SMC2563

ropeginterferon alfa-2b solution for injection in pre-filled pen (Besremi®)

AOP Orphan Ltd

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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 resubmission

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's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the 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.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Ropeginterferon alfa-2b is interferon alfa-2b conjugated with a two-arm methoxypolyethylene glycol. It belongs to the interferon-alfa class of medicines, which have inhibitory effects on proliferation of hematopoietic 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 (PV).[1]

In May 2022, SMC issued advice (SMC2421) following a full submission assessed under the orphan equivalent medicine process that ropeginterferon alfa-2b (Besremi®) is not recommended for use within NHSScotland in the indication under review.

Subcutaneous (SC) ropeginterferon alfa-2b is administered every 2 weeks, at a recommended starting dose of 100 micrograms (or 50 micrograms in patients on another cytoreductive therapy) and gradually increased by 50 micrograms every 2 weeks until stabilisation of the haematological parameters is achieved (haematocrit <45%, platelets <400x10^9/L and leukocytes <10x10^9/L); and the maximum recommended single dose is 500 micrograms every 2 weeks. The dose at which stabilisation of the haematological parameters is achieved should be maintained in a 2-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 4 weeks.[1]

1.2. Disease background

Polycythaemia vera is a myeloproliferative neoplasm characterised by an excess production of erythrocytes, which is often accompanied by increases in leukocytes and platelets. 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). 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.[2]

1.3. Company proposed position

The submitting company has requested that ropeginterferon alfa-2b is restricted for use in patients who are intolerant, resistant to or who demonstrate an incomplete response to treatment with hydroxycarbamide and require a subsequent treatment option.

1.4. Treatment pathway and relevant comparators

The 2019 British Society for Haematology (BSH) guideline advises that in the management of high-risk patients (and some low-risk patients) first-line cytoreductive PV 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.[3]

In December 2019, SMC issued advice (SMC2213) that ruxolitinib phosphate (Jakavi®) is accepted for use in the treatment of adult patients with PV who are resistant to or intolerant of hydroxyurea (hydroxycarbamide).

Ropeginterferon alfa-2b is the first interferon licensed for treatment of PV. Other interferons, including pegylated interferons, have been used off-label for treatment of this condition and are recommended in the BSH guideline, which details several clinical studies demonstrating benefit with interferons and pegylated interferons.[3]

The submitting company identified ruxolitinib as the only relevant comparator. Clinical experts consulted by SMC mentioned ruxolitinib as one of the treatment options for PV; however, they considered that interferons currently used off-label, such as pegylated interferon alfa-2a, are the treatments most likely to be displaced by ropeginterferon alfa-2b.

1.5. Category for decision-making process

Eligibility for a PACE meeting
Ropeginterferon alfa-2b meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of ropeginterferon alfa-2b comes from PROUD-PV and CONTINUATION-PV. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	PROUD-PV[2, 4, 5]	CONTINUATION-PV[2, 4, 6]
Study design	Open-label phase III study	Open-label phase III extension study
Eligible patients	• Adults with PV diagnosis according to the WHO 2008 criteria with mandatory presence of JAK2V617F mutation. • No history of cytoreduction with a documented need for cytoreductive therapy. • Previously treated with hydroxycarbamide for < 3 years with no complete response, resistance or intolerance to hydroxycarbamide according to modified European LeukemiaNet criteria.	Patients having completed PROUD-PV and who fulfilled at least one of the following criteria: • Normalisation of at least two out of three main blood parameters if these parameters were moderately increased (haematocrit <50%, white blood cells <20x10^9/L, platelets <600x10^9/L) at baseline of PROUD-PV, OR • >35% decrease of at least two out of three main blood parameters if these parameters were massively increased at baseline PROUD-PV, OR • Normalisation of spleen size, if spleen was enlarged at baseline of PROUD-PV, OR • Otherwise a clear, medically verified benefit from treatment with ropeginterferon alfa-2b
Treatments	12 months' treatment with: • ropeginterferon alfa-2b SC every 2 weeks at a starting dose of 100 micrograms (or 50	Up to month 72 (12 months in PROUD-PV and 60 months in CONTINUATION-PV): • patients who had received ropeginterferon alfa-2b in PROUD-PV

	micrograms in those transferred from pre-study hydroxycarbamide), or • hydroxycarbamide orally at a starting dose of 500mg daily. In both groups, evaluation for dose change was done every 2 weeks and doses increased until haematologic response, defined as haematocrit <45% without phlebotomy and normal counts of leucocytes (<$10x10^9$/L) and platelets (<$400x10^9$/L) (up to 500 micrograms ropeginterferon alfa 2b every 2 weeks or 3,000mg hydroxycarbamide daily).	continued on this (it was administered SC once every 2, 3 or 4 weeks according to the visit scheme) • patients who had received hydroxycarbamide could receive best available therapy selected by the investigator, which could include hydroxycarbamide, interferon, pegylated interferon (except ropeginterferon alfa-2b), anagrelide, a JAK2 inhibitor, phosphorus-32 or busulfan. In this group, 100% of patients received hydroxycarbamide at least once as the primary treatment for PV. At 72-months, 88% of patients still received hydroxycarbamide as primary treatment.
Randomisation	Patients were randomised equally, stratified for previous hydroxycarbamide exposure, age (≤60 or >60 years) and history of thromboembolic events	-
Primary outcome(s)	At 12 months, composite of: ○ complete haematological response (defined as haematocrit <45% with no phlebotomy in the past 3 months and normal counts of leucocytes [<$10x10^9$/L] and platelets [<$400x10^9$/L]) ○ and normal spleen size (longitudinal diameter ≤12cm for women and ≤13cm for men)	• Complete haematological response (as defined in PROUD-PV) and normal spleen size (as defined in PROUD-PV) • Complete haematological response (as defined in PROUD-PV) with improved disease burden (that is resolution and/or clinically improvement of disease-related signs (clinically significant splenomegaly) and disease-related symptoms (microvascular disturbances, pruritus, and headache).
Other outcome of interest	There were a number of secondary outcomes in both studies. From a clinical point of view, the key secondary outcome was considered to be: complete haematological response (as defined in the primary outcome [without spleen size])	
Statistical analysis	Efficacy was assessed in the 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. There was no statistical or clinical justification for the margin; differences between treatments and results for other outcomes need to be interpreted as exploratory only.	There was no formal hypothesis testing. Outcomes were assessed periodically in a descriptive manner.
Abbreviations: FAS = full analysis set, JAK2 = Janus kinase 2; PV = polycythaemia vera, SC = subcutaneous, WHO = World Health Organisation.		

In PROUD-PV, non-inferiority of ropeginterferon alfa-2b to hydroxycarbamide was not shown for the primary outcome at month 12 (the lower limit of the 95% confidence interval [-17% to 4.1%]

was outside the -10.5% non-inferiority margin). More patients who completed PROUD-PV in the ropeginterferon alfa-2b group, compared with hydroxycarbamide, continued treatment in CONTINUATION-PV (90% [95/106] versus 68% [76/111]). Results for the primary outcomes and other selected efficacy outcomes are detailed in Table 2.2. [2, 4-6]

Table 2.2. Primary and selected secondary outcomes of PROUD-PV and CONTINUATION-PV [2, 4-6]

	PROUD-PV		CONTINUATION-PV
	12-month data		72-month data
	Ropeginterferon alfa-2b (N=127)	Hydroxycarbamide (N=127)	Ropeginterferon alfa-2b (N=95)
Primary outcomes			
Complete haematological response and normal spleen size	21% (26/122)	28% (34/123)	37% (32/86)
Complete haematological response with improved disease burden	NA	NA	40% (35/88)
Other selected outcomes			
Complete haematological response	43% (53/123)	46% (57/125)	55% (48/88)
Molecular response[a]	34% (42/123)	42% (52/123)	47% (35/75)
Maintenance of complete haematological response over the entire treatment period	NA	NA	21% (20/95)

NA = not assessed.
[a]Molecular response = complete or partial response based on European Leukaemia 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.

2.2. Evidence to support the positioning proposed by the submitting company

In PROUD-PV, 32% (82/254) of patients had received previous treatment with hydroxycarbamide for less than 3 years and without complete response, resistance or intolerance. Subgroup analysis by previous hydroxycarbamide treatment indicated that, in PROUD-PV at 12 months, complete haematological response was achieved by 39% (18/46) and 32% (15/47) of patients in the ropeginterferon alfa-2b and hydroxycarbamide groups, respectively, who had received hydroxycarbamide prior to study enrolment.[4] In CONTINUATION-PV, the latest available subgroup analysis by previous hydroxycarbamide treatment are from month 60; complete haematological response (without spleen size criterion) was achieved by 61% (19/31) and 36% (9/25) of the few patients with available data in the ropeginterferon alfa-2b and best available therapy groups, respectively, who had previously received hydroxycarbamide.[7]

2.3. Health-related quality of life outcomes

Quality of life was assessed using EuroQol 5 dimension 3-level questionnaire (EQ-5D-3L). At 12 months and 72 months, there were no notable differences between the groups in mean changes from total score and in visual analogue scale [2, 6]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing ropeginterferon alfa-2b with ruxolitinib, the submitting company presented an indirect treatment comparison. They noted that the results of this comparison were not directly used to justify the cost-minimisation analysis in the economic

analysis; however, the proportion of patients achieving haematological control was used to inform the economic base case.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Unanchored naïve indirect comparison.
Population	Adults with polycythaemia vera.
Comparators	Ropeginterferon alfa-2b was compared with ruxolitinib.
Studies included	For ropeginterferon alfa-2b: PROUD-PV and CONTINUATION-PV studies.[4, 8] For ruxolitinib: RESPONSE study[9, 10], an open-label, multicentre phase III study which compared ruxolitinib with best available therapy, in adults with PV requiring phlebotomy for haematocrit control, a spleen volume of 450cm^3 or more, and no prior treatment with a JAK inhibitor, who had an inadequate response to or had unacceptable side effects with hydroxycarbamide.

Outcomes	Selected outcomes from each of the studies were naively compared. This included:
	• the primary outcome of each study, which was a composite of a measure of haematological response and spleen size; defined differently in each of the studies (in RESPONSE, the primary outcome was haematocrit control without phlebotomy [defined as ineligibility for phlebotomy from week 8 to 32 and no more than one instance of phlebotomy eligibility up to week 8] and a reduction of ≥35% in spleen volume at week 32).
	• haematological control, which was the key finding used in the economic analysis, combining different outcomes at different time points in the studies:
	  ○ in PROUD-PV, this was complete haematological response (defined slightly differently than in the study: haematocrit <45% without phlebotomy [at least 3 months since last phlebotomy], platelets ≤400x10^9/L , leukocytes ≤10x10^9/L), at month 6 (using individual patient data).
	  ○ in RESPONSE, this was haematocrit control without phlebotomy at week 32 (as defined for RESPONSE primary outcome).

Results	Results from different outcomes at different time points were presented narratively. • The composite primary outcome of haematological response and spleen size was achieved by 21% of patients in the ropeginterferon alfa-2b group at month 12 in PROUD-PV, by 37% of patients in the ropeginterferon alfa-2b group at month 72 in CONTINUATION-PV, and by 24% of patients at week 32 in the ruxolitinib group in RESPONSE. • Haematological control: haematocrit control without phlebotomy at week 32 was achieved by 60% of patients in the ruxolitinib group in RESPONSE.

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

3. Summary of Safety Evidence

Regulators noted that the frequency and adverse events (AEs) reported from PROUD-PV for ropeginterferon alfa-2b and hydroxycarbamide were in accordance with the established safety profiles of interferons and hydroxycarbamide. They considered the long-term safety profile of ropeginterferon alfa-2b was well characterised as knowledge can be extrapolated from authorised interferon products. They 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 AEs were reported by 82% (104/127) and 87% (111/127) of patients, respectively, and were treatment-related in 60% and 76% of patients. Serious AEs were reported by 11% and 8.7% of patients in the respective groups. Common treatment-related AEs within the ropeginterferon alfa-2b and hydroxycarbamide groups included hematologic 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 AEs (15% and 0.8%), including arthralgia (5.5% and 0) and myalgia (7.1% and 0); and other AEs 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, AEs 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 AEs. However, available data indicate no specific risk from ropeginterferon alfa-2b in comparison to other interferons.[2]

4. Summary of Clinical Effectiveness Considerations

The key strengths and uncertainties of the clinical case are summarised below:

4.1. Key strengths

- Ropeginterferon alfa-2b showed a cytoreductive effect, which is useful since PV is a disease without spontaneous remission. It was also considered that many clinical studies have characterised the efficacy of interferon-alfa in PV and external validity for the use of interferons in this condition is high.[2]

4.2. Key uncertainties

- There is no direct or indirect evidence comparing ropeginterferon alfa-2b with other interferons currently used off-label, such as pegylated interferon alfa-2a, that are recommended in BSH guidelines and were considered by clinical experts consulted by SMC as the treatments most likely to be displaced by ropeginterferon alfa-2b. There is high uncertainty around the relative efficacy and safety versus other pegylated interferons.
- In PROUD-PV, ropeginterferon alfa-2b failed to achieve non-inferiority to hydroxycarbamide for the composite primary outcome of complete haematological response with normal spleen size at 12 months; regulators suggested the loss of efficacy compared with hydroxycarbamide was not critical as phlebotomy can be used in the short term to compensate any lack of effect. Both outcomes in the composite primary outcome, as well as molecular response, were achieved by fewer patients in the ropeginterferon alfa-2b group, compared with the hydroxycarbamide group.[2, 4, 5]
- The study population was wider than the proposed positioning, and there are limited data available in the proposed positioning population. In PROUD-PV, only 32% of patients had previously received hydroxycarbamide.[2, 4, 5] There is uncertainty about the generalisability of the data from the overall study population to the proposed positioning population. The submitting company justifies that the overall population of PROUD-PV is representative of the proposed positioning population based on expert feedback; however, this assumption does not appear to be fully supported by expert feedback received by the submitting company.[11]

- The naïve indirect comparison of ropeginterferon alfa-2b versus ruxolitinib, from which only selected results were used in the economic analyses, has a number of limitations, including the methods used and potential selection bias. There was substantial methodological heterogeneity between the studies and substantial clinical heterogeneity in the study populations (including in terms of duration and severity of disease, previous experience with hydroxycarbamide). Most of the population in the ropeginterferon alfa-2b study was not representative of the proposed positioning in second- or later lines, and patients in the ruxolitinib study were not strictly reflective of the indication under review, which is in patients without symptomatic splenomegaly (all patients in the ruxolitinib study had splenomegaly). The submitting company compared only a few selected outcomes, including haematological control, which was discussed by comparing different outcomes across the studies; however, it is unclear whether the results are comparable. The submitting company did not provide a clear discussion or a definitive conclusion on the results. Due to these limitations, any interpretations, conclusions and results drawn from this naïve ITC are highly uncertain.
- There were several methodological issues with the key studies, which affect the interpretability of the results. PROUD-PV study was originally designed to assess superiority, but was changed to non-inferiority using an unjustified margin while the study was ongoing. It was considered that differences between treatments and results for outcomes, other than the primary outcome, could be interpreted in an exploratory sense only. After completing PROUD-PV, more patients in the ropeginterferon alfa-2b group, compared with hydroxycarbamide, continued treatment in CONTINUATION-PV. Median time to enrolment in CONTINUATION-PV was shorter in the ropeginterferon alfa-2b group compared with the hydroxycarbamide group (14 days versus 148 days), as the inclusion of the latter was made by a protocol amendment 9 months after the first patient completed PROUD-PV. Data from CONTINUATION-PV are subject to selection bias. In addition, there was no formal hypothesis tested in the CONTINUATION-PV study; results are descriptive only.[2, 4-6]
- There are limited data on long-term efficacy and safety of ropeginterferon alfa-2b. Regulators, however, had noted that the long-term safety and efficacy could be extrapolated from other interferon products.[2]

4.3. Clinical expert input

The introduction of ropeginterferon alfa-2b would provide a licensed interferon alfa for the treatment of PV. Clinical experts consulted by SMC suggested that it could be used mainly as an alternative to peginterferon alfa medicines currently used off-label in accordance with BSH guideline, and also as an alternative to ruxolitinib. Some clinical experts noted that in certain circumstances interferons may be preferred as first line (for example in patients of childbearing age).

Ropeginterferon alfa-2b is administered less frequently than other pegylated interferons alfa: every 2 weeks versus once weekly.[1, 2, 12]

5. 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 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 options: other pegylated interferons (used off-label) and ruxolitinib. There is an unmet need for more treatment options.
- Ropeginterferon 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 would provide reassurance that they have the optimum long-term treatment of their condition 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 is more acceptable. Ropeginterferon 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 is not licensed for use in pregnancy, it may be the preferred choice from a limited number of options.
- As ropeginterferon is specifically licensed for polycythaemia vera, it not be at risk of the potential access and supply issues with other interferons.
- The PACE participants considered that ropeginterferon would be a useful first-line treatment option, 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 27% pharmaceutical company funding in the past two years, with none from the submitting company. MPN Voice has received 30% pharmaceutical company funding in the past two years, with none 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.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

An economic case was provided and is summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-minimisation analysis.
Time horizon	5 years.
Population	The population was adult patients with high-risk PV who are refractory or intolerant to hydroxycarbamide.
Comparators	Ruxolitinib.
Model description	The model compared two arms, ropeginterferon alfa-2b and ruxolitinib. In both arms, a titration phase was included, where patients would be maintained on a dose if they achieved haematological control. Those who did not achieve haematological control at the maximum titrated dose would move to a subsequent treatment. In the ropeginterferon alfa-2b arm, patients would first receive ruxolitinib as a subsequent treatment, and if haematological control was not achieved, patients would then receive sub-optimal care. In the ruxolitinib arm, if patients failed to achieve haematological control, they would progress to receive sub-optimal care. Within the model, suboptimal care was comprised of 90% of patients receiving the maximum titrated dose of ruxolitinib and 10% receiving low cost best supportive care.
Clinical data	Clinical data were from PROUD-PV and CONTINUATION-PV for ropeginterferon alfa-2b ([4, 8]) and RESPONSE for ruxolitinib ([9, 10]). Individual patient level data from PROUD-PV at 6 months were used to generate the dosing distribution showing the percentage achieving haematological control (based on the outcome of complete haematological response) at each dose between 50-500 micrograms. Dosing and haematological control (based on the outcome of haematocrit control without phlebotomy) rates for ruxolitinib at week 32 were taken from RESPONSE ([9, 10]). The company clarified that the naïve indirect comparison described above was not directly used to justify comparable effects, as required for the cost-minimisation approach to be appropriate. The main justification for using cost-minimisation analysis was from an assumption that the treatment pathways within the model have negligible differences in patient health outcomes, supported by several statements from company clinical experts.
Extrapolation	The cost-minimisation model relied on existing data and no extrapolation was present.
Quality of life	Assumed the same in both arms, as from company expert elicitation, any potential for delay in haematological control by trialling ropeginterferon alfa-2b before ruxolitinib would not be anticipated to result in either poorer quality of life, or poorer longer-term health outcomes for patients.
Costs and resource use	Costs included medicine acquisition, adverse events, subsequent treatments and diagnostic testing. Resource use was estimated from clinician input.
PAS	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 alfa-2b due to commercial confidentiality and competition law issues.

6.2. Results

Results of the cost-minimisation analysis were provided for three periods. These were the titration period (62 weeks), a standardised year (once a stable dose is achieved), and five-year cumulative.

Table 6.2: Summary of base case results (list prices)

Arm	Titration period incr. cost		Standardised year incr. cost		5-year cumulative incr. cost	
	Total Cost	Incr. Cost	Total Cost	Incr. Cost	Total Cost	Incr. Cost
Ruxolitinib	£49,890	-	£43,849	-	£ 187,724	-
Ropeginterferon alfa-2b	£58,941	£9,051	£52,996	£9,146	£225,525	£37,801

Abbreviations: Incr, incremental.

6.3. Sensitivity analyses

Key scenarios are summarised in Table 6.3. The largest changes were observed when extending the ropeginterferon alfa-2b administration to 4 weeks, and when placing all patients on low cost best supportive care (BSC) for sub-optimal care.

Table 6.3: Scenario analysis (list prices)

	Base Case	Scenario	Titration period incr. cost	Standardised year incr. cost	5-year cumulative incr. cost
Base case	-	-	**£9,052**	**£9,146**	**£37,801**
1	4-week dose review frequency	2-week dose review frequency	£7,281	£9,146	£39,342
2	2-weekly dosing admin	4-weekly dosing admin	-£14,482	-£2,771	-£23,192
3	Start dose: 50 micrograms	Start dose: 250 micrograms	£14,629	£10,340	£50,120
4	Dose increase: 50 micrograms	Dose increase: 250 micrograms	£875	£3,037	£12,194
5	90% sub-optimal 10% BSC	100% BSC	£23,741	£9,146	£52,491
6a	Ropeginterferon alfa-2b dose distribution (% achieving control) at 6 months from Proud-PV (full population)	3 months Proud-PV	£6,606	£737	£8,923
6b		9 months Proud-PV	£9,193	£10,900	£43,454
6c		18 month CONTINUATION-PV	£10,671	£14,547	£56,396
7a	Ropeginterferon alfa-2b dose distribution (% achieving control) at 6 months from Proud-PV (full population)	3 months Proud-PV (HU exposed)	£6,935	£2,704	£15,433
7b		6 months Proud-PV (HU exposed)	£9,276	£9,612	£39,488
7c		9 months Proud-PV (HU exposed)	£9,498	£10,812	£43,483

7d		18 month CONTINUATION-PV (HU exposed)	£9,356	£11,193	£44,539

Abbreviations: BSC, best supportive care (busulfan); Incr, incremental; HU, hydroxycarbamide.

6.4. Key strengths

- The model structure facilitates adjustment to the starting dose, incremental dose, and dose review periods, reflecting the likely main contributors to cost.
- The clinical data used in the economic model were drawn from phase III studies.[4, 8-10]
- Patient level data were available for dosing distributions for haematological control in PROUD-PV and CONTINUATION-PV facilitating increased accuracy in costing.

6.5. Key uncertainties

- There was uncertainty in whether the cost-minimisation approach was appropriate. The submitting company's justification for using a cost-minimisation approach was based on an assumption that there would be a negligible difference in patient outcomes from the adjustment to the treatment pathway being proposed, based on expert feedback received by the company. Two noted aspects were that any potential impact on long-term health outcomes of trialling ropeginterferon alfa-2b prior to ruxolitinib would be negligible, and that potentially delayed haematological control from trialling ropeginterferon alfa-2b would not impact patient quality of life. While some SMC experts viewed the assumptions as reasonable, limiting factors were noted. Firstly, that if rapid achievement of haematological response is important there may be an impact on long- term health outcomes and quality of life. Secondly, that as patients will often need venesections until interferon 'kicks in' quality of life benefits may also be delayed. There were SMC experts that did not agree with this assumption, noting that it would not be sensible to assume a benign impact on quality of life when moving ruxolitinib to third line and introducing a second line treatment with side effects. One company clinical expert also expressed uncertainty with these aspects, noting that the use of phlebotomies for longer than 12 months to maintain haematological control may lead to a difference in patient outcomes.
- SMC clinical experts noted that (off-label) pegylated interferon would be most likely to be displaced by the introduction of ropeginterferon alfa-2b. Ruxolitinib was also noted as a treatment to be displaced, but by fewer SMC clinical experts. As pegylated interferon was not considered in the cost-minimisation analysis, there has been no demonstration of the economic case against a key comparator.
- As noted in the clinical effectiveness section above, there were issues with the representativeness of the clinical data to the company's proposed positioning. The potential loss of generalisability of the response data increased uncertainty in the cost results. Scenario analysis explored several dosing scenarios (Scenarios 2, 3, 4, 6 and 7). Although these may have been sufficient to support limited uncertainty in the cost results, a degree of uncertainty may remain if these scenarios were not sufficient to fully capture the uncertainty when using response data not reflective of the positioning.
- The dosing and response data for ruxolitinib were from the RESPONSE study, and were identified in the naïve indirect treatment comparison versus ropeginterferon alfa-2b (using outcome data from PROUD-PV and CONTINUATION-PV). There were a few limitations with this comparison as noted above, such as the patient populations were different between the studies and not entirely aligned with the proposed positioning. An unanchored naïve comparison was conducted to provide the best available estimate of comparative treatment

effect between ropeginterferon alfa-2b and ruxolitinib in the target patient population of PV patients who are either hydroxycarbamide resistant or intolerant. Statistical feedback highlighted areas of uncertainty with the naive comparison and suggested that an adjusted analysis could have been conducted, providing more complete information, facilitating a comparison with the naive results. Sensitivity analysis that varied the proportion successfully controlled with ruxolitinib, as well as the dosing proportions controlled with ropeginterferon alfa-2b (Scenarios 6 and 7), showed no changes to conclusions. However, a degree of uncertainty may remain if these scenarios were not sufficient to capture the noted uncertainties.

- The submitting company noted from clinical experience with ropeginterferon alfa-2b that no more than one to two pens would be used every 4 weeks and that after 1-2 years, the dose is expected to be reduced to once every 4 weeks. As a result, the company noted a conservative assumption for ropeginterferon alfa-2b acquisition costs. Scenario 2 considered 4 weekly administration for ropeginterferon alfa-2b where all annual pen usage for each dose was halved. However, in this scenario the annual pen reduction was also applied during the titration phase, which may have overestimated the savings from reduced pen use as it is unlikely that patients would be moved to 4-weekly dosing during this phase. Uncertainty therefore remained on the appropriate assumptions for ropeginterferon alfa-2b acquisition costs.

7. Conclusion

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 interferon alfa-2b for use in NHSScotland.

8. Guidelines and Protocols

Relevant guidelines for the treatment of patients with PV include:

- British Society for Haematology (BSH) 2019 guideline for the diagnosis and management of PV.[3]
- European LeukemiaNet 2021 recommendations on appropriate management of PV with cytoreductive drug therapy.[13]

9. Additional Information

9.1. Product availability date

30 November 2021

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Ropeginterferon alfa-2b	**50 to 500 micrograms SC every 2 weeks***	**23,168 to 92,671**

Costs from BNF online on 31 March 2023. Costs calculated using the full cost of pre-filled pen assuming wastage and accounting, as per the SPC, that a pre-filled pen may be used up to two times within 30 days. Costs do not take any patient access schemes into consideration.
** The administration interval can be prolonged up to every 4 weeks after 1.5 years of treatment.*

10. Company Estimate of Eligible Population and Estimated 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.

SMC is unable to publish the budget impact due to commercial in confidence issues.

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

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13. Marchetti M, Vannucchi AM, Griesshammer M, et al. Appropriate management of polycythaemia vera with cytoreductive drug therapy: European LeukemiaNet 2021 recommendations. Lancet Haematol. 2022;9(4):e301-e311. doi:10.1016/S2352-3026(22)00046-1.

This assessment is based on data submitted by the applicant company up to and including 12 May 2023.

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.