

## ruxolitinib phosphate 5mg, 10mg, 15mg, 20mg tablets (Jakavi®)

Novartis Pharmaceuticals UK Ltd

8 November 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE:** following a full submission assessed under the orphan equivalent process **ruxolitinib phosphate (Jakavi®)** is accepted for use within NHSScotland.

**Indication under review:** The treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea (hydroxycarbamide).

Ruxolitinib was superior to best available therapy in two phase III studies in patients with polycythaemia vera who were resistant to or intolerant of hydroxycarbamide, with or without splenomegaly.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

**Chairman**  
**Scottish Medicines Consortium**

## Indication

The treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea (hydroxycarbamide).<sup>1</sup>

## Dosing Information

The recommended starting dose of ruxolitinib for polycythaemia vera is 10mg orally twice daily.

Doses may be titrated based on safety and efficacy. If efficacy is considered insufficient and blood counts are adequate, doses may be increased by a maximum of 5mg twice daily, up to the maximum dose of 25mg twice daily. The starting dose should not be increased within the first four weeks of treatment and thereafter no more frequently than at 2-week intervals.

There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm<sup>3</sup> and <100,000/mm<sup>3</sup>. The maximum recommended starting dose in these patients is 5mg twice daily and the patients should be titrated cautiously.

A complete blood cell count, including a white blood cell count differential, must be performed before initiating therapy. Complete blood count, including a white blood cell count differential, should be monitored every 2 to 4 weeks until ruxolitinib doses are stabilised, and then as clinically indicated.

Ruxolitinib treatment should only be initiated by a physician experienced in the administration of anti-cancer medicinal products.

Further details are included in the Summary of Product Characteristics (SPC).<sup>1</sup>

## Product availability date

22 January 2015

Ruxolitinib meets SMC orphan equivalent criteria.

## Summary of evidence on comparative efficacy

Polycythaemia vera is a myeloproliferative neoplasm known to be associated with dysregulated signalling of the Janus associated kinases JAK1 and JAK2. Ruxolitinib is a selective inhibitor of JAK1 and JAK2 and is the first in class for this indication.<sup>1</sup>

Key evidence for this indication is from the randomised, open-label, phase III RESPONSE and RESPONSE-2 studies. RESPONSE and RESPONSE-2 recruited adults (≥18 years of age) with polycythaemia vera who had resistance or intolerance to hydroxyurea (hereafter referred to as hydroxycarbamide as per the British National Formulary) according to modified European Leukaemia Net (ELN) international working group criteria. Recruited patients were dependent on phlebotomy for control of haematocrit. Patients in RESPONSE had a spleen volume of ≥450cm<sup>3</sup> (approximately twice the upper limit of normal) and those in RESPONSE-2 did not have splenomegaly. Patients were required to have an ECOG performance status of 0 to 2, a

haematocrit between 40% and 45%, an absolute neutrophil count  $\geq 1.5 \times 10^9/L$  (in RESPONSE) or  $\geq 1 \times 10^9$  (in RESPONSE-2), and a platelet count of  $\geq 100 \times 10^9/L$ .<sup>2-4</sup>

Patients were randomised equally to receive ruxolitinib at a starting dose of 10mg twice daily (RESPONSE n=110, RESPONSE-2 n=74) or single-agent standard therapy considered to be the best available by the investigator (RESPONSE n=112, RESPONSE-2 n=75), stratified by hydroxycarbamide status (inadequate response or unacceptable adverse effects). Ruxolitinib doses could be adjusted for inadequate efficacy or safety reasons with a maximum dose of 25mg twice daily and a minimum of 5mg per day. If specified cytopenias occurred, doses could be reduced or withheld. Best available therapy could include hydroxycarbamide (at a dose that did not cause unacceptable side effects), interferon or pegylated interferon, pipobroman, anagrelide, immunomodulators such as lenalidomide or thalidomide, or no medication. These treatments were prescribed as per the manufacturer's instructions, and doses could be modified due to lack of response or adverse events at the discretion of the investigator. Low dose aspirin 75mg to 150mg daily was given to all patients unless contraindicated.<sup>2-4</sup>

At week 32 in the RESPONSE study or week 28 in RESPONSE-2, patients assigned to best available therapy could cross over to ruxolitinib if the primary outcome was not met, or later for disease progression or safety. Crossover from ruxolitinib to best available therapy was not permitted.<sup>2-4</sup> The intention-to-treat (ITT) population, defined as all randomised patients, was used in the efficacy analyses.<sup>2-4</sup>

At the data cut-off for the primary outcome in RESPONSE, the median duration of therapy was 81 weeks in the ruxolitinib group compared with 34 weeks in the best available therapy group.<sup>2</sup> In RESPONSE-2 the median duration of therapy was 42 weeks in the ruxolitinib group and 28 weeks in the best available therapy group.<sup>4</sup>

The primary and secondary outcome results are detailed in table 1. In RESPONSE, a significantly higher proportion of patients in the ruxolitinib group than in the best available therapy group achieved the primary outcome; absence of eligibility for phlebotomy (haematocrit control) and  $\geq 35\%$  reduction from baseline in spleen volume at week 32.<sup>2</sup> For the individual components of the primary outcome, haematocrit control was achieved in 60% of patients in the ruxolitinib group compared with 19% in the best available therapy group, and a spleen volume reduction  $\geq 35\%$  was observed in 38% versus 0.9%, in the respective groups.<sup>5</sup> Significantly more patients achieved the primary outcome in RESPONSE-2, haematocrit control at week 28, in the ruxolitinib group than in the best available therapy group.<sup>4</sup>

In RESPONSE, the proportion of patients maintaining a response at week 48, a key secondary outcome, was significantly higher in the ruxolitinib group compared with the best available therapy group.<sup>3</sup> The second key secondary outcome, complete haematological remission at week 32, was achieved by significantly more patients in the ruxolitinib group than the best available therapy group.<sup>3</sup> Significantly more patients achieved the key secondary outcome in RESPONSE-2, complete haematological remission at week 28, in the ruxolitinib group compared with the best

available therapy group.<sup>4</sup> Complete haematological remission was defined as haematocrit control, white blood cell count  $<10 \times 10^9/L$ , and platelet count  $\leq 400 \times 10^9/L$ .<sup>3, 4</sup>

**Table 1: Primary and key secondary outcomes from the RESPONSE and RESPONSE-2 studies.**<sup>2-5</sup>

|   | <b>Ruxolitinib</b> | <b>Best available therapy</b> | <b>Odds ratio (95% confidence interval [CI], p value)</b> |
|---|--------------------|-------------------------------|---|
| <b>RESPONSE</b>   | <b>n=110</b>       | <b>n=112</b>                  |   |
| Haematocrit control and $\geq 35\%$ reduction from baseline in spleen volume at week 32 | 23%                | 0.9%                          | 28.6 (95% CI: 4.5 to 1206, $p < 0.001$ )                  |
| Maintaining a response at week 48   | 19%                | 0.9%                          | 26.1 (95% CI: 4.0 to 1080, $p < 0.001$ )                  |
| Complete haematological remission at week 32  | 24%                | 8.9%                          | 3.3 (95% CI 1.4 to 8.3, $p = 0.0028$ )                    |
| <b>RESPONSE-2</b>   | <b>n=74</b>        | <b>n=75</b>                   |   |
| Haematocrit control week 28   | 62%                | 19%                           | 7.3 (95% CI: 3.4 to 15.4, $p < 0.001$ )                   |
| Complete haematological remission at week 28  | 23%                | 5.3%                          | 5.6 (95% CI 1.7 to 18.0, $p = 0.0019$ )                   |

Positive changes were observed in patient reported outcomes in the ruxolitinib group in both studies. At week 32 in the RESPONSE study, 49% of patients in the ruxolitinib group and 5% of the best available therapy group had  $\geq 50\%$  reduction in the 14 item Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) total symptom score (TSS). Patients in the ruxolitinib group showed improvement in Global Health Status, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), the Pruritus Symptom Impact Scale (PSIS), and the Patient Global Impression of Change (PGIC) questionnaire while the best available therapy group had minimum changes.<sup>2, 3</sup> In RESPONSE-2, 45% of patients in the ruxolitinib group had  $\geq 50\%$  improvement in the 10 item MPN-SAF TSS at week 28 compared with 23% in the best available therapy group. Improvements were also observed in PSIS, PGIC, EuroQol-5D-5L (EQ-5D-5L) and the Work Productivity and Activity Impairment Questionnaire (WPAI) in the ruxolitinib group. In general, little or no improvements were observed in the best available therapy group.<sup>4</sup>

There was an extension phase of the RESPONSE study, patients received up to 256 weeks of treatment in total.<sup>2, 3</sup> At study completion, 66% of patients randomised to the ruxolitinib group completed five years of on-study treatment. No patients were receiving best available therapy, 88% of those originally in the best available therapy group crossed over to ruxolitinib. In the ruxolitinib group, 24% (6/25) of patients who achieved the primary outcome and 30% (21/70) of patients who had an overall clinicohaematologic response (defined as haematologic control without phlebotomy, platelets  $\leq 400 \times 10^9/L$ , a white cell count  $\leq 10 \times 10^9/L$ , and a spleen volume

reduction  $\geq 35\%$ ) had progressed. Median duration of response had not been reached. The Kaplan Meier estimate for overall survival at five years was 92% in the ruxolitinib group.<sup>6</sup>

Data are available from RESPONSE-2 for up to 156 weeks treatment. At this data cut-off, 88% of the ruxolitinib group were still receiving study treatment compared with none of the best available therapy group, 77% had crossed over to ruxolitinib. In the ruxolitinib group, durable haematocrit control was achieved in 42% of patients, the median duration had not been reached. Durable complete haematological response was achieved in 24% of patients in the ruxolitinib group, estimated median duration of 35.9 weeks. A  $\geq 50\%$  reduction in MPN-SAF TSS at week 156 was observed in 48% of patients in the ruxolitinib group.<sup>7</sup>

The submitting company presented a matching adjusted indirect comparison (MAIC) to compare ruxolitinib with best available therapy using individual patient data (IPD) for patients treated with ruxolitinib in the RESPONSE study and real world IPD for patients treated with best available therapy as recorded in the Grupo Español de Enfermedades Mieloproliferativas Crónicas Filadelfia Negativas (GEMFIN) registry. Only patients resistant/intolerant to hydroxycarbamide were included from the GEMFIN registry. Matched covariates were age, sex, history of thrombosis at time of resistance/intolerance to hydroxycarbamide, and cytopenia at the lowest hydroxycarbamide dose. Propensity scores were calculated by fitting a multivariable logistic regression model that included the selected covariates for matching as predictor variables and the treatment received as the dependent variable. Propensity score matching was performed using caliper matching with a caliper width of 20% of the standard deviation of the logit-transformed propensity scores, using sampling without replacement. Hazard ratios (HRs) were estimated from Cox proportional hazards models. The submitting company concluded that patients treated with ruxolitinib in the RESPONSE study had a significantly reduced risk of mortality compared to those with matched characteristics receiving best available therapy in the GEMFIN registry.

### Summary of evidence on comparative safety

The EMA concluded that overall, ruxolitinib is well tolerated in patients with polycythaemia vera with a similar safety profile to that previously observed in patients with myelofibrosis.<sup>3</sup>

Adverse events (AEs) presented below were evaluated until week 32 in RESPONSE and week 28 in RESPONSE-2 (before crossover was allowed). Safety was assessed in all patients who received study treatment.<sup>2</sup>

In the RESPONSE study AEs were reported in most patients, 96% in the ruxolitinib group and 94% in the best available therapy group. Grade 3 or 4 AEs were reported in 33% and 29%, serious AEs in 14% and 9.0% and AEs leading to discontinuation in 6.4% and 0.9% of the respective groups.<sup>3</sup> Commonly reported AEs in RESPONSE included anaemia (18% and 2.7%), headache (16% and 19%), diarrhoea (15% and 7.2%), fatigue (15% and 15%), pruritus (14% and 23%), dizziness (12% and 9.9%), muscle spasms (12% and 4.5%), and dyspnoea (10% and 1.8%).<sup>3</sup> Herpes zoster infections occurred in 6.4% of the ruxolitinib group and no patients in the best available therapy

group. Eight patients in the ruxolitinib group and two patients in the best available therapy group had newly diagnosed non-melanoma skin cancer. Thromboembolic events occurred in one patient in the ruxolitinib group and six patients in the best available therapy group.<sup>2</sup>

In RESPONSE-2 AEs were reported in 80% of patients in both groups. Grade 3 or 4 AEs were reported in 18% and 27% of the ruxolitinib and best available therapy groups respectively. Treatment discontinuation due to AEs occurred in 1.4% and 8% of the groups.<sup>4</sup> In RESPONSE-2, commonly reported AEs included anaemia (14% and 2.7%) headache (9.5% and 11%), constipation (9.5% and 5.3%), weight gain (9.5% and 1.3%), hypertension (9.5% and 4.0%), pruritus (5.3% and 20%) and upper respiratory tract infections (2.7% and 9.3%). One patient had a thrombotic event in the ruxolitinib group compared with three patients in the best available therapy group.<sup>4</sup>

Long term safety data for up to 256 weeks of ruxolitinib treatment are available from the RESPONSE study and up to 156 weeks from the RESPONSE-2 study extension phases. The safety profile was generally similar to previously reported.<sup>6, 7</sup>

### Summary of clinical effectiveness issues

Polycythaemia vera is characterised by unregulated production of red and white blood cells and platelets. This results in increased blood viscosity leading to thrombosis and cardiovascular complications. Complications can also include extramedullary haematopoiesis, myelofibrosis, and acute leukaemia.<sup>3</sup> Patients may experience symptoms such as severe pruritus, headache and fatigue which can negatively affect quality of life. Treatment aims include reducing symptoms, reducing the risk of cardiovascular events and decreasing the risk of transformation to myelofibrosis and acute leukaemia. Assessment and management of cardiovascular risk factors, such as hypertension, hypercholesterolaemia, diabetes mellitus and smoking, is essential in patients with polycythaemia vera. All patients should receive daily low dose aspirin. Venesection is used with the aim of achieving and maintaining haematocrit <45%. If cytoreductive therapy is required, hydroxycarbamide or interferon (unlicensed indication), can be used as first and second line options.<sup>3, 8</sup> Further treatments in patients with limited life expectancy include busulfan, phosphorus-32 or pipobroman. In patients where platelet control is difficult anagrelide (unlicensed indication) in combination with hydroxycarbamide can be helpful.<sup>8</sup> Clinical experts consulted by SMC considered that ruxolitinib fills an unmet need in this therapeutic area as treatment options are limited for patients who are resistant/intolerant to hydroxycarbamide. Ruxolitinib meets SMC orphan equivalent criteria.

In the RESPONSE study, in patients with polycythaemia vera who were resistant/intolerant to hydroxycarbamide and had splenomegaly, ruxolitinib was superior to best available therapy for the primary outcome of haematocrit control and  $\leq 35\%$  reduction in spleen volume. In RESPONSE-2 (patients without splenomegaly), ruxolitinib was superior to best available therapy for the primary outcome of haematocrit control. Complete haematological response, a key secondary outcome in both studies, was achieved by more patients in the ruxolitinib groups than the best available therapy groups.<sup>2-4</sup> Haematocrit control is not a direct health outcome however is recommended as a treatment goal in patients with polycythaemia vera.<sup>3, 8</sup> Maintaining haematocrit <45% has

been associated with a lower risk of cardiovascular death and major thrombosis. The EMA considered that data from RESPONSE demonstrated that ruxolitinib had a clinically relevant effect on patients with polycythaemia vera who are resistant/intolerant to hydroxycarbamide.<sup>3</sup>

The key studies were open label which could have introduced bias particularly for patient reported quality of life outcomes and adverse event data. Patients with clinically significant cardiac disease were excluded which may affect the generalisability to some of the Scottish population. Patients were allowed to receive hydroxycarbamide in the best available therapy arm and this was the most common treatment (60% and 49% of patients in the RESPONSE and RESPONSE-2 studies) and reflects the lack of treatment options. Interferon, although unlicensed for this indication, may be a relevant comparator in this patient group. Only 12% and 13% of patients in the best available therapy group of the RESPONSE and RESPONSE-2 studies received interferon. Patients with haematocrit >45% and patients with platelets <100x10<sup>9</sup>/L were not included in the key studies.

A large majority of patients crossed over from the best available therapy group to ruxolitinib at week 28 (RESPONSE-2) or week 32 (RESPONSE) therefore comparative efficacy and safety data are limited to those time points. Long term comparative data, for example on reduction of complications, such as cardiovascular risk, and overall survival are not available. Data for ruxolitinib treatment are also available from long-term extension studies (up to 256 weeks treatment in RESPONSE and 156 weeks in RESPONSE-2). The EMA has specified that a Post-Authorisation Efficacy Study is to be submitted to provide long-term efficacy and safety of ruxolitinib data including (late) achievement of response, duration of (various) responses, as well as incidence of AEs including haematological transformation and second malignancies from the RESPONSE study.<sup>3</sup>

The MAIC presented by the submitting company evaluated overall survival using individual patient data for patients receiving ruxolitinib from RESPONSE compared with best available therapy from the GEMFIN registry. The HR for this comparison indicates an overall survival benefit with ruxolitinib treatment however the MAIC is associated with some limitations. The absence of a common comparator arm should be noted as an important limitation, because validation of the matching or the use of relative effect measures will not be possible. The GEMFIN registry is a Spanish database. Clinical experts consulted by SMC considered that interferon may be a relevant comparator in this patient population and only small percentage of patients included from GEMFIN received interferon/pegylated interferon. There was a considerable difference in follow-up time between patients in the ruxolitinib arm of the RESPONSE study and patients from GEMFIN registry (256 weeks versus 728 weeks). Considering the limited numbers of deaths that had occurred in the RESPONSE study by week 256, the long-term survival benefit of ruxolitinib is uncertain beyond week 256. It may not be appropriate to compare results at different degrees of maturity. The MAIC evaluated overall survival however, no other outcomes were included for example haematocrit control, haematologic response, complications, patients reported quality of life outcomes or safety. There were some additional prognostic factors/treatment effect modifiers that were not matched in the MAIC.

The introduction of ruxolitinib would provide a further licensed treatment for patients with polycythaemia vera who are resistant/intolerant to hydroxycarbamide. Clinical experts consulted by SMC considered that ruxolitinib is a therapeutic advancement as there are very limited treatments available and ruxolitinib has demonstrated better efficacy than current treatments in this patient group. It is administered orally and the clinical experts do not anticipate any service implications. They considered that the place in therapy is as per the licensed indication, for patients with polycythaemia vera who are resistant/intolerant to hydroxycarbamide.

## Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of ruxolitinib, as an orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Polycythaemia vera (PV) is a rare and incurable blood cancer that affects people of working age. In the small group of patients whose disease is uncontrolled on currently available treatments, symptoms may be severe and long-lasting. In particular, patients may suffer from severe, debilitating fatigue and intense skin itching/ burning sensation, which can be difficult to control and severely impact on quality of life.
- Patients may have to reduce or give up work and may be unable to care for others. They may become depressed due to the chronic and relentless nature of the symptoms.
- There are limited treatment options for patients who are uncontrolled on or cannot tolerate hydroxycarbamide, and these are not suitable for many patients.
- Ruxolitinib fills an unmet need for a better tolerated treatment in patients who are uncontrolled or intolerant of hydroxycarbamide

Relief of symptoms could allow patients to return to normal levels of activity, which could be life-changing for patients.

### **Additional Patient and Carer Involvement**

We received patient group submissions from: Bloodwise, Leukaemia CARE and MPN Voice. All three organisations are registered charities. Bloodwise has received 0.7% pharmaceutical company funding in the past two years, including from the submitting company. In the past two years, MPN Voice has received 5.3% pharmaceutical company funding and Leukaemia CARE has received 12.6% pharmaceutical company funding, both including from the submitting company. Representatives from all three organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

## Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing ruxolitinib with best available therapy for adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea (hydroxycarbamide). The composition of best available therapy was based on the weighted average of costs for each of the individual treatment, with the proportion of patients receiving each treatment based on the cohort of best available therapy patients from GEMFIN matched to RESPONSE. The composition affected medicine acquisition costs only.

The analysis employed a three-state partitioned survival model, with states of on-ruxolitinib, off-ruxolitinib (best available therapy) and death. A lifetime horizon (maximum age 100) was used.

Due to extensive treatment switching in the clinical studies, the analysis was based on the RESPONSE and RESPONSE-2 clinical study populations matched to the GEMFIN registry from which best available therapy overall survival is derived using the MAIC described above.<sup>2-4</sup>

The MAIC used in the economic model was updated using the week 256 data from the RESPONSE study. The submitting company explored the feasibility of conducting a MAIC using pooled data from both RESPONSE and RESPONSE-2. This would have involved considerable overlap in the number of GEMFIN patients that could be matched to RESPONSE and RESPONSE-2 and therefore matching to the pooled data was not deemed to be feasible. Matching to patients in the RESPONSE-2 alone was also rejected as no deaths had occurred in the ruxolitinib arm at the data cut (80 weeks) used for the analysis. The hazard ratio from the MAIC for overall survival was applied throughout patients' time on-ruxolitinib in the base case, with shorter durations of effect explored in scenario analyses. An exponential model was also chosen for time in the on-ruxolitinib state, modelled according to data from the RESPONSE (week 256 data) and RESPONSE-2 (week 156 data) studies.

Parametric survival functions were fitted to the GEMFIN individual patient data. Extrapolation of overall survival was modelled using an exponential distribution based on goodness-of-fit statistics, visual inspection, and clinical plausibility, for both RESPONSE and RESPONSE-2 matched cohorts. Projected life expectancy was slightly better in the RESPONSE-2 (without splenomegaly) cohort, which the submitting company suggests may be due to patients with splenomegaly potentially having a slightly poorer prognosis, due to additional symptom burden and reduced time to transformation to myelofibrosis or acute myeloid leukaemia.

The model considered grade 3+ treatment related AEs in both arms of the RESPONSE studies. In addition thromboembolic events were modelled. The number of patients experiencing thromboembolic events each cycle was calculated for the model assuming a constant rate of thromboembolic events throughout the entire time horizon. Rates were 1.2 and 8.2 per 100 patient years for ruxolitinib and best available therapy respectively based on week 256 in the RESPONSE study (data for RESPONSE-2 were not available).

Quality adjusted life years (QALYs) were modelled based on treatment specific utilities on and off ruxolitinib. Health state utilities were derived using a disease specific measure, the MF-8D. EORTC QLC-C30 and EUROQoL EQ-5D were also available in RESPONSE and RESPONSE-2. Adverse events

were assumed to be captured in the treatment specific utility estimates. However, separate estimates were applied based on literature for thromboembolic events.

Costs included medicine acquisition and monitoring costs. No administration costs were included as medicines were either administered orally or assumed to be self-administered by patients. Other costs included were those for adverse and thromboembolic events, and aspirin and phlebotomy. Lower recourse to phlebotomy on ruxolitinib was applied based on RESPONSE. Medicine costs in the best available therapy arm represented the weighted average of costs for doses of each of the component treatments based on cited sources such as the London Cancer Alliance. For ruxolitinib, doses were costed based on the proportions of patients at each dose in the cohort of best available therapy patients from GEMFIN matched to RESPONSE, though cost per day was largely invariant to dose.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. The base case results and selected sensitivity analysis with the PAS are presented in tables 2 and 3.

**Table 2: Base case results versus best available therapy – with PAS for ruxolitinib**

| Intervention | ICER<br>cost per QALY gained |
|--------------|------------------------------|
| Ruxolitinib  | £28,574                      |

QALY = quality-adjusted life year, ICER = incremental cost-effectiveness ratio

Sensitivity analyses (including 95% confidence intervals for relevant parameters), showed the model was sensitive to the fitted overall survival exponential rate, and overall survival hazard ratio for ruxolitinib, with the ICER increasing by more than £10,000 and £6,000 respectively.

**Table 3: Selected sensitivity analysis results with PAS**

|   | ICER<br>(cost/QALY) |
|---|---------------------|
| Base case   | £28,574             |
| 1 Best available therapy consists of IFN- $\alpha$ and pegylated IFN only | £15,010             |
| 2 Overall survival for best available therapy: Weibull                    | £29,158             |
| 3 Overall survival hazard ratio of 1 applied after end of study           | £40,160             |
| 4 Overall survival hazard ratio waned over 3 years post study             | £35,890             |
| 5 Overall survival hazard ratio waned over 5 years post study             | £33,743             |
| 6 ToT (RESPONSE): Weibull   | £29,939             |
| 7 RESPONSE-2 EQ-5D for utility values                                     | £32,905             |

IFN = interferon, ToT = time on treatment, QALY = quality adjusted life-year, ICER = incremental cost-effectiveness ratio, PAS = patient access scheme

There are a number of limitations of the analysis:

- The utility estimates employed in the model base case are based on a condition- specific measure (which required additional assumptions in order to be used), rather than the available

EQ-5D data. Only point estimates based on an 'average' patient were available for the condition specific estimates, with uncertainty, particularly in the BAT arm, demonstrated in the EQ-5D estimates. Use of RESPONSE-2 EQ-5D utility estimates increased the ICER to £32,905.

- The overall survival treatment effect is based on a MAIC comparison with the registry data due to the extent of treatment switching in the RESPONSE studies. This is understandable, but the reliance on such an estimate of treatment effect is a limitation. Results were relatively sensitive to the overall survival estimates used in the model. The effect is applied indefinitely in the base case. Imposing an immediate stop on the overall survival treatment effect (HR=1 after the study follow-up) caused the ICER to rise to over £40,000 per QALY, with less pessimistic scenarios also increasing the ICER (sensitivity analyses 4 and 5 in table 3).
- The MAIC based estimate is based on RESPONSE, which is also applied to the RESPONSE-2 population. Although the 95% confidence interval for the HR for overall survival does not include 1, there is notable uncertainty in the HR, and therefore in the estimate of the ICER.

The Committee also considered the benefits of ruxolitinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that [the criterion for a substantial improvement in quality of life was. In addition, as ruxolitinib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted ruxolitinib for use in NHSScotland.

*Other data were also assessed but remain confidential.\**

### Additional information: guidelines and protocols

The British Society for Haematology published updated guidance in 2018: A guideline for the diagnosis and management of polycythaemia vera. This guideline states that the aims of treatment are to reduce complications and improve survival. Thromboembolic events are the main cause of death and therefore reducing the risk is the key aim of treatment. The guideline recommends that targeted assessment and management of cardiovascular risk factors, such as hypertension, hypercholesterolaemia, diabetes mellitus and smoking, is essential. All patients should receive daily low dose aspirin 75mg to 100mg. Venesection is used in patients with polycythaemia vera with the aim of achieving and maintaining haematocrit of <45%. If frequent venesection is required, a cytoreductive medication can be considered for high risk patients and some low risk patients (for example those with progressive splenomegaly, progressive leucocytosis, thrombocytosis, haemorrhagic symptoms, progressive/symptomatic splenomegaly, uncontrolled/progressive disease-related symptoms, or poor tolerance of venesection). Hydroxycarbamide is recommended as a first line cytoreductive treatment option. In high-risk patients, hydroxycarbamide or interferon (preferably pegylated) can be used first line. The second line option is either hydroxycarbamide or interferon depending on which was used first line.

Pegylated interferon can be considered as a second line option in patients who have had non-pegylated interferon first line and were unable to tolerate it. The guideline recommends ruxolitinib as a second or third line option in patients resistant/intolerant to hydroxycarbamide. Further treatments in patients with limited life expectancy include busulfan, phosphorus-32 or pipobroman. In patients where platelet control is difficult anagrelide in combination with hydroxycarbamide can be helpful.<sup>8</sup>

### Additional information: comparators

Very limited treatment options. Interferon may be used but is not licensed for this indication.

### Cost of relevant comparators

| Medicine                     | Dose Regimen   | Cost per year (£)       |
|------------------------------|--|-------------------------|
| <b>Ruxolitinib phosphate</b> | <b>10mg twice daily, titrated based on safety and efficacy, maximum dose of 25mg twice daily</b> | <b>37,128 to 55,692</b> |

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 02.08.19. Costs do not take any patient access schemes into consideration.*

### Additional information: budget impact

The submitting company estimated there would be 47 patients eligible for treatment with ruxolitinib in year 1, with 45 in year 5. Of patients eligible under the licence, 4% are assumed to be treated in year 1 rising to 15% in year 5. Discontinuation is assumed to rise from 2% in year 1 to 16% in year 5. The resulting number of newly treated patients ranges from 2 in year 1 to 6 in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.\**

## References

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This assessment is based on data submitted by the applicant company up to and including 13 September 2019.

*\*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: [http://www.scottishmedicines.org.uk/About\\_SMC/Policy](http://www.scottishmedicines.org.uk/About_SMC/Policy)*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*