Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2421

ropeginterferon alfa-2b 250 micrograms/0.5 mL solution for injection in pre-filled pen (Besremi®)

AOP Orphan Ltd

8 April 2022

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 medicine process

ropeginterferon alfa-2b (Besremi®) is not recommended for use within NHSScotland.

Indication under review: as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly.

In a phase III study, ropeginterferon alfa-2b failed to demonstrate non-inferiority to hydroxycarbamide in treatment-naïve patients who required cytoreductive therapy and in patients who had a partial response to hydroxycarbamide.

The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

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

Chairman
Scottish Medicines Consortium

Indication

As monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly.

Dosing Information

The dose is titrated individually with a recommended starting dose of 100 micrograms by subcutaneous (SC) injection (or 50 micrograms in patients under another cytoreductive therapy). The dose should be gradually increased by 50 micrograms SC every two weeks (in parallel, other cytoreductive therapy should be decreased gradually, as appropriate) until stabilisation of the haematological parameters is achieved (haematocrit <45%, platelets <400 x 10^9/L and leukocytes <10 x 10^9/L). The maximum recommended single dose is 500 micrograms injected SC every two weeks. Phlebotomy as rescue treatment to normalise blood hyperviscosity may be necessary.

The dose at which stabilisation of the haematological parameters is achieved should be maintained in a two-week administration interval for at least 1.5 years. After that, the dose may be adapted and/or the administration interval prolonged up to every four weeks, as appropriate for the patient. Dose modification to manage adverse events and haematological parameters are detailed in the summary of product characteristics (SPC). Treatment should be initiated under supervision of a physician experienced in the management of the disease.[1]

Product availability date

November 2021.
Ropeginterferon alfa-2b meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Ropeginterferon alfa-2b is interferon alfa-2b conjugated with a two-arm methoxypolyethylene glycol (mPEG), that is, a pegylated interferon. It belongs to the interferon alfa class of medicines, which have inhibitory effects on proliferation of haematopoietic and bone marrow fibroblast progenitor cells and antagonise growth factors and other cytokines. These actions may be involved in the therapeutic effects of interferon alfa in polycythaemia vera.[1]

The submitting company has requested that SMC considers ropeginterferon alfa-2b when positioned for use in high-risk patients who are intolerant, resistant or who demonstrate an incomplete response to their first treatment option and require a second treatment option.

An open-label phase III study (PROUD-PV) recruited adults with polycythaemia vera (according to World Health Organisation [WHO] 2008 criteria) including JAK2V617F mutation of the tyrosine kinase janus-activated kinase-2 (JAK2). Treatment-naïve patients had a need for cytoreductive therapy and patients who had received hydroxycarbamide for less than three years could enter the study if they did not have a complete response, resistance or intolerance to hydroxycarbamide (that is, they had a partial response as defined by European Leukemia Net criteria). Randomisation

was stratified by previous hydroxycarbamide use, age (≤60 or >60 years) and prior thromboembolic events. Patients were equally assigned to 12 months' treatment with ropeginterferon alfa-2b SC every two weeks at a starting dose of 100 micrograms (or 50 micrograms in those transferred from pre-study hydroxycarbamide) or hydroxycarbamide orally at a starting dose of 500mg daily. In both groups doses increased until there was a complete haematologic response, defined as haematocrit <45% without phlebotomy and normal counts of leucocytes (<$10x10^9$/L) and platelets (<$400x10^9$/L). All patients received low dose aspirin 100mg once daily unless contraindicated. The primary outcome was a composite of complete haematologic response (as defined previously) and normal spleen size (longitudinal diameter ≤12cm for women and ≤13cm for men) at 12 months. This was assessed in the full analysis set (FAS), which comprised all randomised patients who received at least one dose of study treatment and had post-baseline data. Results in the FAS were expressed as a proportion of patients with 12-month data available. The study was originally designed to assess superiority, but was changed to non-inferiority at -10.5% margin prior to unblinding.[2,3]

Patients who completed PROUD-PV could opt to enrol in an open-label phase III 5-year extension study (CONTINUATION-PV) if they had normalisation (after moderately elevated baseline levels) or >35% reduction (after massively elevated baseline levels) in at least two of the three main blood parameters (haematocrit, platelets and white blood cells), normalisation of spleen size or clinical benefit (that is, normalisation of disease-related microvascular symptoms or substantial reduction in JAK2 allelic burden). Patients who had received ropeginterferon alfa-2b in PROUD-PV continued on this and patients who had received hydroxycarbamide received best available therapy selected by the investigator (at the latest analysis [36 months], 97% of patients in the best available therapy group were primarily treated with hydroxycarbamide). There was no formal hypothesis tested.[2,3]

In PROUD-PV, non-inferiority of ropeginterferon alfa-2b to hydroxycarbamide was not shown for the primary outcome at month 12, as the difference was -6.6% and the lower limit of the 95% confidence interval (CI), -17% to 4.1%, was outside -10.5% non-inferiority margin. More patients in the ropeginterferon alfa-2b group, compared with hydroxycarbamide, continued treatment in CONTINUATION-PV: 90% (95/106) versus 68% (76/111). Results from an interim analysis of CONTINUATION-PV when all patients had 36 months treatment (12 months in PROUD-PV and 24 months in CONTINUATION-PV) are detailed in Table 1.[2-5]

The majority of patients with polycythaemia vera (>95%) have a mutation (JAK2V617F or JAK2 exon 12 mutation) in JAK2. The proportion of mutant JAK2 alleles expressed as a percentage of the total (mutant plus wild-type) is the allelic burden. This was used to calculate the proportion of patients with molecular response, as detailed in Table 1, and in an indirect comparison that supported the economic analyses.[4,6]

Table 1: Outcomes of PROUD-PV and CONTINUATION-PV studies.[2-5]

	12 months		36 months	
	Ropeginterferon alfa-2b (N=127)	**Hydroxycarbamide (N=127)**	**Ropeginterferon alfa-2b (N=95)**	**Best available therapy (N=76)**
CHR + normal spleen	21% (26/122)	28% (34/123)	*	*
CHR	43% (53/123)	46% (57/125)	*	*
Normal spleen	36% (44/122)	49% (60/123)	*	*
Molecular response	34% (42/123)	42% (52/123)	*	*

CHR = complete haematological response, defined as haematocrit was <45% without phlebotomy and normal counts of leucocytes (<10x10^9/L) and platelets (<400x10^9/L). Normal spleen size, defined as longitudinal diameter ≤12cm for women and ≤13cm for men. Molecular response = complete or partial response on European Leukemia Net criteria, where complete response is defined as a reduction of any specific molecular abnormality to undetectable levels and a partial response is defined as (1) ≥50% reduction in patients with <50% allele burden at baseline OR (2) ≥25% reduction in patients with >50% allele burden at baseline. * marked confidential by company.

Health Related Quality of Life was assessed using Euroqol 5 dimension 3 levels questionnaire (EQ-5D-3L). At 12 months and 36 months, there were no notable differences between the groups in mean changes from total score and in visual analogue scale.[2,3]

The company proposed that ropeginterferon alfa-2b be positioned for use in high-risk patients who are intolerant, resistant or who demonstrate an incomplete response to their first treatment option and require a second treatment option. The subgroup of patients in PROUD-PV study who had previously had a partial response to hydroxycarbamide after ≤3 years' treatment (37% study population) are most representative of this positioning. In this subgroup, complete haematological response at 12 months was achieved in the ropeginterferon alfa-2b and hydroxycarbamide groups by 39% (18/46) and 32% (15/47) of patients, respectively.[3]

To support the economic analyses there was a naïve indirect comparison of ropeginterferon alfa-2b (data from PROUD-PV and CONTINUATION-PV)[2,3] versus ruxolitinib (data from RESPONSE)[6,7] for the proportion of patients with JAK2 allelic burden <50%. There were substantial differences in mean JAK2 allelic burden at baseline in the ropeginterferon alfa-2b and ruxolitinib groups: 42% versus 76%. Mean JAK2 allelic burden data at all time points in the ropeginterferon alfa-2b group was adjusted by multiplying by 1.82 (the relative difference in mean baseline JAK2 allelic burden [76%/42%]) and by an unclear method to adjust for age difference. These data and mean JAK2 allelic burden data from the ruxolitinib study were used to estimate the proportion of patients with a response, defined as JAK2 allelic burden <50%, at time-points through to week 156. These response data were applied within a naïve indirect comparison in the economic analyses.

Summary of evidence on comparative safety

The European Medicines Agency (EMA) review noted that the frequency and adverse events reported from PROUD-PV for ropeginterferon alfa-2b and hydroxycarbamide were in accordance with the established safety profiles of interferons and hydroxycarbamide. It considered the long-term safety profile of ropeginterferon alfa-2b was well characterised as knowledge can be

extrapolated from authorised interferon products. It noted that an established safety benefit of interferons compared with hydroxycarbamide is the absence of genotoxicity and carcinogenicity.[2]

In PROUD-PV within ropeginterferon alfa-2b and hydroxycarbamide groups treatment-emergent adverse events were reported by 82% (104/127) and 87% (111/127) of patients, respectively, and were treatment-related in 60% and 76% of patients. Serious adverse events were reported by 11% and 8.7% of patients in the respective groups. Common treatment-related adverse events within the ropeginterferon alfa-2b and hydroxycarbamide groups included haematologic adverse effects, such as anaemia (5.5% and 22%), leucopenia (8.7% and 21%) and thrombocytopenia (14% and 27%); hepatic adverse effects, such as elevations of liver enzymes (5.5% and 0), gamma-glutamyl-transferase (9.4% and 0) and alanine aminotransferase (5.5% and 0); gastrointestinal effects, including nausea (0.8% and 9.4%) and diarrhoea (3.1% and 5.5%); musculoskeletal adverse events (15% and 0.8%), including arthralgia (5.5% and 0) and myalgia (7.1% and 0); and other adverse events such as flu-like illness (5.5% and 0), pruritus (5.5% and 3.1%) and fatigue (7.9% and 6.3%).[2]

In PROUD-PV, adverse events of special interest included major disease-related cardiovascular and thromboembolic events. These were reported by 8.7% (11/127) and 5.5% (7/127) of patients in the ropeginterferon alfa-2b and hydroxycarbamide groups, respectively. Interferons are known to be associated with depression, anxiety and immunological adverse events. However, available data indicate no specific risk from ropeginterferon alfa-2b in comparison to other interferons.[2]

Summary of clinical effectiveness issues

Polycythaemia vera is a myeloproliferative neoplasm characterised by an excess production of erythrocytes, which is often accompanied by increases in leukocytes and platelets. The majority of patients (>95%) have a mutation (JAK2V617F or JAK2 exon 12 mutation) in the tyrosine kinase JAK2, which cause the enzyme to be constitutively active leading to overproduction of cell lines that express erythropoietin receptors. Clinical symptoms can be non-specific and related to increased blood cell count resulting in high blood viscosity, for example headache, fatigue, dizziness, vision disturbances, vertigo, tinnitus, pruritus, or erythromelalgia. The condition is long-term, debilitating and life-threatening as it is associated with increased risk of thrombosis, haemorrhage and a long-term propensity to develop myelofibrosis and secondary acute myeloid leukaemia. Diagnosis is primarily based on laboratory parameters such as increased haemoglobin or haematocrit and the presence of JAK2 mutations.[2]

The 2019 British Society of Haematology (BSH) guideline defines high-risk patients as those aged at least 65 years old and/or with prior polycythaemia vera-associated arterial or venous thrombosis, with some low-risk patients considered at higher risk in the presence of cardiovascular risk factors, elevated white blood cell count, extreme thrombocytosis or haematocrit uncontrolled with venesection. It notes that in the management of high-risk patients recommended first-line treatments are hydroxycarbamide or interferon (preferably pegylated interferon), with either of these used as second-line treatment in patients who did not receive the medicine first-line. Consideration can be given to the use of pegylated interferon as second line in those patients who have had non-pegylated interferon first-line and could not tolerate it. Ruxolitinib is recommended as second or third line treatment in hydroxycarbamide resistant or intolerant patients.

Ropeginterferon alfa-2b is the first interferon licensed for the treatment of polycythaemia vera. Interferon, including pegylated interferons, have been used off-label for treatment of polycythaemia vera for many years and have shown benefits in several clinical studies described in the BSH guidelines.[8]

PROUD-PV failed to demonstrate non-inferiority of ropeginterferon alpha-2b to hydroxycarbamide for the primary outcome complete haematological response with normal spleen size.[2,3] Both outcomes in this composite were achieved by fewer patients in the ropeginterferon alpha-2b group. Molecular response was achieved by fewer patients given ropeginterferon alpha-2b.[2,4,5]

The majority (68%) of patients in the PROUD-PV study were naïve to cytoreductive therapy and are not representative of the proposed positioning: in high-risk patients who are intolerant, resistant or who demonstrate an incomplete response to their first treatment option and require a second treatment option. The other 32% of patients in PROUD-PV, who had received previous treatment with hydroxycarbamide for less than three years and had a partial response to it (that is, not a complete response, resistance or intolerance), were most representative of the proposed positioning. In this subgroup, complete haematological response at 12 months was achieved by 39% (18/46) and 32% (15/47) of patients in the ropeginterferon alfa-2b and hydroxycarbamide groups respectively who had a partial response to hydroxycarbamide prior to study enrolment.[4]

After completing PROUD-PV, more patients in the ropeginterferon alfa-2b group, compared with hydroxycarbamide, continued treatment in CONTINUATION-PV: 90% (95/106) versus 68% (76/111). Median time to enrolment in CONTINUATION-PV was shorter in the ropeginterferon alfa-2b group compared with the hydroxycarbamide group: 14 versus 148 days, as the inclusion of the latter was made by a protocol amendment nine months after the first patient completed PROUD-PV. Selection bias in the CONTINUATION-PV enrolment is possible. There was no formal hypothesis tested in the CONTINUATION-PV study and results are descriptive.[2,3]

In the PROUD-PV study there was a prolonged dose titration phase in the ropeginterferon alfa-2b group, compared with hydroxycarbamide, with maximum median dose plateau level (end of titration phase) reached at week 28 and week 8, respectively. This may have contributed to reduced efficacy and incidence of adverse events with ropeginterferon alfa-2b compared with hydroxycarbamide. Some adverse events, such as haematotoxicity, are linked to the mechanism of action and efficacy. The SPC contains a warning that the recommended posology for the titration phase of ropeginterferon alfa-2b results in a prolonged time to reach optimal dose compared to hydroxycarbamide. Other products (for example, hydroxycarbamide) may be preferred in patients for whom an early reduction in elevated blood counts is necessary to prevent thrombosis and bleeding. During the titration phase, efficacy to reduce the cardiovascular and thromboembolic risk of the underlying disease may not be fully established. Patients should be closely monitored and phlebotomy as rescue treatment to normalise blood hyperviscosity may be necessary.[1,2]

There are limited data on long-term efficacy and safety. However, the EMA review noted that the long-term safety profile of ropeginterferon alfa-2b was well characterised as knowledge can be extrapolated from other interferon products. Also, as many clinical trials have characterised the efficacy of interferon alfa in polycythaemia vera, external validity for the use of interferons in this condition is high, but reflects off-label use.[2]

There was no comparison of ropeginterferon alfa-2b with other interferons, such as pegylated interferon alfa, that are recommended in BSH guidelines.[5] These have shown benefit in clinical studies, detailed in the BSH guidelines, and have been used off-label in practice for many years.

The naïve indirect comparison of ropeginterferon alfa-2b versus ruxolitinib, which supported the economic analyses, has a number of limitations. Study selection was based on the availability of data for mean JAK2 allelic burden, which is not one of the main clinical criteria used for disease management and was an exploratory outcome in the included studies. The BSH guidelines note that the clinical utility of JAK2 allelic burden is not well established. The ropeginterferon alfa-2b studies (PROUD-PV and CONTINUATION-PV) recruited patients who had a partial response to hydroxycarbamide (and excluded those with resistance or intolerance), whereas the ruxolitinib study (RESPONSE) only recruited patients with resistance or intolerance to hydroxycarbamide. Most patients in the ropeginterferon alfa-2b study had no splenomegaly, while all patients in the ruxolitinib study had splenomegaly and were phlebotomy-dependent. There was heterogeneity in other disease characteristics across the studies with the ropeginterferon alfa-2b group having earlier less severe disease. Most of the population in the ropeginterferon alfa-2b study was not representative of the positioning at second-line or later and patients in the ruxolitinib study were not reflective of the indication under review, which is in patients without symptomatic splenomegaly. Data from the ropeginterferon alfa-2b group were adjusted by age and baseline JAK2 allelic burden, but not by any other prognostic factors or treatment effect modifiers. The method of adjusting the ropeginterferon alfa-2b data for age was not clear. Due to these limitations, the company's results are highly uncertain.

The introduction of ropeginterferon alfa-2b would provide a licensed interferon alfa for treatment of polycythaemia vera. Clinical experts consulted by SMC suggest that it could be used as an alternative to peginterferon-alfa medicines currently used off-label in accordance with BSH guideline and as an alternative to ruxolitinib. Ropeginterferon alfa-2b is administered less frequently than other pegylated interferons: every 2 weeks versus 1 week.[1,7]

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

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 ropeginterferon alfa-2b, as an orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Polycythaemia vera is a chronic debilitating condition with a range of symptoms that can have life-changing effects, limiting patients' ability to take part in social, family and work activities. This can lead to social isolation and financial difficulties. Patients have an increased risk of thrombotic events and progression to myelofibrosis or acute myeloid leukaemia. Altogether, this can have a substantial negative psychological impact for the patient their family and friends.

- After first-line therapy (hydroxycarbamide), there are limited treatment option: other pegylated interferons (used off-label) and ruxolitinib. There is an unmet need for more treatment options.
- Ropeginterferon alpha-2b would increase the limited number of treatment options. Like other interferons, it can normalise blood counts leading to improvements in health and may reduce the proportion of cells with JAK2 mutations. The latter is considered to suggest a disease modifying effect, which patients value. Accessing ropeginterferon alpha-2b would provide reassurance that they have the optimum long-term treatment of their conduction and this could have a positive effect on their mental health. As blood counts normalise, the patient may feel better and be able to participate more in social, family and work activities. They may need fewer trips to the clinic.
- The alternative second-line treatment, ruxolitinib, has been associated with immunosuppression and increased risk of cancers and this is a particular concern for younger population who may have long-term exposure. In contrast, interferons are not expected to increase the risk of cancer.
- Some patients who have discontinued other interferons due to adverse events, report that ropeginterferon alpha-2b is more acceptable. Ropeginterferon alpha-2b has a less frequent dosing schedule than other interferons: every 2 to 4 weeks rather than every week. The PACE participants noted that, although ropeginterferon alpha-2b is not licensed for use in pregnancy, it may be the preferred choice from a limited number of options.
- As ropeginterferon alpha-2b is specifically licensed for polycythaemia vera, it may not be at risk of the potential access and supply issues with other interferons.
- The PACE participants also considered that ropeginterferon alpha-2b could be a useful first-line treatment option for some, particularly in younger patients and women of child bearing potential.

Additional Patient and Carer Involvement

We received patient group submissions from Leukaemia Care and MPN Voice, which are both registered charities. Leukaemia Care has received 14.3% pharmaceutical company funding in the past two years, with none from the submitting company. MPN Voice has received 37% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both 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 ropeginterferon alfa-2b with ruxolitinib in a sub-population of the licensed indication: adult patients with high-risk polycythaemia vera without symptomatic splenomegaly, who are intolerant, resistant or who demonstrate an incomplete response to their first treatment option and require a second

treatment option. This analysis was based on the PROUD-PV and CONTINUATION-PV studies[3] for ropeginterferon alfa-2b and the RESPONSE study[7] for ruxolitinib.

The analysis employed a cohort-based, state transition Markov model which comprised of four key health states: low JAK2 (<50), high JAK2 (≥50), disease progression and death. The disease progression health state was subdivided into three types of progression events: leukaemic transformation (also referred to as acute leukaemia in the submission), thrombosis and myelofibrosis.

Patients entered the model in the low JAK2 (<50) or high JAK2 (≥50) health state, with proportions determined by baseline JAK2 levels in the PROUD-PV and RESPONSE studies. At the end of each cycle, patients could remain in their JAK2 health state, transition to the alternative JAK2 health state, experience a progression event, or die.

The cycle length in the model was 13 weeks and no half-cycle correction was applied. Patients entered the model at 62 years of age and a lifetime horizon (24 years) was assumed. No adverse events were included in the model. The submitting company discounted the Markov trace by 3.5% per year to discount costs and benefits.

The submitting company adjusted JAK2 levels in the ropeginterferon alfa-2b arm to match the severity of patients in the RESPONSE study. This was done by adjusting for age and calculating the relative difference between the mean baseline JAK2 values (76%/42%=1.82). This relative difference (multiplier) was then applied to the baseline mean JAK2 value and the following mean JAK2 values until week 156. From week 156 and onwards, the submitting company assumed that the mean JAK2 level was at a constant level. Table 1 shows the percentage of patients with low JAK2 (<50) levels applied in the model.

Table 1. Percentage of low JAK2 (<50) applied in the base case analysis

Week	Percentage of low JAK2 (<50)		
	Ropeginterferon alfa-2b (unadjusted)	Ropeginterferon alfa-2b (adjusted)	Ruxolitinib (unadjusted)
Base line	69.3	29.7	30.7
13	73.3	38.6	34.7
26	78.2	46.5	38.6
39	81.2	51.5	42.6
52	83.2	56.4	45.5
65	85.1	60.4	45.5
78	88.1	64.4	47.5
91	91.1	71.3	48.5
104	94.1	78.2	50.5
117	93.1	77.2	54.5
130	93.1	76.2	58.4
143	93.1	79.2	61.4
156+	94.1	81.2	60.4

The submitting company identified studies which linked JAK2 levels to progression event risks. The studies and risks used to inform the base case analysis are summarised in Table 2.

Table 2. Cycle probabilities of progression events applied in the base case analysis

Progression event	Source	Cycle probability	
		JAK2 ≥50	JAK2 <50
Thrombosis	Alvarez-Larrán *et al.* 2014[9]	0.0090	0.0042
Myelofibrosis	Alvarez-Larrán *et al.* 2014[9]	0.0070	0.0003
Leukaemic transformation	Finazzi *et al.* 2005[10]	0.0007	0.0007

Additional sources were used to inform mortality due to progression events. General population mortality was applied to patients who had not progressed (that is, patients in the JAK2<50 and JAK2≥50 health states).

Discontinuation was estimated from the PROUD-PV and CONTINUATION-PV studies for ropeginterferon alfa-2b and from the RESPONSE study for ruxolitinib. Reasons for discontinuation included adverse events or lack of efficacy. The same discontinuation probability was applied to both JAK2 health states. Patients who discontinued treatment were assumed to revert to the baseline JAK2 level (as derived from RESPONSE), which was kept constant throughout the time horizon. It was also assumed that discontinued patients were treated with phlebotomy. These patients were still subject to the JAK2-based risks of progression as before discontinuing.

Health benefits were measured in quality adjusted life years (QALYs). Utility values in the low JAK2 (<50) and high JAK2 (≥50) health states were estimated directly from patients in the PROUD-PV and CONTINUATION-PV studies, using the EQ-5D-3L questionnaire (Table 3). Utility values in the progressed disease health states were obtained from the literature.

Table 3. Utility scores for non-progressive PV using patient level data from PROUD-PV and CONTINUATION-PV studies

JAK2 cut-off Total number of observations	JAK2 <50 (n=892)	JAK2 ≥50 (n=250)	Difference
EQ-5D utility mean (SD)	0.881 (0.152)	0.876 (0.148)	0.005 (p=0.6036)

Medicine costs covered ropeginterferon alfa-2b and ruxolitinib. In the base case analysis, the dose frequency of ropeginterferon alfa-2b was based on the average prescribed dosages for Scotland's leading key opinion leaders (12 pens per year). The dose frequency of ruxolitinib was based on the RESPONSE study. The submitting company also assumed that when patients take ruxolitinib more than 20mg daily, they will take the tablets twice daily (for example two 10mg tablets a day for a total of 20mg daily).

Patients who received ropeginterferon alfa-2b were assumed to incur a one-off cost to learn how to administer the medicine. No administration costs were assumed for ruxolitinib. The submitting company also included phlebotomy costs, monitoring costs and costs to treat leukaemic transformation, thrombosis and myelofibrosis (MF).

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. Under the PAS, a discount was offered on the list price.

A PAS discount is also in place for ruxolitinib and this was included in the results used for decision-making by using estimates of the comparator PAS price.

The results presented do not take account of the PAS for ruxolitinib or the PAS for ropeginterferon alfa-2b but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for ruxolitinib due to commercial confidentiality and competition law issues.

Table 4 shows the costs and benefits resulting from the base case analysis using list prices. In this base case analysis, ropeginterferon alfa-2b dominates ruxolitinib (ropeginterferon alfa-2b is less expensive and more effective than ruxolitinib).

Table 4. Base case results at list prices

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	NMB (WTP threshold £20,000/QALY)
Ruxolitinib	£430,448	9.94	-	-	-	-
Ropeginterferon alfa-2b	£196,822	10.09	-£233,626	0.15	Dominant	£236,567
Abbreviations: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality adjusted life year; WTP, willingness-to-pay						

The probabilistic results (10,000 simulations) were comparable to the deterministic results. The submitting company presented the top 10 most influential parameters in a tornado diagram and found that results were most sensitive to the long-term JAK2 level and JAK2 multiplier. Ropeginterferon alfa-2b continued to dominate ruxolitinib using high and low values for these parameters.

The submitting company also conducted several scenarios to assess the impact of alternative assumptions. The key scenarios provided by the submitting company related to the number of ropeginterferon alfa-2b pens a patient will use (12 pens was assumed in the base case). At 30.4 pens per year the incremental cost-effectiveness ratio (ICER) was £21,456. At 30.7 pens per year the ICER was £47,708. The dose received in PROUD-PV and CONTINUATION-PV was around 36 pens per year to achieve a dose of 385 micrograms every two weeks. The maximum observed limit in the study was 56.2 pens per year. This value provided an ICER of £2,279,119. Scenarios which used alternative sources to predict progression event risks and progression event mortality had a minimal impact on the results.

The major limitations of the economic analysis relate to the reliability of the clinical effectiveness data on JAK2 used to inform the model; the appropriateness of JAK2 as a model response parameter; and, the comparability of the modelling approach to the ruxolitinib appraisal (SMC2213). These issues are discussed below:

- Having a robust analysis of clinical effectiveness is fundamental to having reliable estimates of cost-effectiveness. As noted in the clinical effectiveness section above, the indirect comparison provided by the submitting company is highly uncertain and lacks robustness for decision-making. This was principally due to the extent of the clinical heterogeneity observed between the studies, lack of evidence for ropeginterferon alfa-2b in patients without a complete response, resistance or intolerance to hydroxycarbamide and use of data for ruxolitinib from a study (RESPONSE) in patients with splenomegaly. The populations in the ropeginterferon alfa-2b studies appeared to be at an earlier and less severe stage in their disease than the population in the ruxolitinib study, and the submitting company did not adjust for all treatment effect modifiers and prognostic factors in the indirect comparison. As such, cost-effectiveness results are likely to be biased and in favour of ropeginterferon alfa-2b.

- There are also major concerns regarding the model response parameter included in the indirect comparison. This was a laboratory type outcome (JAK2 level) that was translated into final outcomes (progression events) in the model. This resulted in layers of assumptions which adds a substantial amount of uncertainty to the cost-effectiveness results. The 2019 BSH guidelines[8] also note that "*Prospective analysis indicates that a JAK2 mutant allele burden of >50% is also associated with increased risk of MF (but not of AML or thrombosis) but the clinical utility of this measurement is not yet well-established*". As such, the model may not reliably estimate the cost-effectiveness of ropeginterferon alfa-2b for high-risk polycythaemia vera. More relevant model response parameters, such as haematological response, should have been considered.

- The submitting company's approach differs from the approach used in SMC2213. This economic evaluation of ruxolitinib employed a three-state partitioned survival model, with states of on-ruxolitinib, off-ruxolitinib (best available therapy) and death.

Additional scenarios to investigate other concerns were not requested from the submitting company given the fundamental flaws in the indirect comparison. Other shortcomings of the model include:

- There was no comparison of ropeginterferon alfa-2b with other interferons, such as pegylated interferon alfa, that are recommended in BSH guidelines.

- The submitting company separated costs and benefits in the model by using assumptions to inform the dose of ropeginterferon alfa-2b. The assumed dose in the base case was a lot lower than the dose received in PROUD-PV and CONTINUATION-PV. As presented above, the cost-effectiveness results were sensitive to changes in the assumed dose.

- The submitting company assumed myelofibrosis would be treated with ruxolitinib, as per NICE TA386.[11] This is a questionable assumption as patients in the ruxolitinib arm may not be re-treated with ruxolitinib in clinical practice.

- Patients in the JAK2 health states were only subject to general population mortality. This is a questionable assumption in a population with high-risk polycythaemia vera.

- Patients could only experience one type of progression event in the model.
- Utility values in the low JAK2 (<50) and high JAK2 (≥50) health states were above general population values and therefore lack face validity. Age-related utility decrements were also omitted from the model.
- In the model the discount rate was applied to the Markov trace and not the costs and benefits that result from the trace.
- To prevent over or under-estimation of costs QALYs, the submitting company should have included a half-cycle correction in the model. The submitting company should also have explored a 1-month cycle length as a 13-week cycle length could be too long to capture important changes in the health states of patients.

The Committee considered the benefits of ropeginterferon alfa-2b in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as ropeginterferon alfa-2b is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept ropeginterferon alfa-2b for use in NHSScotland.

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

Additional information: guidelines and protocols

The 2019 BSH guideline recommends cytoreductive therapy for certain low-risk patients and for all high-risk patients. In the management of high-risk patients recommended first-line treatments are hydroxycarbamide or interferon (preferably pegylated interferon), with either of these used second-line treatment in patients who did not receive the medicine first-line. Consideration should be given to the use of pegylated interferon as second line in those patients who have had non-pegylated interferon first-line and could not tolerate it. Ruxolitinib is recommended as second or third line treatment in hydroxycarbamide resistant or intolerant patients. Third and later line treatment options include busulfan or ^{32}P or pipobroman in those with limited life expectancy. Anagrelide in combination with hydroxycarbamide may be helpful in those where platelet control is difficult.[8]

Additional information: comparators

Other interferon alfa preparations, including pegylated interferon alfa, and ruxolitinib.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Ropeginterferon alfa-2b	50 to 500 microgram subcutaneously every two weeks	23,168 to 92,671

Costs from new product assessment form. Costs calculated using the full cost of pre-filled pen assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 4 patients estimated to receive treatment in year 1 rising to 13 patients in year 5.

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8. McMullin MR, Harrison CN, Ali S, et al. A guideline for the diagnosis and management of polycythaemia vera. A British Society for Haematology Guideline. Br J Haematol 2019: 184: 176–191.

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11. National Institute for Health and Care Excellence (NICE). Technology appraisal 386: Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis, 23 March 2016.

This assessment is based on data submitted by the applicant company up to and including 11 February 2022.

**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*

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.