofibrosis with moderate to severe anaemia who have not had a JAK inhibitor or have had ruxolitinib.

2 Information about momelotinib

Marketing authorisation indication

2.1 Momelotinib (Omjjara, GSK) is indicated for 'the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus Kinase (JAK) inhibitor naïve 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 momelotinib.

Price

2.3 The list price of momelotinib is £5,650 for a 30-tablet pack of 100 mg, 150 mg or 200 mg tablets (excluding VAT; company submission).

2.4 The company has a commercial arrangement. This makes momelotinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by GSK, 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 cancer of the bone marrow that replaces the marrow with scar tissue. Myelofibrosis can be a primary condition, or secondary to either polycythaemia vera or essential thrombocythaemia. As the bone marrow becomes more scarred, it becomes less able to produce blood cells. To compensate for this, the spleen and liver produce blood cells, causing the spleen and liver to enlarge. The patient expert explained that people with myelofibrosis experience symptoms including anaemia, fatigue, itching and night sweats. They explained that these symptoms affect many aspects of life for people with myelofibrosis. People with myelofibrosis may have their day-to-day activities restricted, may have to stop working and may need assistance from carers. The committee recognised the high symptom burden in people with myelofibrosis.

Clinical management

Treatment options

3.2 There are limited treatment options available for myelofibrosis. Allogeneic stem cell transplant is the only potential curative treatment available, but it is unsuitable for many people with myelofibrosis. Myelofibrosis has 4 different risk categories according to the Dynamic International Prognostic Scoring System (DIPSS) and DIPSS Plus: low, intermediate-1, intermediate-2 and high risk. Clinicians can use these risk scores to guide treatment. Most people with intermediate-2 or high-risk myelofibrosis will initially 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. People who have previously had ruxolitinib or for whom ruxolitinib is unsuitable, have treatment with best available therapy (BAT). BAT includes hydroxyurea, prednisone, erythropoiesis-stimulating agents (ESAs), androgens, aspirin, anagrelide, and thalidomide. 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 BAT because no other treatments are available. The patient expert and the clinical experts noted that ruxolitinib can make some symptoms of myelofibrosis worse, particularly anaemia. They commented that momelotinib appears to improve anaemia and would be very valuable as an option to treat myelofibrosis. The committee agreed that people with myelofibrosis and clinicians would welcome a new treatment option for myelofibrosis.

Comparators

3.3 Momelotinib's marketing authorisation is for people with primary or secondary myelofibrosis (regardless of risk category) who have moderate to severe anaemia and who have either not had a Janus kinase (JAK) inhibitor, or have had ruxolitinib. But the company positioned momelotinib only for people with intermediate-2 or high-risk myelofibrosis. The company proposed that the committee consider people who had not previously had a JAK inhibitor (from now, JAK inhibitor-naive) and people who had previously had ruxolitinib (from now, JAK inhibitor-experienced) separately. For the JAK inhibitor-naive population, the comparator was ruxolitinib. For the JAK inhibitor-experienced population, the comparator was BAT. The committee concluded that the positioning of momelotinib was appropriate. It also concluded that it was reasonable to consider these populations separately and that the comparators in each population were appropriate.

Defining moderate to severe anaemia

3.4 Momelotinib's marketing authorisation specifies its use in adults with moderate to severe anaemia. The company defined moderate to severe anaemia as

'treatment-requiring anaemia'. The company used a haemoglobin level of less than 12 g/dL as a threshold for people who may need treatment for their anaemia. The company noted that while not all people with a haemoglobin level of less than 12 g/dL would be considered to have moderate or severe anaemia, it was advised that a lower threshold may exclude some people who would need treatment for anaemia. But the EAG commented that a threshold of haemoglobin less than 10 g/dL was more likely to represent people who would be considered to have moderate or severe anaemia in NHS practice. The EAG also highlighted that the National Cancer Institute used a threshold of haemoglobin less than 10 g/dL to define moderate to severe anaemia. The committee concluded that results from separate subgroups for each threshold should be used to inform decision making. The committee also concluded that results including people without moderate to severe anaemia or people with intermediate-1 myelofibrosis should not be considered for decision making.

Clinical evidence

Data sources

3.5 Clinical evidence in the JAK inhibitor-naive population came from SIMPLIFY-1, a double-blind, phase 3 non-inferiority trial which compared momelotinib with ruxolitinib. Clinical evidence in the JAK inhibitor-experienced population came from SIMPLIFY-2, an open-label, phase 3 superiority trial which compared momelotinib with BAT. Both trials included people who did not have moderate to severe anaemia and people with intermediate-1 risk myelofibrosis. There were 280 people in SIMPLIFY-1 and 111 people in SIMPLIFY-2 with a haemoglobin level of less than 12 g/dL and intermediate-2 or high-risk myelofibrosis. The dose of momelotinib used in both studies was 200 mg per day. The primary outcome in both studies was spleen response, defined as the proportion of people with a spleen volume reduction of 35% or more from baseline at 24 weeks. Other key outcomes in both trials were total symptom score (TSS) and rate of blood transfusion independence. Both trials also included a longer follow-up period, in which everyone had momelotinib, which was 216 weeks in SIMPLIFY-1 and 204 weeks in SIMPLIFY-2. The committee concluded that the trials were suitable for decision making.

Trial results

3.6 The committee concluded that results including people without moderate to severe anaemia or people with intermediate-1 myelofibrosis should not be considered for decision making (see section 3.4). So, only evidence from people with intermediate-2 and high-risk myelofibrosis who had haemoglobin levels of less than 12 g/dL was considered. The results of the SIMPLIFY-1 trial were mixed. They showed that for the primary outcome of spleen response, momelotinib was statistically significantly non-inferior to ruxolitinib (the company considers the exact results to be confidential so they cannot be reported here). The EAG noted that the non-inferiority margin used in SIMPLIFY-1 was wider than what is usually considered acceptable in clinical practice. But it also noted that spleen response rates were similar in the momelotinib and ruxolitinib arms. The results from SIMPLIFY-1 also suggested that momelotinib was significantly superior to ruxolitinib in terms of blood transfusion independence rate. But the trial found that momelotinib was not statistically significantly non-inferior in terms of TSS (the company considers the exact results to be confidential so they cannot be reported here). The company noted that people in SIMPLIFY-1 were not stratified using TSS, so there were differences in the baseline TSS of each arm of the trial, which may have affected the results. The committee noted that TSS response was defined as 50% reduction in symptom score at week 24, which meant that the reduction in absolute TSS differed based on the baseline score. The committee raised concerns about the rate of adverse events leading to treatment discontinuation in the momelotinib arm. But the EAG noted that this was likely because of the lower number of dose reductions allowed for people in the momelotinib arm of SIMPLIFY-1 compared with the ruxolitinib arm of SIMPLIFY-1. The results from SIMPLIFY-2 showed that momelotinib was not statistically significantly superior to BAT in terms of spleen response (the company considers the exact results to be confidential so they cannot be reported here). The company stated that this may have been because of the high proportion of people who had treatment with ruxolitinib in the BAT arm (88.5%) and the lack of a washout period. It noted that few people in either arm of the trial had a spleen response at 24 weeks. The EAG considered this explanation reasonable. The results from SIMPLIFY-2 also showed that momelotinib was statistically significantly superior to BAT in terms of TSS response and rate of blood transfusion independence (the company considers the exact results to be confidential so they cannot be reported here). The committee concluded that the

results from the SIMPLIFY trials suggest that momelotinib is clinically effective at treating myelofibrosis.

Generalisability

3.7 The EAG noted that in SIMPLIFY-1 and the momelotinib arm of SIMPLIFY-2, ESAs were prohibited. It also noted that ESAs were also not commonly used in the BAT arm of SIMPLIFY-2 (5.8% of people in the BAT arm of the trial used an ESA). ESAs stimulate the bone marrow to produce red blood cells which can help reduce anaemia. The EAG commented that in NHS practice, ESAs are used to manage anaemia in people with myelofibrosis. The EAG raised concerns that ESA use may reduce the need for blood transfusions, so the rate of blood transfusion independence in the SIMPLIFY trials may not be generalisable to the NHS. The company stated that there was no clear evidence that ESA use improves clinical outcomes in people treated with ruxolitinib. The clinical experts stated that most people with myelofibrosis would not have ESAs and most who did would not become blood transfusion independent. They also noted that it was extremely difficult for people to become blood transfusion independent while having ruxolitinib even with the use of ESAs. But they did note that they would expect that a higher proportion of people in the SIMPLIFY trials would be transfusion independent if ESAs were allowed. The committee concluded that not allowing use of ESAs in the SIMPLIFY trials may have resulted in more favourable blood transfusion independence results for momelotinib.

Economic models

Company's JAK inhibitor-naive modelling approach

3.8 The company developed separate models for the JAK inhibitor-naive and JAK inhibitor-experienced populations. For the JAK inhibitor-naive population, the company developed a cost-comparison model which compared momelotinib with ruxolitinib. In the cost-comparison model, all clinical outcomes were assumed to be the same for momelotinib and ruxolitinib except for transfusion rates and adverse events. The cost-comparison model used a 10-year time horizon and it

assumed there were no deaths during the model. The company base case used data from the intention-to-treat population in SIMPLIFY-1, which included people who did not have moderate to severe anaemia and people who had intermediate-1 risk myelofibrosis (see section 3.5), to maximise the available data for the model. The EAG provided 2 subgroup analyses that only considered people with intermediate-2 and high-risk myelofibrosis: 1 analysis included people who had haemoglobin levels of less than 12 g/dL and 1 analysis included people with haemoglobin less than 10 g/dL (see section 3.4). Because of the mixed results of SIMPLIFY-1 (see section 3.6), the EAG was concerned with the suitability of a cost-comparison model. NICE's manual on health technology evaluations states that a cost-comparison analysis can be used to assess technologies that are likely to provide similar or greater health benefits at similar or lower cost than the relevant comparators. The EAG noted that in SIMPLIFY-1, the non-inferiority margin for spleen response was wide and non-inferiority was not proven for TSS (see section 3.6). It noted that this cast doubt over the suitability of a cost-comparison analysis. But it also noted that spleen response rates were similar in the momelotinib and ruxolitinib arms and that post-hoc analysis showed there was little difference between treatment arms when assessing individual symptom scores and absolute change in TSS from baseline. The EAG also noted that improvements in blood transfusion independence would compensate for lower responses in other areas. The clinical experts commented that the non-inferiority margin for spleen response in SIMPLIFY-1 was acceptable. The clinical experts highlighted that momelotinib achieved favourable results when considering all 3 key outcomes. They also noted that spleen response and transfusion independence were considered more important for future myelofibrosis outcomes, but TSS was still important for considering patient outcomes. The committee was concerned about the costs of blood transfusions in the model. The EAG commented that the unit cost for blood transfusion was similar to NHS unit costs. But the committee was still concerned that the average resource use for blood transfusions was high in the model. The committee noted the uncertain effect that not allowing ESAs had on the results of SIMPLIFY-1 (see section 3.7). It considered a scenario which removed the benefit of blood transfusion independence rate for momelotinib compared with ruxolitinib. The committee also noted the concerns with the TSS results from SIMPLIFY-1. The committee concluded that a cost-comparison analysis was suitable to assess momelotinib in the JAK inhibitor-naive population.

Company's JAK inhibitor-experienced modelling approach

3.9 For the JAK inhibitor-experienced population, the company developed a cost-utility analysis which compared momelotinib with BAT. The cost-utility model was a Markov model that included 4 health states (transfusion-independent, transfusion-requiring, transfusion-dependent, and death). The cost-utility model had a time horizon of 33 years with a cycle length of 4 weeks. The company's base case cost-utility model only included people with intermediate-2 and high-risk myelofibrosis who had haemoglobin levels of less than 12 g/dL. The EAG provided a subgroup analysis with people who had intermediate-2 and high-risk myelofibrosis who had haemoglobin levels of less than 10 g/dL (see section 3.4). The baseline distribution of people in each health state was set to be equal in both treatment arms using a pooled baseline distribution across both treatment arms from SIMPLIFY-2. People could transition between health states starting from the third cycle, using data from SIMPLIFY-2 to produce health state transition probabilities. It was assumed that after 24 weeks, there were no improvements in transfusion status. In its base case cost-utility model, the company assumed survival was related to blood transfusion requirement status at week 24 (see section 3.10). It also assumed that people who stopped treatment with momelotinib would not have further treatment with ruxolitinib (see section 3.11). The committee concluded that the structure of the cost-utility model for the JAK inhibitor-experienced population was suitable for decision making.

Link between transfusion independence and survival

3.10 The company's base case cost-utility model used transfusion independence after week 24 to determine overall survival. This meant that from week 24 in the model, people who were blood transfusion independent lived longer than people who were blood transfusion requiring or dependent. The company used results from the SIMPLIFY-2 follow-up period (see section 3.5), which showed a non-statistically significant survival benefit for people who were transfusion independent, to extrapolate the survival curves. The EAG disagreed with the company's assumption that transfusion independence would impact survival. It used a scenario that removed survival benefit based on being blood transfusion independent as its base case. The EAG highlighted the results from the pooled

COMFORT trials (which assessed the effectiveness of ruxolitinib in treating myelofibrosis). They showed that there was no difference in survival based on being blood transfusion independent. The clinical experts noted that anaemia is predictive of survival and is linked to transfusion status. They also noted that transfusion dependence is considered a risk factor in the DIPSS Plus risk scoring system. The EAG commented that treatment with a JAK inhibitor appeared to improve survival and it was unclear whether the survival benefit in SIMPLIFY-2 was from treatment with a JAK inhibitor or because of transfusion status. The committee agreed with the EAG that the survival benefit of being blood transfusion independent was unclear and concluded that it preferred the EAG's scenario of removing survival benefit for decision making.

Retreatment with ruxolitinib

3.11 In the company's base case cost-utility model, after treatment with momelotinib had stopped, people had BAT that did not include ruxolitinib. In the BAT arm of the model, 88.5% of people had treatment with ruxolitinib. The company stated that treatment with ruxolitinib after stopping momelotinib was unlikely. The EAG disagreed with the company's assumption. It noted that the assumption resulted in people in the momelotinib arm having treatment with a JAK inhibitor for a shorter time than people in the BAT arm of the model. The EAG highlighted that clinicians would like the option to treat people with ruxolitinib after treatment with momelotinib was stopped. The EAG's preferred assumption was that people who stopped momelotinib would have BAT with the same proportion of ruxolitinib use as people in the BAT arm. The clinical experts agreed with the EAG that, wherever possible, people should be treated with a JAK inhibitor. The committee agreed with the EAG and clinical experts and concluded that the most plausible assumption was that people who stop treatment with momelotinib would be treated with ruxolitinib.

Cost-effectiveness estimates

Committee's preferred cost-effectiveness estimates

3.12 For the JAK inhibitor-naive population, the company's and EAG's base case assumptions for the cost-comparison analysis were the same. But the committee recalled issues with the generalisability of the blood transfusion independence rates from SIMPLIFY-1 and uncertainty around average resource use. So, the committee considered a scenario which removed the benefit of momelotinib on blood transfusion independence (see section 3.8). Because of confidential commercial arrangements for momelotinib, ruxolitinib, and other treatments in the model, the exact cost estimates are confidential and cannot be reported here. The cost-comparison analysis showed that momelotinib has similar costs to ruxolitinib in both the haemoglobin less than 12 g/dL subgroup and the haemoglobin less than 10 g/dL subgroup.

3.13 For the JAK inhibitor-experienced population, there were 2 differences between the company's and the EAG's base cases in the cost-utility analysis:

- The company preferred the assumption that being blood transfusion independent increased survival. The EAG preferred removing this assumption (see section 3.10).
- The company preferred the assumption that after stopping treatment with momelotinib, people would not have treatment with ruxolitinib. The EAG preferred the assumption that after stopping treatment with momelotinib, people have treatment with BAT using the same proportion of ruxolitinib as the BAT arm in the model (see section 3.11).

  The committee preferred the EAG's assumptions in both cases. Because of confidential commercial arrangements for momelotinib, ruxolitinib, and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. When using the committee's preferred assumptions, the cost-effectiveness estimates were below the threshold NICE usually considers to be an acceptable use of NHS resources in both the haemoglobin less than 12 g/dL subgroup and the haemoglobin less than 10 g/dL subgroup.

Other factors

Equality

3.14 The committee considered that age over 65 is a prognostic characteristic for myelofibrosis. 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 that there were no equality issues relevant to the recommendations.

Conclusion

Recommendation

3.15 The committee concluded that for people who had not previously had treatment with a JAK inhibitor, the costs of treatment with momelotinib were similar to the costs of treatment with ruxolitinib. The committee also concluded that for people who had previously had treatment with a JAK inhibitor (ruxolitinib), the cost-effectiveness estimates were below the range that NICE considers to be an acceptable use of NHS resources. So, it recommended momelotinib as an option for treating splenomegaly or symptoms of myelofibrosis in adults with moderate to severe anaemia who have not had a JAK inhibitor or have had ruxolitinib, only if they have intermediate-2 or high-risk myelofibrosis.

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 an adult has myelofibrosis-related splenomegaly or symptoms with moderate to severe anaemia and they have not had a JAK inhibitor or have had ruxolitinib, and the doctor responsible for their care thinks that momelotinib 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 C.

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

Stephen O'Brien
Chair, technology appraisal committee C

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 and a project manager.

George Millington
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