NICE National Institute for Health and Care Excellence

NICE guidance

Ruxolitinib for treating polycythaemia vera

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

This guidance replaces TA356.

1 Recommendations

1.1 Ruxolitinib is recommended, within its marketing authorisation, for treating polycythaemia vera in adults who cannot tolerate hydroxycarbamide (also called hydroxyurea) or when the condition is resistant to it. It is only recommended if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

Standard treatment to control blood cell count (cytoreductive therapy) in polycythaemia vera is hydroxycarbamide or interferon alfa. Ruxolitinib would be used for people who cannot tolerate hydroxycarbamide or when the condition is resistant to it.

Results from clinical trials suggest that ruxolitinib is more effective than standard treatment at controlling blood cell counts and reducing spleen size. But whether it increases how long people live is uncertain.

Because of the uncertainty in the clinical-effectiveness evidence, the cost-effectiveness estimates need to be towards the lower end of the range that NICE considers an acceptable use of NHS resources. They are below this lower end, so ruxolitinib is recommended.

2 Information about ruxolitinib

Marketing authorisation indication

2.1 Ruxolitinib (Jakavi, Novartis Pharmaceuticals) is indicated for 'the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea [hydroxycarbamide]'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for ruxolitinib.

Price

2.3 The list prices of ruxolitinib for 56-capsule packs are £1,428 (5 mg), £2,856 (10 mg), £2,856 (15 mg) and £2,856 (20 mg; all prices excluding VAT; BNF online accessed May 2023).

2.4 The company has a commercial arrangement. This makes ruxolitinib 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 Novartis Pharmaceuticals, 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

Polycythaemia vera

3.1 Polycythaemia vera is a bone marrow condition that leads to an increase in the number of cells in the blood. It mostly affects the number of red blood cells. As more red blood cells are made, the blood becomes thicker. This can lead to complications such as gout, bleeding problems and blood clots. These clots can cause strokes, heart attacks, or blockage of an artery in the lungs (pulmonary embolism) or in a vein deep in a muscle (deep vein thrombosis). There can also be severe itching, the cause of which is unknown. Polycythaemia vera can also cause an increase in white blood cells. In some cases, the extra white blood cells collect in the spleen, which may then become enlarged (splenomegaly). In addition, polycythaemia vera can lead to other problems such as scarring of the bone marrow (myelofibrosis) and acute myeloid leukaemia. The clinical experts noted that ruxolitinib is already in widespread use for treating myelofibrosis. Ruxolitinib is recommended in NICE's technology appraisal guidance on ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis. The patient experts highlighted that polycythaemia vera is a debilitating illness that significantly affects people living with the condition, and their families and carers. They said that the symptoms that affect people the most are severe fatigue, bone pain, itching and having an enlarged spleen. They also noted how highly disruptive frequent venesections are (when blood is removed from a person to reduce excess red blood cells). The patient experts also highlighted the extra psychological burden of being diagnosed with a rare condition. People with polycythaemia vera explained how the condition can worsen very quickly because they can be feeling good, but the next day be in considerable pain and have to

rest. They emphasised the significant disruption this has on their lives, and on families and carers. The patient experts also noted how 25% of people surveyed by MPN Voice and Leukaemia Care reported stopping first-line treatments because of side effects or declining treatment effectiveness. People with polycythaemia vera also explained how current treatment options can fail to have the desired effect and result in significant side effects. The clinical experts identified that current treatment options carry a high risk of developing leukaemia, which can be fatal within 3 to 6 months. They noted that, in people who cannot tolerate hydroxycarbamide or when their condition is resistant to it, there are few options other than busulfan. With busulfan treatment, there is a 20% risk of developing leukaemia. The clinical experts highlighted the unmet need for a treatment option that reduces symptoms and improves quality of life compared with current treatments. The committee concluded that polycythaemia vera is a debilitating condition. It also concluded that there is high unmet need for effective treatments that improve survival and quality of life, and have manageable side effects.

Clinical management

Treatment pathway

3.2 The clinical and patient experts, and the company, identified the British Society for Haematology 2018 guidelines on treating polycythaemia vera as the most appropriate for the NHS. The guidelines recommend venesection and low-dose aspirin for everyone with polycythaemia vera. Cytoreductive therapy is recommended for people who are at high risk (65 years and over or with a history of thrombosis), have an uncontrolled haematocrit (percentage of red blood cells in the blood) or whose tolerability of venesections is poor. First-line cytoreductive therapy is hydroxycarbamide or interferon alfa. Second-line cytoreductive therapy is interferon alfa if hydroxycarbamide is used first line, or hydroxycarbamide if interferon alfa is used first line. Third-line cytoreductive therapies include anagrelide plus hydroxycarbamide, busulfan and radioactive phosphorous. Pipobroman is recommended by the British Society for Haematology for people with a limited life expectancy, but was not included in the NICE scope for this evaluation.

The company explained that the clinical experts it consulted said that radioactive phosphorus is rarely used, so it was not included in the company's submission. The comparator presented in the company's submission was called 'best available therapy'. It included hydroxycarbamide, interferon alfa, anagrelide and busulfan, with the use of each weighted by use in the MAJIC-PV clinical trial (see section 3.6). The EAG noted that the clinical experts it consulted agreed with the exclusion of radioactive phosphorous, and highlighted the limited use (if at all) of anagrelide and busulfan. The clinical experts also explained during the committee meeting that anagrelide, busulfan, radioactive phosphorous and pibobroman are very rarely used in clinical practice. They explained that this is because they are not licensed for, and have not been shown to be effective for, treating polycythaemia vera. The EAG commented that the company's definition of best available therapy was appropriate, and that hydroxycarbamide and interferon alfa were the most used treatments. The committee concluded that hydroxycarbamide and interferon alfa were the most relevant treatment options for polycythaemia vera, and that the company had appropriately defined best available therapy.

Treatment positioning of ruxolitinib

3.3 The committee recalled the wording of the marketing authorisation for ruxolitinib. It noted that ruxolitinib is indicated for people with polycythaemia vera when there is resistance or intolerance to hydroxycarbamide. The company explained that this meant ruxolitinib would be used as second- or third-line cytoreductive therapy. It added that this would depend on which line hydroxycarbamide was used and whether there was resistance or intolerance to it (see section 3.2). The clinical experts highlighted that ruxolitinib does not have to be used immediately after hydroxycarbamide. They said that this is because ruxolitinib eligibility can be based on previous intolerance to hydroxycarbamide. They noted that the availability of ruxolitinib would give people another treatment option besides interferon alfa when there is resistance or intolerance to hydroxycarbamide. They explained that interferon alfa can exacerbate some of the symptoms of polycythaemia vera, such as itching. The patient experts described their experience of treatment with ruxolitinib. They noted that they had significant

improvements in their condition and reduced side effects compared with hydroxycarbamide and interferon alfa. The patient and clinical experts highlighted that ruxolitinib can lead to improved control of blood cell counts and improve symptoms. For example, it can reduce fatigue, spleen size, pain and itchy skin. The clinical experts noted that there are potential risks with ruxolitinib, such as infections, skin cancer, weight gain, raised blood pressure and high cholesterol levels. But they noted that these side effects can be mitigated against. The committee concluded that the company's proposed positioning of ruxolitinib in the treatment pathway was appropriate. It concluded that best available therapy, as defined in the company's submission (see section 3.2), was an appropriate comparator at this point in the pathway.

Clinical effectiveness

RESPONSE and RESPONSE-2 trials

3.4 The main clinical evidence provided by the company for ruxolitinib was from the phase 3 RESPONSE and RESPONSE-2 trials. Both were multicentre open-label randomised trials funded by the company. They compared ruxolitinib with best available therapy and both trials lasted 5 years. Crossover from the best available therapy arm to the ruxolitinib arm was allowed (see section 3.5). Both trials included adults with polycythaemia vera who could not tolerate hydroxycarbamide or when the condition was resistant to it. RESPONSE included people with splenomegaly and RESPONSE-2 included people without splenomegaly. Everyone in the trials had to have an Eastern Cooperative Oncology Group performance status of 0, 1 or 2. RESPONSE recruited 222 people from 18 countries including 3 UK sites. RESPONSE-2 recruited 149 people from 12 countries not including the UK. The median age of people was about 61 years in RESPONSE and about 65 years in RESPONSE-2. The median time since diagnosis was about 8.8 years in RESPONSE and about 6.6 years in RESPONSE-2. The primary outcome of RESPONSE was primary response (controlled volume of red blood cells in the blood and a more than 35% reduction in spleen volume) at 32 weeks. This was statistically significantly improved for ruxolitinib compared with best available therapy (22.7% compared with 0.9%; $p<0.001$). The

primary outcome of RESPONSE-2 was controlled volume of red blood cells in the blood at 28 weeks. This was statistically significantly improved for ruxolitinib compared with best available therapy (62.2% compared with 18.7%; p<0.0001). Overall survival for ruxolitinib at 5 years was 92% in RESPONSE and 96% in RESPONSE-2. Overall survival for best available therapy was not reported because crossover confounded results (see section 3.5). The committee concluded that RESPONSE and RESPONSE-2 show clinical advantages with ruxolitinib over best available therapy in controlling the volume of red blood cells in the blood and reducing spleen volume.

Crossover in RESPONSE and RESPONSE-2

3.5 Crossover was permitted in RESPONSE at 32 weeks and RESPONSE-2 at 28 weeks. Crossover from best available therapy to ruxolitinib was 88% in RESPONSE and 77% in RESPONSE-2. The company acknowledged the limitations of crossover in RESPONSE and RESPONSE-2. It explained that adjusting for crossover was not feasible because of the low number of deaths in RESPONSE and RESPONSE-2. So, it developed an indirect treatment comparison from overall survival data from RESPONSE for ruxolitinib and from real-world GEMFIN registry data for best available therapy. Propensity score matching was done using individual patient level data from the respective sources. RESPONSE-2 data was not included because of considerable overlap with RESPONSE in the number of people in GEMFIN that could be matched. Using a combined population with RESPONSE and RESPONSE-2 would have resulted in a poor fit when estimating propensity scores for matching because these people could not be double counted. The indirect treatment comparison was not used to inform the company's base case. The overall survival results are academic in confidence so cannot be reported here. But the company noted that they showed statistically significantly improved survival for ruxolitinib compared with best available therapy. The company did identify limitations associated with the results because of:

- limited generalisability of the GEMFIN registry because of uncertainty about whether the Spanish population and treatments used reflect NHS clinical practice

- shorter follow-up time in GEMFIN than in RESPONSE
- the lack of inclusion of RESPONSE-2 data
- matching only being feasible for a limited number of covariates.

The EAG agreed with the limitations of the indirect treatment comparison and emphasised its limited scope because of only using RESPONSE data. It suggested that MAJIC-PV (see section 3.6) provided the best source of unconfounded evidence. The committee noted the efforts of the company to explore the effect of crossover on overall survival data in RESPONSE and RESPONSE-2. It concluded that overall survival data from the 2 trials was not suitable for decision making because of being confounded. It also concluded that the indirect treatment comparison was informative. But it did not think that it was sufficient to be used in cost-effectiveness modelling as a source for overall survival data. This was because of the limitations described by the company and because it only included RESPONSE data. The committee also agreed with the EAG that the best source of unconfounded evidence for overall survival was from MAJIC-PV (see section 3.6).

MAJIC-PV trial

3.6 Additional clinical evidence for ruxolitinib was from the phase 2 MAJIC-PV trial. This was a multicentre open-label randomised trial funded by Blood Cancer UK, with an unrestricted funding grant from the company. It investigated ruxolitinib compared with best available therapy over 5 years. MAJIC-PV was a UK only trial, recruiting 190 people from 38 sites. Crossover was not specified in the trial protocol for MAJIC-PV, but the clinical experts noted that 10 people did crossover to ruxolitinib. MAJIC-PV recruited adults with high-risk polycythaemia vera who were intolerant of hydroxycarbamide or in whom the condition was resistant to it. High risk was defined as meeting at least 1 of these criteria:

- being 60 years or over
- previously having documented thrombosis deemed to be secondary to polycythaemia vera
- having significant or symptomatic splenomegaly

- having a platelet count of more than 1,000x10^9/litre
- having diabetes or hypertension needing pharmacological therapy for longer than 6 months.

The median age of people was 66 years and the median time since diagnosis was 7.6 years. The primary outcome in MAJIC-PV was complete haematological remission in year 1. This was statistically significantly improved with ruxolitinib compared with best available therapy (43% compared with 26%; p=0.02). The committee noted that the choice of a 90% level of confidence for the primary outcome was not typical. It added that a 95% level of confidence was used in RESPONSE and RESPONSE-2. There was no statistically significant difference in overall survival for ruxolitinib compared with best available therapy (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.36 to 1.50). The committee noted that the confidence interval for overall survival was very wide. It also noted that, because the confidence interval crossed 1, it was not known whether ruxolitinib improves or worsens survival. There was also no statistically significant difference in progression-free survival (84% for ruxolitinib compared with 75% for best available therapy; HR 0.64, 95% CI 0.36 to 1.15, p=0.13). The clinical experts noted that ruxolitinib statistically significantly improved event-free survival compared with best available therapy (HR 0.58, p=0.03). Event-free survival was defined as time to first occurrence of major thrombosis, haemorrhage, disease transformation or death. The committee noted that the mean dose of ruxolitinib in MAJIC-PV was 10 mg twice daily, with dose intensity increasing over time. The clinical experts noted that some people will have an increased dose for better control of their blood counts. They were unsure why dose intensity increased over time in MAJIC-PV, but considered that this was likely because the number of people in the trial reduced over time. The committee concluded that MAJIC-PV showed clinical advantages with ruxolitinib over best available therapy in inducing haematological remission and improving event-free survival.

Effect of ruxolitinib on overall survival

3.7 The committee considered whether ruxolitinib improved overall survival compared with best available therapy. It noted that none of the 3 clinical trials showed an overall survival benefit with ruxolitinib compared with best available therapy. This was because of confounded data in

RESPONSE and RESPONSE-2 (see section 3.4 and section 3.5) and lack of statistical significance in MAJIC-PV (section 3.6). The committee noted the small number of deaths in the clinical trials over their 5-year follow-up durations:

- RESPONSE: 9 deaths in 112 people having best available therapy and 10 deaths in 110 people having ruxolitinib
- RESPONSE-2: 6 deaths in 75 people having best available therapy and 3 deaths in 74 people having ruxolitinib
- MAJIC-PV: 17 deaths in 87 people having best available therapy and 15 deaths in 93 people having ruxolitinib.

It considered that the small number of events causes considerable uncertainty in the estimated hazard ratios for overall survival. The clinical experts explained that the primary benefit of ruxolitinib was to improve quality of life for people with polycythaemia vera. They highlighted that ruxolitinib showed statistically significant improved event-free survival compared with best available therapy in MAJIC-PV (see section 3.6). They explained that this means people treated with ruxolitinib have fewer events that are known to be associated with increased risk of death, such as major thromboembolic events. The clinical experts considered that it was plausible that this would lead to improved overall survival. The committee concluded that it was plausible that ruxolitinib may improve overall survival compared with best available therapy, but that this and the size of any effect was uncertain.

Generalisability

3.8 The committee considered the generalisability of RESPONSE, RESPONSE-2 and MAJIC-PV to NHS clinical practice. MAJIC-PV only included people from the UK. RESPONSE included people from 3 UK sites and RESPONSE-2 did not include anyone from the UK. The EAG highlighted that the clinical experts it consulted agreed that all 3 trial populations were reflective of NHS clinical practice. But it considered that MAJIC-PV was most generalisable to the NHS because of the age of those included (see section 3.4 and section 3.6). It also noted a concern expressed by the clinical experts that the definition of hydroxycarbamide intolerance in all 3 trials may not have reflected that used in NHS clinical

practice. This was because there is no standard definition. The EAG also highlighted uncertainty on how much the MAJIC-PV population represented a high-risk subgroup. This was because baseline characteristics seemed similar to the other trials, but mortality was substantially higher. The company considered that all 3 trial populations represented people who would benefit from ruxolitinib and were relevant to decision making. The clinical experts thought that all 3 trials were relevant to NHS clinical practice. One clinical expert expressed a preference for MAJIC-PV because of the very specific entry criteria and crossover present in RESPONSE and RESPONSE-2 (see section 3.4, section 3.5 and section 3.6). The clinical experts explained that this specific entry criteria likely meant people recruited to RESPONSE and RESPONSE-2 were generally fitter than people in MAJIC-PV and in the NHS. The clinical experts noted that most people they saw in NHS clinical practice would have been eligible for MAJIC-PV. They also considered that most people in RESPONSE and RESPONSE-2 would have been eligible for MAJIC-PV. The committee noted that MAJIC-PV was considered to enrol a broader range of people than RESPONSE and RESPONSE-2. So, it considered that evidence from MAJIC-PV was likely to be most appropriate for assessing the use of ruxolitinib within its marketing authorisation, rather than just within a high-risk subgroup. It also considered that the population recruited in MAJIC-PV best represented the polycythaemia vera population in NHS clinical practice, compared with RESPONSE and RESPONSE-2. The committee also recalled its previous conclusion that MAJIC-PV was the best source of unconfounded evidence because it had limited treatment arm crossover (see section 3.6). So, it concluded that MAJIC-PV was the most appropriate source of clinical-effectiveness evidence for its decision making.

Effect of splenomegaly on treatment choice

3.9 RESPONSE included people with splenomegaly whereas RESPONSE-2 included people without splenomegaly. The company's base-case economic model included separate cost-effectiveness estimates for people with and without splenomegaly (see section 3.10). The clinical experts explained that treatments offered do not vary by whether or not splenomegaly is present. But they said that identifying splenomegaly

helps clinicians adopt more targeted disease monitoring. This is because splenomegaly may increase the chance of the condition being resistant to hydroxycarbamide or people being intolerant of it. Also, it may indicate that the condition is transforming into myelofibrosis. The clinical experts added that the presence of splenomegaly is not routinely checked or measured in clinical practice. Instead, splenomegaly investigations are prompted by people reporting symptoms, but the effect on quality of life can vary significantly. The clinical experts explained that, for some people, splenomegaly means difficulty in eating, which leads to weight loss, but others have very few symptoms. One clinical expert also highlighted that subgroup results from MAJIC-PV showed no evidence of a differential benefit for ruxolitinib in people with and without splenomegaly. The committee concluded that the presence of splenomegaly was not a treatment- or outcome-altering factor, so was not a subgroup-defining characteristic for decision making.

Economic model

Original model based on RESPONSE and RESPONSE-2 data

3.10 The company initially developed a state-transition model to model the cost effectiveness of ruxolitinib compared with best available therapy. In its base case, the company presented cost-effectiveness results separately for people with and without splenomegaly. The baseline characteristics of people in the model were aligned with RESPONSE and RESPONSE-2. The time to treatment discontinuation and overall survival in the ruxolitinib arm for each population was informed by individual patient data from RESPONSE and RESPONSE-2 (section 3.4, section 3.5). The time to treatment discontinuation and overall survival in the best available therapy arm for each population was informed by data from MAJIC-PV (see section 3.6). The company also developed a separate model based on MAJIC-PV data for the high-risk subgroup (see section 3.11). In the RESPONSE and RESPONSE-2 model, people were modelled to enter and have treatment in either a 'ruxolitinib' or 'best available therapy' state. People in the 'ruxolitinib' state could move to the 'best available therapy' state or 'death'. People in the 'best available therapy' state could move only to 'death'. In the 'best available therapy'

state, people were also separated by treatment line (first, second and beyond, or no treatment). For each treatment state, the model captured:

- treatment-related adverse events
- key complications including thromboembolic events, bleeding or haemorrhage, progression to myelofibrosis and cancer
- venesections
- health-related quality of life
- resource use.

The EAG noted the company's model was appropriate and developed with suitable methods but expressed concern with the company's model structure. It outlined that a model based on disease stages rather than treatment stages would incorporate progression outcomes that are more prognostic of long-term survival than treatments. The committee concluded that the company's RESPONSE and RESPONSE-2 model was developed appropriately but shared the EAG's concerns about a model structure based on treatment rather than disease stages.

Original model based on MAJIC-PV data

3.11 The company also developed a partitioned survival model for the MAJIC-PV high-risk subgroup population. A partitioned survival model was used because of the lack of individual patient data that is needed to estimate transition probabilities for a state-transition model. The MAJIC-PV model used the same model structure and modelled treatment stages as the RESPONSE and RESPONSE-2 model (see section 3.10). The EAG preferred the MAJIC-PV model, based on generalisability to the NHS (see section 3.8). But it noted the same concerns with the treatment stage-based model structure as for the RESPONSE and RESPONSE-2 model (see section 3.10). The committee recalled that it considered that MAJIC-PV data was the most appropriate source of unconfounded clinical-effectiveness evidence for assessing the cost effectiveness of ruxolitinib for polycythaemia vera (see section 3.8). It concluded that the company's MAJIC-PV model was also developed appropriately but

subject to the same model structure concerns as with the RESPONSE and RESPONSE-2 model.

Progression-based model structure

3.12 During technical engagement, the company developed an updated model structure based on stages of disease progression. In the updated model structure, people entered the model in 'progression-free on ruxolitinib' or 'progression-free on best available therapy' health states. People in the 'progression-free on ruxolitinib' health state could then move to 'progression-free on best available therapy', 'progressed disease' or 'death' health states. People in the 'progression-free on best available therapy' health state could then move to 'progressed disease' or 'death' health states. The progressed disease state was further divided into:

- low- or intermediate 1-risk myelofibrosis
- intermediate 2- or high-risk myelofibrosis

- acute myeloid leukaemia or myelodysplastic syndrome.

At the first committee meeting, the company did not use the progression-based model in its base case. This was because that model relied on more assumptions and was associated with more uncertainty than the original model structure. It noted that the cost-effectiveness results of the progression-based model were more favourable to ruxolitinib than the original model structure, so suggested that the original model structure was conservative. The EAG noted that the progression-based model used progression-free survival, with overall survival modelled as a surrogate for disease progression or transformation (see section 3.15). This was to capture the prognostic value of progression on survival. The company stated that it was not possible to construct a model based on event-free survival. This was because of the lack of information in the MAJIC-PV published data on the number of event-free survival events and lack of individual patient data. The EAG preferred the progression-based model structure in principle because it modelled progression directly. But it did not use this model structure in its base case for the first committee meeting because it did not have sufficient opportunity to review and validate the model inputs. The clinical experts highlighted that they would prefer a model based on clinical events, so favoured the updated model structure. But they also noted that treatment changes usually follow changes in clinical events anyway. The committee noted that, typically, it is more appropriate to model overall survival directly but also noted the absence of robust overall survival data for ruxolitinib. So, it agreed that it was more appropriate to model survival indirectly based on the expected effect of progression and other clinical events on survival. The committee concluded that it preferred the company's updated progression-based model structure. It requested inputs and assumptions to be validated (see section 3.13) and requested validation of the model outputs (see section 3.14). It preferred the progression-based model because it captured the prognostic value of preventing progression on survival, rather than modelling overall survival directly (see section 3.15).

Inputs and assumptions for progression-based model structure

3.13 For the second committee meeting, the company provided an updated progression-based model based on MAJIC-PV data. This included the committee's preferred assumptions at the first committee meeting (see section 3.18). The company also provided:

- full probabilistic results for the updated progression-based model
- independent clinical assessment of the progression-based model at a virtual advisory board (see section 3.13)
- validation of the model results for the relative effects on overall survival compared to MAJIC-PV results and longer-term, real-world GEMFIN registry data (see section 3.14).

Before the second committee meeting, the EAG also did a review of the inputs and assumptions of the progression-based model. Progression in the model was based on progression-free survival in MAJIC-PV because it was not possible to develop a model based on event-free survival (see section 3.12). Progression-free survival was defined as transformation to myelofibrosis, myelodysplastic syndrome, acute myeloid leukaemia or death from any cause. Event-free survival was defined as major thrombosis and major haemorrhage events, and transformation or death from any cause. The EAG noted that this meant that the model may not have fully captured the effect on survival of thromboses and bleeds. So, it could have underestimated the benefit of ruxolitinib. In the model, time spent in progression-free health states was determined by:

- preprogression survival, which is defined as the mortality before transformation
- myelofibrosis-free survival, which is defined as the time from baseline to fibrotic transformation to myelofibrosis

- leukaemia-free survival, which is defined as the time from baseline to transformation to acute myeloid leukaemia or myelodysplastic syndrome.

The EAG noted that there was some uncertainty about the most appropriate extrapolation curves for preprogression survival, myelofibrosis-free survival and leukaemia-free survival. But it considered that the visual fit of the company's preferred Weibull distributions seemed reasonable. To estimate leukaemia-free survival for best available therapy, the company used a 5-year estimate of myelofibrosis and acute myeloid leukaemia from Alvarez-Larran et al. (2022). This was because clinical experts consulted by the company considered that the MAJIC-PV estimate was lower than would be expected in clinical practice. The EAG noted that using the lower probability of acute myeloid leukaemia estimated from MAJIC-PV resulted in a more favourable leukaemia-free survival curve for best available therapy. The company modelled time to treatment discontinuation using a hazard ratio for treatment discontinuation compared with progression-free survival, estimated from MAJIC-PV. The EAG agreed with this approach, and noted that the uncertainty about the hazard ratio was captured in the probabilistic sensitivity analysis. The postprogression survival extrapolations were based on external sources from the literature. The EAG considered that the company did not provide clear justification for some of the external sources. The company set up a virtual advisory board with 10 clinical experts, 5 of whom were not previously consulted by the company. These clinical experts concluded that the inputs and assumptions within the model were reasonable. The EAG considered the clinical experts were likely representative of those who manage polycythaemia vera in the NHS. But the EAG noted that the company did not disclose how many experts agreed or disagreed with each of the issues discussed. So, the EAG concluded that this external clinical validation exercise done by the company did not reduce the uncertainty around validity and plausibility of the model inputs. The committee noted the concerns raised by the EAG about the model inputs and assumptions. Overall, the committee concluded that the model structure, inputs and assumptions were appropriate for decision making.

Validation of the outputs of the progression-based model

3.14 At the first committee meeting, the committee also requested validation of the model results for the relative effects on overall survival compared with MAJIC-PV results and longer-term registry data. The company

provided a comparison of the model predictions using the progression-based model against MAJIC-PV results. The company stated that the predictions for progression-free survival and overall survival were generally aligned with observed data from MAJIC-PV at 5 years. This was despite the assumptions and the use of external data in the model. The EAG commented that overall survival and progression-free survival predictions had reasonable fit to the trial results, given the variation in the Kaplan–Meier curves. The EAG also noted that MAJIC-PV was not powered for the progression-free survival and overall survival outcomes. It added that the number of deaths and incidence of myelofibrosis, acute myeloid leukaemia and myelodysplastic syndrome were low. The company also presented validation of the predicted overall survival for best available therapy against longer-term registry data. The company did targeted searches to identify studies reporting survival in people with polycythaemia vera that is resistant or intolerant to hydroxycarbamide. They identified 2 studies that were relevant, both of which reported results from the GEMFIN cohort. The company selected the larger cohort with longer follow-up for validation. The study included 272 people with polycythaemia vera resistant or intolerant to hydroxycarbamide treated with best available therapy. The company presented the model predictions for overall survival in the best available therapy arm alongside survival for best available therapy reported in MAJIC-PV and in the GEMFIN cohort. The company considered that survival reported in the GEMFIN cohort was broadly aligned with the best available therapy arm of MAJIC-PV and the model predictions. The committee noted that the company had not provided fit statistics for the data from the GEMFIN cohort compared with the model predictions. The company explained that this was because the model was not fitted to the data from the GEMFIN cohort, and this curve was presented for visual comparison only. The EAG had some concerns with the targeted searches done but noted the clinical experts did not identify any additional studies. So, the EAG thought it was likely that all relevant studies had been identified. The committee considered that the overall survival predictions from the progression-based model were broadly aligned with the MAJIC-PV and GEMFIN registry data.

Long-term treatment effect on overall survival in the progression-based model structure

3.15 The committee preferred the company's updated progression-based model structure. This was because it captured the prognostic value of preventing progression on survival, rather than modelling overall survival directly (see section 3.12). The committee noted that the clinical trials did not show a statistically significant overall survival benefit with ruxolitinib compared with best available therapy. But it noted that ruxolitinib did statistically significantly improve event-free survival compared with best available therapy in MAJIC-PV (see section 3.7). It also noted that it was plausible that ruxolitinib may improve overall survival by:

- reducing the occurrence of events that are associated with an increased risk of death and
- delaying disease progression.

In the base case of the progression-based model, time spent in the progression-free survival health states was determined by preprogression survival, myelofibrosis-free survival and leukaemia-free survival (see section 3.12). At the second committee meeting, the company presented 2 additional scenario analyses, which varied the size of treatment effect for overall survival:

- A 'conservative scenario': in this scenario, ruxolitinib only affected deaths due to reduced myelofibrosis (via myelofibrosis-free survival) and acute myeloid leukaemia or myelodysplastic syndrome (via leukaemia-free survival). There was no treatment effect of ruxolitinib on preprogression survival.

- A second scenario: in this scenario, ruxolitinib affected deaths due to reduced myelofibrosis and acute myeloid leukaemia or myelodysplastic syndrome and a reduction in other deaths (via preprogression survival), but not as much compared with the company and EAG base case. This was implemented by applying a hazard ratio to the preprogression survival curve for the best available therapy arm.

  During the company's clinical validation exercise, some experts found it difficult to comment on model predictions for long-term survival. This was because of the limited follow-up data in MAJIC-PV trial and absence of long-term data. The EAG used the same assumptions as the company in their base case. It considered that the conservative scenario provided a reasonable bound on uncertainty over the treatment effect of ruxolitinib on overall survival. The company emphasised how challenging it was to show a survival gain in polycythaemia vera. This was because of the relatively low risk of death in polycythaemia vera, and low number of deaths in trials, which reduced statistical power. At consultation, the patient group MPN Voice noted that, because polycythaemia vera is rare, it is not possible to do clinical trials that are large enough to assess overall survival. The committee noted that mortality in polycythaemia vera is relatively low, which makes it challenging to assess whether there is a survival benefit for ruxolitinib. The committee considered the extent to which the company's model accurately predicted long-term treatment effects, specifically an estimated survival gain. It recalled the small number of deaths in the clinical trials and the very similar mortality rate across treatment arms (see section 3.7). It also noted that the overall survival predictions from the company and EAG base were broadly aligned with the MAJIC-PV and GEMFIN registry data (see section 3.14). The committee considered that there was still substantial uncertainty about the long-term treatment effect on overall survival. So, it was unable to choose 1 preferred cost-effectiveness estimate. The committee preferred a range of cost-effectiveness estimates between the company's (and EAG's) base case, and the 'conservative' overall survival treatment effect scenario provided by the company.

Long-term treatment effect on overall survival in the original model structure

3.16 Overall survival for ruxolitinib in the MAJIC-PV model with the original

model structure was estimated by applying the overall survival hazard ratio for ruxolitinib compared with best available therapy from the MAJIC-PV trial to the estimated overall survival for best available therapy from MAJIC-PV. This was because of the lack of individual patient data for MAJIC-PV (see section 3.11). At the second committee meeting, the company provided a scenario analysis that assumed there was no difference in overall survival between best available therapy and ruxolitinib using the original model structure. This was done by setting the hazard ratio for overall survival to 1. Although the committee preferred the progression-based model structure (see section 3.12), it considered that this scenario provided a reasonable bound to uncertainty.

Utility values

Source of utility values

3.17 The NICE reference case stipulates that EQ-5D utility values should be used in company submissions unless there is empirical evidence to deviate from this measure. Data for the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) measures were collected in RESPONSE. Data for EQ-5D-5L and MPN-SAF measures were collected in RESPONSE-2 and MAJIC-PV. The EQ-5D and EORTC measures are generic measures of quality of life, whereas MPN-SAF is a disease-specific measure for myeloproliferative neoplasms. The company used Myelofibrosis 8 dimensions (MF-8D; a myelofibrosis disease-specific measure) utility values in its economic model. It did this by incorporating 3 items from EORTC QLQ-30 and 5 items from MPN-SAF data from the RESPONSE trial in its base case. Only RESPONSE data was used because it was the only trial to collect EORTC QLQ-30 data. The company explained the decision based on this evidence from RESPONSE-2:

- EQ-5D has a ceiling effect. This limited the maximum score that could be recorded because a higher percentage of people reported no problems in all 5 EQ-5D measures at baseline compared with items from MPN-SAF.

- EQ-5D lacks construct validity (or how accurate it can assess its intended measure) because convergence was inconsistent across MPN-SAF domains at baseline.
- EQ-5D lacks responsiveness because medium to large changes in scores for MPN-SAF were small to very small for EQ-5D.

The company also noted that NICE's technology appraisal guidance on ruxolitinib and on fedratinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis accepted the use of MF-8D over EQ-5D. The company highlighted that the symptoms of polycythaemia vera and myelofibrosis are very similar. The EAG considered that the company did not provide sufficient evidence to reject the use of EQ-5D and used it in its base case. It noted that there was a strong correlation between EQ-5D and MPN-SAF total symptom score. This suggested that, even if some polycythaemia vera symptoms are not explicitly included in the EQ-5D descriptive system, the symptoms may still be reflected in one or more of the EQ-5D dimensions. The EAG also noted that the estimated utility differences in the treatment arms of the clinical trials were similar whether EQ-5D or MF-8D measures were used. The clinical and patient experts explained that symptom improvements for people with polycythaemia vera are highly underestimated in EQ-5D measures. This is because key symptoms such as itching and fatigue are not well captured. This is because, in this context, itching is severe and highly debilitating. They added that EQ-5D is not validated in polycythaemia vera and MF-8D best reflects the lived experience of people with the condition. The EAG noted that itching should be captured within EQ-5D measures because it captures pain. But it suggested that there was uncertainty in how well it captures fatigue. The committee acknowledged the substantial burden on quality of life of polycythaemia vera, including the substantial burden of symptoms such as itching and fatigue. It recalled that the EAG explained about the strong correlation between EQ-5D and MF-8D scores. This suggested that the effect of symptoms on quality of life should still have been reflected in EQ-5D scores and overall utility. The committee concluded that EQ-5D was the most appropriate utility measure to use in the economic model, but that MF-8D should be used in scenario analyses.

Cost-effectiveness estimates

Committee's preferred assumptions

3.18 At the second committee meeting, the company's base case and the EAG's base case were the same. They were also aligned with the committee's preferred assumptions at the first committee meeting and included that:

- best available therapy as defined in the company's submission was an appropriate comparator (see section 3.3)
- MAJIC-PV was the most appropriate trial for decision making for the full marketing authorisation (see section 3.8)
- the updated progression-based model structure was appropriate for decision making (see section 3.12)
- EQ-5D was the most appropriate utility measure (see section 3.17).

The committee also considered that there remained substantial uncertainty about the long-term treatment effect on overall survival. So, the committee considered that it was unable to choose a single preferred assumption for treatment effect on overall survival. Instead, the committee's preferred cost-effectiveness estimates ranged between the company's (and EAG's) base case and the 'conservative' scenario provided by the company (see section 3.15).

Uncertainty in the cost-effectiveness estimates

3.19 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjust life year (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. After the first committee meeting, the committee considered that there was substantial uncertainty in the cost-effectiveness estimates generated using its

preferred assumptions because of uncertainty in the:

- size of the overall survival treatment effect estimated for ruxolitinib compared with best available therapy (see section 3.15)
- updated model structure because the EAG had not had chance to fully review the model inputs and assumptions, and the outcomes had not been validated (see section 3.13).

At the second committee, the company provided:

- scenario analyses results presenting more conservative assumptions for survival gain, including an overall survival hazard ratio equal to 1 in the original model structure (see section 3.16)
- probabilistic results for the updated progression-based model with committee preferred assumptions (see section 3.13)
- full independent clinical assessment of the progression-based model at a virtual advisory board (see section 3.13)
- validation of the model results for the relative effects on overall survival compared to MAJIC-PV results and longer-term, real-world GEMFIN registry data (see section 3.14).

The committee considered that there remained substantial uncertainty about the size of the overall survival treatment effect estimated for ruxolitinib compared with best available therapy (see section 3.15). It also thought that the uncertainty remained in the modelling approach done by the company (see section 3.12). The patient group MPN Voice noted that, because of the rarity of polycythaemia vera, it can be challenging to do large clinical trials in this disease area, which contributes to uncertainty about the overall survival benefit. The committee considered that the uncertainty in the survival benefit was mostly because of the relatively low mortality in polycythaemia vera. Taking these factors into account, the committee concluded that an ICER of around £20,000 per QALY gained would be considered a cost-effective use of NHS resources.

Company and EAG cost-effectiveness estimates

3.20 The cost-effectiveness results included confidential prices for ruxolitinib and other treatments. So, the exact results cannot be reported here. The company's and EAG's base-case ICER for ruxolitinib against best available therapy was below £20,000 per QALY gained. In the 'conservative scenario', in which ruxolitinib only affected deaths due to a reduction in myelofibrosis and acute myeloid leukaemia or myelodysplastic syndrome, the ICER was also below £20,000 per QALY gained. The original model structure, in which the overall survival hazard ratio was equal to 1, was not the committee's preferred modelling approach. But it noted that the scenario using the original model structure was also within the range of what NICE considers to be a cost-effective use of NHS resources. The committee considered the uncertainty and the range of the cost-effectiveness estimates. It agreed that the most plausible ICERs were below £20,000 per QALY gained, so considered that ruxolitinib represented a cost-effective use of NHS resources.

Other factors

Equality

3.21 The committee did not identify any equality issues.

Conclusion

Recommendation

3.22 The committee recalled the substantial uncertainty associated with the long-term treatment effect of ruxolitinib on overall survival (see section 3.15). But it agreed that the most likely cost-effectiveness estimates for ruxolitinib were within what NICE considers a cost-effective use of NHS resources. So, ruxolitinib is recommended for treating polycythaemia vera in adults who cannot tolerate hydroxycarbamide or when the condition is resistant to it.

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 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.

4.3 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 polycythaemia vera and the doctor responsible for their care thinks that ruxolitinib 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 D.

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

Dr Stephen Smith
Vice chair, technology appraisal committee D

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.

Owen Swales and Alice Pritchard
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Accreditation