ruxolitinib (as phosphate), 5mg, 15mg, & 20mg tablets (Jakavi®)

SMC No. (867/13)

Novartis Pharmaceuticals UK Ltd.

06 February 2015

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 NHS Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission considered under the orphan process.

ruxolitinib (Jakavi®) is accepted for use within NHS Scotland.

**Indication under review**: the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

In patients with myelofibrosis, a significantly greater proportion of patients achieved a spleen response (reduction in spleen volume of at least 35% from baseline) at 48 weeks when treated with ruxolitinib compared with best available therapy. Ruxolitinib was also associated with a greater proportion of patients reporting a clinically significant reduction in myelofibrosis-related symptoms when compared with placebo.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost effectiveness of ruxolitinib. It is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

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

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

Published 09 March 2015
### Indication
The treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

### Dosing Information
The recommended starting dose is 15mg twice daily for patients with a platelet count between 100,000/mm$^3$ and 200,000/mm$^3$ and 20mg twice daily for patients with a platelet count of >200,000/mm$^3$. There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm$^3$ and <100,000/mm$^3$. The maximum recommended starting dose in these patients is 5mg twice daily and the patients should be titrated cautiously.

Doses may be titrated based on safety and efficacy. Treatment should be discontinued for platelet counts less than 50,000/mm$^3$ or absolute neutrophil counts less than 500/mm$^3$. After recovery of platelet and neutrophil counts above these levels, dosing may be re-started at 5mg twice daily and gradually increased based on careful monitoring of complete blood cell count, including a white blood cell count differential. Dose reductions should be considered if the platelet count decreases below 100,000/mm$^3$, with the goal of avoiding dose interruptions for thrombocytopenia. If efficacy is considered insufficient and platelet and neutrophil counts are adequate, doses may be increased by a maximum of 5mg 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.

The maximum dose is 25mg twice daily.

Treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

### Product availability date
August 2012

Ruxolitinib meets SMC criteria for orphan status.
Myelofibrosis is a myeloproliferative neoplasm that can either be secondary to polycythaemia vera or essential thrombocythaemia, or present as a de novo disorder, primary myelofibrosis. Myelofibrosis is known to be associated with dysregulated signalling of the Janus Associated Kinases (JAK1 and JAK2). The clinical features of myelofibrosis include progressive anaemia, leucopenia, leucocytosis, thrombocytopenia, thrombocytosis, and extra-medullary haematopoeisis resulting in hepatomegaly or symptomatic splenomegaly. At diagnosis, the median age of patients is 65 years with median survival ranging from 135 months (low prognostic risk) to 27 months in high risk groups. Ruxolitinib is a selective inhibitor of JAK1 and JAK2.

COMFORT-II was a multi-centre, randomised open-label, controlled phase III study which recruited adults with a diagnosis of either primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis, who had a palpable spleen at least 5cm below the costal margin, and had no previous treatment with a JAK inhibitor. Patients had a platelet count ≥100x10^9/L, peripheral-blood blast count <10%, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3, classed at intermediate-2 risk or high risk according to the International Prognostic Scoring System (IPSS), and a life expectancy of at least six months. Patients were not considered candidates for allogeneic stem-cell transplantation.

Patients were randomised, stratified by prognostic category (intermediate-2 risk versus high risk), in a 2:1 ratio to ruxolitinib or best available therapy (any commercially available agent[s] or no therapy at the discretion of the local investigator). The initial dose of ruxolitinib was based on baseline platelet count: ≤200x10^9/L (15mg twice daily), >200x10^9/L (20mg twice daily). The dose of ruxolitinib could be adjusted to increase efficacy to a maximum of 25mg twice daily or reduced to manage toxicity (if neutropenia or thrombocytopenia developed). Best available therapy could be changed during the treatment phase of the study. Patients continued on randomised treatment until disease progression (either an increase in spleen volume >25% from study nadir, splenic irradiation or splenectomy, leukaemic transformation or death). Patients who underwent splenic irradiation or had leukaemic transformation were withdrawn from the study, whereas those with an increase in spleen volume or splenectomy were discontinued from the randomised treatment phase of the study and could enter an extension phase, at which point those on best available therapy could cross-over to ruxolitinib.

The primary endpoint was a reduction of at least 35% in spleen volume (spleen response) from baseline at week 48, as assessed by the central, blinded radiologist from magnetic resonance imaging (MRI) or computed tomography (CT) scans. At week 48, the proportion of patients with a spleen response was 28% in the ruxolitinib group (n=144) compared with 0% in the best available therapy group (n=72), p<0.001. At week 48, the mean change in spleen volume from baseline was a 30% decrease in the ruxolitinib group compared with a 7.3% increase in the best available therapy group. The median time to achieve a 35% reduction in spleen volume was 12.3 weeks in the ruxolitinib group. At a median follow up of 151 weeks, incorporating the randomised and extension phases of the study, Kaplan-Meier estimated probabilities of maintaining a spleen response at 48 and 144 weeks were 73% and 50% respectively. At a median follow-up of 3.5 years, analysis of the accrued 70 deaths (27% [40/146] ruxolitinib, and 41% [30/73] best available therapy) suggested a significant reduction in the risk of death for ruxolitinib, hazard ratio=0.58 (95% CI: 0.36 to 0.93), p=0.022. Estimated survival probability at 3.5 years was 71% and 54% for ruxolitinib and best available therapy respectively. The survival estimates are confounded by patient cross-over.
COMFORT-I was a double-blind, multi-centre, randomised, placebo-controlled, phase III study with similar inclusion and exclusion criteria as COMFORT-II, except in COMFORT-I, patients were not suitable for best available therapy and other treatments for myelofibrosis had been discontinued four weeks prior to the first baseline visit. Patients were randomised equally to ruxolitinib (n=155, dose regimen as per COMFORT-II) or matched placebo (n=154). The study remained blinded until the last randomised patient had undergone week 24 assessment and 50% of patients had a 36-week assessment, at which point placebo patients were eligible to crossover to ruxolitinib. Early unblinding was permitted up to week 24 if there was worsening splenomegaly accompanied by either worsening early satiety with weight loss or increased splenic pain requiring increased analgesics. Early unblinding was permitted after week 24 upon worsening splenomegaly. Unblinded patients assigned to placebo were permitted to cross-over to ruxolitinib, whereas those assigned to ruxolitinib could continue this if asymptomatic progression occurred after week 24.

The primary outcome, proportion of patients with a spleen response (≥35% reduction in spleen volume) at week 24, was significantly greater in the ruxolitinib group (42%) compared with the placebo group (0.7%), p<0.001. The Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 was used to record patients’ symptoms, scoring from 0 (absent) to 10 (worst imaginable) for each myelofibrosis-associated symptom: night sweats, pruritis, abdominal discomfort, pain under the ribs on the left side, early satiety, muscle/bone pain, and inactivity. The total symptoms score (TSS) was the sum of the scores (excluding inactivity). Baseline TSS was the mean of daily scores for seven days prior to commencing treatment. 24-week TSS was the mean of daily scores for the previous 28 days. Baseline mean TSS was 18.0/60 in the ruxolitinib group and 16.5/60 in the placebo group. A significantly greater proportion of patients in the ruxolitinib group compared with the placebo group achieved at least a 50% improvement in TSS from baseline to week 24, 46% versus 5.3% respectively, p<0.001. Patients in the ruxolitinib group had a mean improvement in TSS of 8.6 points from baseline to week 24, whereas patients in the placebo group had a mean worsening in TSS of 3.2 points, p<0.0001.

The median follow-up was 32 weeks at the date of the primary data cut-off and with 10 deaths accrued in the ruxolitinib group and 14 deaths in the placebo group, the hazard ratio was not statistically significant (0.67 [95% CI: 0.30 to 1.50], p=0.33). Analyses at later data cuts are available, but are confounded by patient cross-over following the primary efficacy analysis. After a median follow-up of 149 weeks, the hazard ratio was 0.69 (95% CI: 0.46 to 1.03), p=0.067. Median survival in either group had yet to be reached. Health-related quality of life was measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire core model (QLQ-C30) in both studies. In COMFORT-II, at week 24, global health status scores had a mean increase of 45% from baseline in the ruxolitinib group and 8.7% in the placebo group. Physical, role and social functioning all had a mean increase from baseline in the ruxolitinib group and mean decreases in the placebo group. In COMFORT-II the mean score for global health status and quality of life and role functioning improved from baseline at week 48. There were improvements in symptom scores for myelofibrosis associated symptoms (e.g. fatigue, dyspnoea, insomnia, appetite loss).
Summary of evidence on comparative safety

During the randomised phase of COMFORT-II, haematological adverse events such as anaemia and thrombocytopenia occurred more frequently in ruxolitinib patients compared with the best available therapy group. They were managed by dose modification and/or red cell transfusion rather than treatment discontinuation. At the time of primary efficacy analysis, dose modification to manage thrombocytopenia occurred in 41% of ruxolitinib patients and in 1% of best available therapy patients. Anaemia was responsible for 5% of ruxolitinib patients requiring dose interruption or reduction compared with 1% in the best available therapy group. Red-cell transfusion was required in 51% and 38% of ruxolitinib and best available therapy patients respectively.4

After three years of follow-up, it was noted that the rate of haematological adverse events (i.e. anaemia and thrombocytopenia) and other adverse events of special interest (bleeding and infection) were greatest during the first six months of ruxolitinib treatment but reduced over time. Leukaemic transformation occurred in 3.4% of ruxolitinib and 5.5% of best available therapy patients. Non-haematological toxicity was predominantly of severity grade 1 or 2 with similar incidence in each group. Common adverse events (incidence between 10 and 20 per 100 patient years) in the ruxolitinib group were: peripheral oedema, diarrhoea, asthenia, pyrexia, dyspnoea, fatigue, and cough.

After three years of follow-up 16% (24/146) ruxolitinib patients had discontinued the study due to adverse events; adverse event was the primary reason for discontinuation in 6.8% (5/73) of patients taking best available therapy and in 13% (6/45) of patients on ruxolitinib who had crossed over from best available therapy. Following discontinuation of ruxolitinib, 30% of patients reported new or worsening adverse events within the following 28 days, the most common being infection (13%) and thrombocytopenia (9.7%).5

During treatment or within four weeks after discontinuation there were 18 deaths: 13 in the ruxolitinib group, 4 in the best available therapy group (during randomised treatment), and 1 after crossover from best available therapy to ruxolitinib. In ruxolitinib patients the cause of death was unique to each patient.5

Summary of clinical effectiveness issues

Primary myelofibrosis is estimated to affect approximately 0.3 people in 10,000, and secondary myelofibrosis <0.3 people in 10,000 people in the European Union. Ruxolitinib has been designated an orphan medicine by the European Medicines Agency,10 is the first JAK inhibitor to be licensed in the UK, and the first medicine to have a marketing authorisation in the UK for the management of myelofibrosis.2 Ruxolitinib meets SMC orphan criteria.

In the UK, the mainstay of treatment of myelofibrosis is medical management. However no treatment delivers sustained or robust responses. Prior to the availability of ruxolitinib, treatment guidelines produced by the British Committee for Standards in Haematology (BCSH) recommended hydroxycarbamide as first line option for patients with symptomatic splenomegaly or to manage hyperproliferative manifestations of the disease. In patients who are fit enough, allogeneic stem-cell transplant is potentially curative,1 however clinical experts consulted by SMC suggest this is a small proportion of the total patient group. Updated BCSH guidelines recommend ruxolitinib for first-line use in myelofibrosis-related splenomegaly and constitutional symptoms.11
Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely a lack of effective therapies that alleviate constitutional symptoms of myelofibrosis and symptomatic splenomegaly.

The primary outcome in the COMFORT studies, “spleen response” is a surrogate marker for symptoms related to splenomegaly and to health-related quality of life. In both studies, spleen response rates were significantly greater in the ruxolitinib groups compared with control. COMFORT-I also demonstrated symptomatic improvement for patients treated with ruxolitinib, with a significantly greater proportion having a clinically relevant reduction in symptoms (50% reduction in TSS).

Neither study was designed to assess the overall survival of ruxolitinib and control. Furthermore, patient crossover has confounded the analyses. Despite these issues the latest results from COMFORT-II suggest a survival advantage for ruxolitinib when compared with best available therapy.

A limitation of COMFORT-II was the open-label design. This may have contributed to the imbalance in the drop-out rates of the study; different proportions of patients withdrew consent (1.4% of ruxolitinib patients compared with 12% of best available therapy patients). While the primary outcome was assessed by a central, blinded radiologist, the open-label design complicates the interpretation of the quality of life assessments in this study.

The European Medicines Agency noted that non-haematologic adverse events were mild to moderate in severity and the major haematological adverse events of anaemia and thrombocytopenia (consistent with the mechanism of action of ruxolitinib) could be managed either by dose modification or interruption.

Clinical experts consulted by SMC considered that ruxolitinib is a therapeutic advancement since it targets the underlying disease process, improves constitutional symptoms and reduces splenomegaly.

Summary of patient and clinician engagement

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 medicine, in the context of treatments currently available in NHS Scotland, specifically in the treatment of splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

The key points expressed by the group were:

- Symptoms of myelofibrosis (MF) and splenomegaly can be extreme and vary between patients. Symptoms such as itch can be severely debilitating and have a devastating effect on quality of life for patients and their families.

- There are currently no medical treatments that effectively address the symptoms of MF including gross splenomegaly, which is particularly distressing. There are currently no non-transplant treatments that suggest a prolongation of survival.

- Ruxolitinib can reduce the burden of disease related symptoms – some patients are even able to return to work and participate in normal life. Reduced dependency on carers can improve family relationships. No other treatment offers the combination of symptom improvement, spleen reduction and improved quality of life seen with ruxolitinib.
Clinicians involved in the PACE meeting highlighted that they would not use ruxolitinib in patients with asymptomatic splenomegaly unless varices or other constitutional symptoms were present. Patients unsuitable for transplant may also benefit. It was also emphasised that responders were able to be identified quickly.

PACE participants expressed strong support for the availability of ruxolitinib in Scotland and considered that this is an innovative treatment which markedly improves the quality of life of patients. There are no other licensed medicines that improve symptoms or impact on overall survival in MF.

**Summary of comparative health economic evidence**

The company submitted a lifetime cost-utility analysis comparing ruxolitinib against best available therapy for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF), post-polycythaemia vera MF (PPV-MF) or post-essential thrombocythaemia (PET-MF). Best available therapy consisted of a range of commercially available agents and no treatment. The most commonly used treatment within best available therapy was hydroxycarbamide followed by prednisone, epoetin and anagrelide.

The economic model took the form of a discrete event simulation (DES) and an individual-based approach was chosen over a cohort approach in order to model the progressive nature of the disease. In terms of model structure, patients followed a sequence of treatments and moved to the next treatment phase on stopping the previous therapy. Patients who commenced therapy with ruxolitinib remained on ruxolitinib until discontinuation and then received best available therapy or died. Patients who initiated best available therapy (either after stopping ruxolitinib or when starting therapy for MF) remained on best available therapy until they exhausted the number of therapies that provided some symptom relief. Following withdrawal from best available therapy, patients received supportive care and then progressed to end of life/palliative care and then finally death.

The economic model was based on three years of efficacy data from the two phase III randomised studies described above, COMFORT-I and COMFORT-II.

The utility values for each phase of treatment were derived from a new condition-specific health-related quality of life measure, the MF-8D. The baseline utility values were as follows: 0.732 for baseline, 0 for the change in health-related quality of life in patients treated with best available therapy, -0.025 for the change every 24 weeks in patients on supportive care, +0.153 for the change at 4 weeks in patients who achieved a response to ruxolitinib (maintained up to 24 weeks), 0 for the change after 24 week in patients treated with ruxolitinib that achieved a response, and +0.037 for change in patients at 4 weeks in patients who did not respond to ruxolitinib (maintained up to 24 weeks).

Drug acquisition costs for ruxolitinib and the various medicines that constituted best available therapy in the COMFORT-II study were included. The model also considered medical visit costs, adverse events and the cost of death.

Following the NDC meeting, a patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a simple discount was offered on the list price of the medicine. With the PAS, the base case results reported an incremental cost effectiveness ratio (ICER) of £49,774 per quality adjusted life year (QALY) based on an incremental cost of £98,982 and a QALY gain of 1.99 QALYs.
Sensitivity analyses identified that the model was sensitive to using different overall survival estimates for patients initiated to best available therapy. When the log-normal curve was used in the analysis the ICER increased to £57,825 per QALY gained. In addition when the historical cohort and the ITT population from the COMFORT studies were used the ICERs increased to £58,374 and £66,226 per QALY gained respectively. The model was also sensitive to all patients who responded to ruxolitinib dying upon cessation and the ICER in this case increased to £61,050 per QALY gained.

The key uncertainties identified with the analysis were as follows:

- The economic model reported a survival advantage for patients treated with ruxolitinib however neither of the COMFORT studies was powered to detect differences in survival and therefore there may be some uncertainty regarding the survival estimates. The survival estimates for patients who responded to ruxolitinib were extremely variable and although the Weibull curve used in the base case provided a reasonable fit to the data, the Gompertz curve was also a good fit according to the Akaike Information Criteria (AIC). The Weibull curve produced an overall survival estimate for ruxolitinib responders of 324.83 weeks and the Gompertz curve an overall survival estimate of 220.38 weeks, which is a difference of approximately 2 years. A sensitivity analysis was requested from the company which used different parametric curves to estimate survival for ruxolitinib responders. However the company did not report the analysis as the Gompertz curve provided inconsistent long-term extrapolation compared with the discontinuation rate used in the model. The exponential and log-normal distributions were considered overly optimistic and not appropriate for the analysis. The company did provide a supporting analysis where post-treatment survival was estimated separately from treatment duration. This analysis produced a with PAS ICER of £50,165 with PAS.

- This analysis has been re-requested from the company as there is uncertainty regarding the overall survival for patients in the economic model and it has not been possible to examine the impact of using different parametric curves to estimate overall survival for ruxolitinib responders. If it not possible for the company to provide the analysis due to the issues outlined above, an alternative proxy sensitivity analysis has also been requested which decreases overall survival by 2 years. In addition the company has also been requested to provide a breakdown of the base case ICER of £57,847 in terms of quality of life gain, and life year gain for ruxolitinib versus best available therapy.

- The overall survival for patients initiated to best available therapy was estimated through a pooled analysis of the COMFORT studies adjusted for crossover. However the clinical data suggested that the overall survival for patients treated with best available therapy in the COMFORT- II study may be greater than that of the placebo patients treated in the COMFORT- I study. In addition the placebo patients that were included in the COMFORT- I study were not suitable for best available therapy and therefore there may be differences between this group of patients and the patients included in the best available therapy arm of the COMFORT- II study. As a result the overall survival estimates for best available therapy patients in the economic model may be underestimated as placebo patients that were associated with worse survival and not eligible for best available therapy were included in the estimates. The sensitivity analyses displayed that the results of the economic model were sensitive to changes in overall survival for best available therapy patients. The with PAS ICER increased to £66,226, £58,374 and £57,825 per QALY gained when using the COMFORT intention to treat cohort, a matched historical cohort and the lognormal curve respectively. The company did provide an analysis where OS for best available therapy patients was derived directly from patients in the COMFORT- II study. When the COMFORT- II data was adjusted for crossover the with PAS cost per QALY was estimated as £49,716 and when the ITT population was used the cost per QALY was reported as £56,962.

- Due to the model structure patients on best available therapy cannot experience an
improvement in disease status. This phase of treatment is reserved for patients on ruxolitinib only and therefore the improvements in utility and quality of life associated with this treatment phase are not accessible for best available therapy patients. Only patients receiving ruxolitinib could benefit from treatment and experience an improvement in their quality of life. The company provided a sensitivity analysis which explored potential uncertainty in model structure and where patients treated with best available therapy could experience an improvement in utility of 0.053. This analysis increased the ICER to £50,732 with PAS.

- Although the model did account for disease progression the analysis assumed that when patients discontinued ruxolitinib, they automatically moved to receiving best available therapy and could not move directly to the supportive or palliative care states of the model. The best available therapy state is associated with a controlling of the disease and then patients remain in this phase for as long as those patients who have not previously received ruxolitinib. If patients have ceased ruxolitinib treatment due to disease progression, this may however mean that benefits have been over-estimated. The company provided a sensitivity analysis where all patients that discontinued ruxolitinib moved directly to supportive care therefore experiencing immediate disease progression following discontinuation. This analysis produced an ICER of £50,612 with PAS.

- The utility values used in the base case were derived from a new condition-specific measure the MF-8D. Therefore the utility estimates were associated with uncertainty. In addition the utility value used in the model for those who responded to ruxolitinib is relatively large when compared to other values used in previous economic models. Sensitivity analyses were requested from the company which altered the utility values used in the analysis. When the gain in utility for the ruxolitinib responders was reduced by 10% this increased the with PAS ICER to £50,697 per QALY gained. In addition, when the change in utility for ruxolitinib non-responders was specified as 0, this increased the ICER to £49,924 per QALY gained. An analysis which reduced the utility gain for ruxolitinib responders by 0.037 and assumed no change in utility for the non-responders increased the ICER to £52,235.

The committee also considered the benefits of ruxolitinib in the context of the SMC decision modifiers and agreed that a number of the criteria were satisfied: a substantial improvement in quality of life; and the absence of other treatments of proven benefit. In addition, as ruxolitinib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

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

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

### Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from MPN voice, Leukaemia and Lymphoma Research and Leukaemia Care, which are all registered charities.
- All three charities have received pharmaceutical company funding in the past two years, including funds from the submitting company for MPN voice and Leukaemia Care.
- People with myelofibrosis in the later stages of the disease experience a variety of symptoms that affects all areas of their lives. The degree of fatigue in particular can render them unable to do many of the things in normal life making them dependent on family. The enlarged spleen can
cause pain as well as a sense of embarrassment as patients can look like they are in the late stages of pregnancy.

- Current treatments do not control the most severe symptoms such as enlarged spleen and fatigue. A bone marrow transplant is the only potentially curative treatment available but is not appropriate for most patients.
- Ruxolitinib, orally administered may reduce the most disabling symptoms such as enlarged spleen, pain and fatigue and could lead to less dependence on carers and a better quality of life for patients. It would also provide an alternative therapy option for patients who cannot undergo bone marrow transplant and who currently have no other treatment option.

**Additional information: guidelines and protocols**

The British Committee for Standards in Haematology (BCSH) published a guideline for the diagnosis and management of myelofibrosis in 2012.1

- In patients with symptomatic splenomegaly, medical treatment remains the treatment of choice.
  - First line options are: hydroxycarbamide (in the absence of cytopenia) or in the presence of cytopenia, immunomodulation with thalidomide and prednisolone. Lenalidomide should be considered if the platelet count is $>100 \times 10^9/L$ and the patient is anaemic.
  - Janus Associated Kinase (JAK) inhibitors are recommended second-line, either as part of a clinical trial or via expanded-access programmes.
- Constitutional symptoms such as fatigue, weakness, abdominal pain, weight loss, pruritis, night sweats and bone pain are difficult to manage and there is no evidence of benefit for conventional agents, therefore patients should be considered for experimental therapy with JAK inhibitors.
- Hydroxycarbamide is recommended as the first choice for the control of hyperproliferation manifestations of myelofibrosis.
- At the time of preparation of the guideline, JAK inhibitors did not have a marketing authorisation in the UK, and it was noted that “should these agents be approved then they would be considered as first-line agents for patients with troublesome splenomegaly and disease-related symptoms.”

The guideline was revised in 2014 following the award of a marketing authorisation for ruxolitinib.11 As a result of the findings of the COMFORT-II study, ruxolitinib is recommended as the first-line therapy for myelofibrosis-related constitutional symptoms and/or symptomatic splenomegaly. The guideline recommends that ruxolitinib is indicated (in descending order of strength of evidence):

- Symptomatic splenomegaly
- Myelofibrosis-symptoms that reduce quality of life
- Portal hypertension and hepatomegaly.

The guideline suggests that the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) may be a useful objective symptom monitoring tool that could be used in clinical practice. Factors to consider when deciding to continue ruxolitinib treatment include: symptomatic improvement, degree of benefit in splenomegaly, and the presence of haematological toxicity. While the clinical trials considered a spleen response to be a 50% reduction in palpable spleen length, it is acknowledged that this may differ in clinical practice and targets should be individualised.

**Additional information: comparators**

There are no currently available licensed treatments for myelofibrosis. Hydroxycarbamide is the predominant pharmacological treatment used for splenomegaly and other agents such as anagrelide, thalidomide, danazol are used to manage haematological manifestations of myelofibrosis. None are specifically licensed for use in myelofibrosis.
### Cost of relevant comparators

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<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
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<tr>
<td>Ruxolitinib</td>
<td>15mg to 25mg orally twice daily</td>
<td>43,680</td>
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<tr>
<td>Hydroxycarbamide**</td>
<td>15mg/kg orally daily and adjusted to response</td>
<td>38 to 152*</td>
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Doses are for general comparison and do not imply therapeutic equivalence. Cost of ruxolitinib from [www.MIMs.co.uk](http://www.MIMs.co.uk) on 31 October 2014. *Cost of hydroxycarbamide from eVadis on 03 October 2014 and based on dose 500mg to 2g daily. **Unlicensed use.

### Additional information: budget impact

The submitting company estimated there to be 26 patients eligible for treatment with ruxolitinib in year 1 and then 9 new incident patients in year 2 falling to 5 new incident patients in year 5. Assuming uptake rates of 70%-80% per year, the company estimated that 18 patients would be treated in year 1, 15 in year 2 and rising to 17 in year 5 and that some patients would continue to receive treatment over more than one year.

Without the PAS, the submitting company estimated the gross medicines budget impact to be £574k in year 1 and £665k in year 5. As other medicines were assumed to be displaced the net medicines budget impact was estimated to be £555k in year 1 and £647k in year 5.

*Other data were also assessed but remain commercially confidential.*
References

The undernoted references were supplied with the submission.


This assessment is based on data submitted by the applicant company up to and including 12 December 2014.

*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_Statements/Policy_Statements*

Drug 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 drug 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 NHS Scotland 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 NHS Scotland 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.