NCPE Assessment

Technical Summary

Ropeginterferon alfa-2b (Besremi®)

HTA ID 23004

15/08/24

Applicant: AOP Pharma

Ropeginterferon alfa-2b is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of ropeginterferon alfa-2b (Besremi®).

Following assessment of the Applicant's submission, the NCPE recommends that ropeginterferon alfa-2b (Besremi®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (AOP Pharma) Health Technology Assessment of ropeginterferon alfa-2b (Besremi®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In July 2023, AOP Pharma submitted a dossier of evidence which investigated the comparative clinical effectiveness, cost effectiveness and budget impact of ropeginterferon alfa-2b (Besremi®) as monotherapy in adults for the treatment of polycythaemia vera (PV) without symptomatic splenomegaly. AOP Pharma is seeking reimbursement of ropeginterferon alfa-2b on the high-tech drug arrangement. Ropeginterferon alfa-2b is a recombinant interferon alfa-2b conjugated with a two-arm methoxypolyethylene glycol. The ropeginterferon alfa-2b dose is titrated individually, starting at 100mcg (or 50mcg in patients under another cytoreductive therapy), and gradually increased by 50mcg over two weeks until stabilisation of the haematological parameters is achieved. The maximum recommended single dose is 500 micrograms injected every two weeks. After at least 18 months, the dose may be adapted and/or the administration interval prolonged up to every four weeks, as appropriate for the patient. Ropeginterferon alfa-2b has a longer half-life compared with conventional pegylated interferon alfa-2a allowing for subcutaneous administration every two to four weeks compared with weekly administration of pegylated interferon alfa. The standard of care for the treatment of PV without symptomatic splenomegaly, is hydroxyurea or pegylated interferon alfa-2a (unlicensed but widely used for PV), depending on patient characteristics. The Applicant anticipates that ropeginterferon alfa-2b will be used for adult patients over 60 years, with PV without symptomatic splenomegaly, who are intolerant, resistant to or who demonstrate an incomplete response to treatment with hydroxyurea and require a subsequent treatment option, as an alternative to ruxolitinib. This represents a narrow subgroup of the product license, and does not align with clinical opinion which indicates a preference to use ropeginterferon alfa-2b as an alternative first-line therapy, in younger patients. Ruxolitinib is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

1. Comparative effectiveness of ropeginterferon alfa-2b

The efficacy and safety of ropeginterferon alfa-2b, compared with hydroxyurea, was assessed in the PROUD-PV trial. This was an open-label, randomised, controlled, parallel-group, non-inferiority study comparing the safety and efficacy of ropeginterferon alfa-2b over hydroxyurea over 12 months. Ropeginterferon alfa-2b failed to show non-inferiority

with respect to the pre-specified primary efficacy endpoint outcome (complete haematological response and spleen size normality). Non-inferiority was demonstrated following a post-hoc change in the primary endpoint (to complete haematological response *without* spleen size normality, as significant splenomegaly was only present in a few patients at baseline). Given that PV is a disease without spontaneous remission, an absolute benefit of ropeginterferon alfa-2b compared with baseline was demonstrated. However, a robust assessment of comparative effectiveness versus hydroxyurea, on the basis of the PROUD-PV study, is not possible. A further limitation of the trial design was the conservative ropeginterferon alfa-2b dose titration, and early efficacy assessment. Exploratory results from the CONTINUATION-PV extension study (an extension study of PROUD-PV) indicated a similar efficacy for ropeginterferon alfa-2b as reported for interferon alpha in the literature. The Applicant's target population (HU resistant/intolerant) is represented by a minority of the PROUD-PV trial, and analysis of this subgroup was not pre-specified.

Direct comparative trials of ropeginterferon alfa-2b versus ruxolitinib or pegylated interferon alfa-2a, the other comparators of relevance to the submission, were not conducted by the Applicant. The Applicant submitted an indirect comparison of ropeginterferon alfa-2b versus ruxolitinib. Instead of conducting an anchored analysis (the preferred methodology for indirect comparisons) the Applicant provided an unanchored naïve comparison of ropeginterferon alfa-2b (using the ropeginterferon alfa-2b arm of PROUD-PV) and ruxolitinib (using the ruxolitinib arm of RESPONSE). The RESPONSE study was a randomized, open label, two-arm, multicentre, phase III study comparing the efficacy and safety of ruxolitinib to best-available therapy in patients with PV who are resistant to or intolerant of hydroxyurea. Considerable differences in key baseline demographics and disease characteristics are notable between the RESPONSE and PROUD-PV, as expected from the key differences in the enrolment criteria. The primary response outcomes investigated in both the PROUD-PV and RESPONSE trials were also defined differently. The Review Group considered that alternative evidence was available which could have facilitated a potentially more robust comparison. For the purposes of demonstrating comparative effectiveness, the Applicant selected "haematocrit control" as the outcome of greatest relevance on which to base a comparison of ropeginterferon alfa-2b and ruxolitinib. This is the primary outcome in the RESPONSE trial, and is similar to "Haematocrit <45% without phlebotomy" outcome in the PROUD-PV study. A naïve comparison would demonstrate that ruxolitinib is more effective on this outcome

(60% for ruxolitinib in the RESPONSE trial vs 45.2% for ropeginterferon alfa-2b in the PROUD-PV trial), however outcomes in the comparator arm were also very different between the studies (19.6% for best-available therapy in the RESPONSE trial vs 55.1% in the PROUD-PV study), and as mentioned throughout this section, differences between the trials limits the validity of any unadjusted comparison.

2. Safety of ropeginterferon alfa-2b

The most common adverse reactions in ropeginterferon alfa-2b clinical trials are leukopenia (20.2%), thrombocytopenia (18.5%), arthralgia (13.5%), fatigue (12.4%), increased gamma-glutamyltransferase (11.2%), influenza-like illness (11.2%), myalgia (10.7%), and anaemia (9.6%). Given the similarity of ropeginterferon alfa-2b to pegylated interferon, additional evidence on safety can also be extrapolated from previously authorised products. Patients should be closely monitored, particularly during the titration phase, when the efficacy to reduce the cardiovascular and thromboembolic risk of the underlying disease may not be fully established and phlebotomy may be necessary as a rescue treatment. Other products (e.g., hydroxyurea) may be preferred in patients for whom an early reduction in elevated blood counts is necessary to prevent thrombosis and bleeding. The absence of genotoxicity, carcinogenicity and leukogenic transformation potential is a relevant benefit over hydroxyurea for patients considering the long duration of treatment needed, particularly in younger patients and those of reproductive age. Regarding safety benefits over pegylated interferon, the absence of direct comparative evidence limits any conclusions that may be drawn, but it is expected that two-weekly administration schedule of ropeginterferon alfa-2b may be an advantage over weekly pegylated interferon injections, in terms of those adverse events which occur promptly after injection (e.g. flu-like illness, arthralgia, myalgia and fever).

3. Cost effectiveness of ropeginterferon alfa-2b

Methods

The cost-effectiveness of ropeginterferon alfa-2b was investigated by the Applicant in a sub-population of the licensed population, as described. The model submitted by the Applicant was primarily structured as a cost-minimisation model, although utility decrements for

adverse events were also considered. The validity of the model is limited by the omission of PV symptoms or other aspects of disease burden which are expected to impact on health related quality of life (HRQoL), such as thromboembolic events. Haematocrit control is considered only indirectly in the model through dosing and treatment switching assumptions, and does not impact HRQoL. The assumption of utility equivalence across different states of haematocrit control lacks clinical plausibility and is a serious limitation of the Applicant's model. A cost-minimisation approach, in the absence of a robust comparative effectiveness analysis indicating equivalent treatment effects, is not considered to be appropriate by the NCPE Review Group.

In the model, patients are assumed to start on a low dose of treatment followed by a period of upwards dose titration: of either ruxolitinib (up to maximum 25mg daily over 22 weeks) or ropeginterferon alfa-2b (up to maximum 500 micrograms every two weeks over 40 weeks). At the end of the dose titration period, patients who do not achieve haematocrit control are assumed to switch treatments (from ropeginterferon alfa-2b to ruxolitinib, and from ruxolitinib to best-supportive care). It is not clear if this reflects treatment switching in clinical practice. Longer-term discontinuations are not modelled. The cost-effectiveness model is highly sensitive to assumptions regarding treatment discontinuation and switching.

The proportions of patients achieving haematocrit control, the dosing distribution, and adverse events were informed by data from the PROUD-PV trial for ropeginterferon alfa-2b and the RESPONSE trial for ruxolitinib. Adverse events are included in the model, but only during the dose titration phase. The model does not consider the risk of progressing to myelofibrosis or leukaemia.

There were errors in the model which were corrected by the Review Group. The results of the corrected Applicant base case indicate that ropeginterferon alfa-2b is more costly and less effective than ruxolitinib (Table 1).

Results

Table 1: Corrected Applicant base case incremental cost-effectiveness results [a,b,c,d]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Ruxolitinib	504,646	8.063	-	-	-
Ropeginterferon alfa-2b	603,182	8.062	98,536	-0.001	Dominated (less effective, more costly)

QALY=Quality-adjusted life year; ICER: incremental cost effectiveness ratio

[a] Figures in the table are rounded, and so calculations may not be directly replicable.

[b] The Review Group corrected drug costs for ropeginterferon alfa-2b and ruxolitinib, and logic errors in the model.

[c] A commercial-in-confidence PAS applies to ruxolitinib, not included in this table.

[d] The Results in the uncorrected Applicant's model are as follows: total costs of ropeginterferon alfa-2b are €31,228.45 ***less*** than the total costs of ruxolitinib; the total QALYs with ropeginterferon alfa-2b are 0.001 ***less*** than the total QALYs of ruxolitinib – indicating that ropeginterferon alfa-2b is less costly and less effective than ruxolitinib.

Despite the Review Group's corrections to the errors in the Applicant's model, the reliability of these results is still highly uncertain given the limitations of the model structure and the supporting assumptions. These limitations cannot be addressed by the inclusion of alternative data, or feasible changes to the model structure, and the specification of an NCPE-adjusted base case was therefore not appropriate.

The probabilistic analysis in the model provided by the Applicant in response to the NCPE Preliminary Review did not function correctly. Therefore, probabilistic results are not presented.

4. Budget impact of ropeginterferon alfa-2b

The price to wholesaler for a ropeginterferon alfa-2b pen (250 micrograms/0.5 mL solution) is €1,848.15. The total cost of ropeginterferon alfa-2b or ruxolitinib per patient depends on a number of factors including dose, duration of use, and potential ropeginterferon alfa-2b wastage (due to the restriction on the use of a ropeginterferon alfa-2b pen only twice). The Applicant estimated a ropeginterferon alfa-2b usage of 20 pens per year, costing €46,704 (€37,523 excluding VAT). The annual cost of ruxolitinib is estimated to vary within an estimated range of €22,228 and €43,551 (no VAT on oral medicines), assuming a daily dose of 20mg per day (approximated from the median dose of ruxolitinib observed in the RESPONSE 2 study) up to 26.7mg per day (estimated by the Applicant). The total yearly cost of pegylated interferon alfa-2a, based on an estimated mean daily dose of 89.4mg is €10,226

(€8,332 excluding VAT). The Applicant submitted a budget impact model estimating the population of eligible patients and the proportion expected to receive treatment with ropeginterferon alfa-2b. The budget impact model has been reviewed by the NCPE Review Group, however many of the inputs are very uncertain and there is therefore considerable uncertainty associated with the budget impact estimates. The Applicant predicted that 16 patients will be treated in Year 1 rising to 49 patients in Year 5, resulting in a 5-year cumulative gross drug budget impact of €7.2 million (€5.8 million excluding VAT). The NCPE Review Group considered the gross drug budget impact could be much higher, up to €13.5 million (€10.8 million excluding VAT) due to the Applicant's underestimation of the eligible population, overestimation of the annual discontinuation rate and overestimation of the rate of switching to four-weekly dosing. The Applicant's estimated net drug budget impact resulted in some cost offsets due to the displacement of ruxolitinib. If less costly therapies such as pegylated interferon alfa-2a are displaced, the cost-offsets may be much less than estimated by the Applicant. The gross and net drug-budget impact is expected to be considerably higher if ropeginterferon alfa-2b is also used in the first-line setting, as an alternative to pegylated interferon alfa-2a.

5. Patient Organisation Submission

A patient organisation submission was received from MPN Voice.

6. Conclusion

The NCPE recommends that ropeginterferon alfa-2b not be considered for reimbursement, unless cost effectiveness can be improved relative to existing treatments*.

Ropeginterferon alfa-2b has demonstrated clinical efficacy in the licensed population, and is an additional treatment option for patients with PV in the licensed population. However, a robust assessment of added therapeutic benefit, through comparative-effectiveness analysis, compared with standard-of-care in the first-line setting (compared with hydroxyurea or pegylated interferon alfa-2a), or in subsequent lines of therapy (compared with hydroxyurea, pegylated interferon alfa-2a or ruxolitinib) has not been submitted. The

proposed positioning of ropeginterferon alfa-2b, solely as an alternative to ruxolitinib, and only in the second-line setting, does not align with expected clinical practice in Ireland. For the Applicant's proposed positioning of ropeginterferon alfa-2b, the Applicant's cost-effectiveness model is not considered to be fit-for-purpose, due to the absence of key comparators, the omission of important clinical outcomes, the reliance on a number of very uncertain assumptions, and the use of the cost-minimisation approach in the absence of robust evidence of comparative-effectiveness. No evidence has been submitted by the Applicant to justify a price-premium of ropeginterferon alfa-2b compared with standard-of-care.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.