HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

16 DECEMBER 2020

The legally binding text is the original French opinion version

ropeginterferon alfa-2b

BESREMI 250 micrograms/0.5 ml solution for injection in pre-filled pen

First assessment

Key points

Unfavourable opinion for reimbursement as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly.

Role in the care pathway?

In the absence of a curative treatment, the objective of treatments for polycythaemia vera is to minimise the morbidity and mortality associated with the disease, represented by sometimes bothersome symptoms, vascular complications (primarily thrombosis) and a risk of haematological progression to secondary myelofibrosis or acute myeloid leukaemia. The severity of the symptoms and the risk of vascular complications are correlated with haematocrit control.

Phlebotomy combined with antiplatelet therapy are the emergency treatments following discovery of the disease in order to quickly lower haematocrit levels. These have an immediate action on the thrombosis risk by reducing blood viscosity. In the long term, they induce iron deficiency, inhibiting erythropoiesis, which must be respected. Maintenance of long-term phlebotomy treatment is restrictive and it is no longer considered to be a maintenance therapy.

As maintenance therapy, the first-line chemotherapy treatment for polycythaemia vera (PV) is hydroxyurea (HYDREA). The usually effective initial dose is 500 mg/d orally. Once normalised (apart from MCV, which increases constantly under the effect of hydroxyurea), and after modification of the initial dose if necessary (over a few months), the blood count remains stable for a long period, meaning

that laboratory monitoring can be conducted at three-month intervals with an annual specialist opinion. It is usual to have to progressively increase the dose in increments, due to a reduction in initial efficacy. At doses of over 1.5 g/day, the medicinal product is less well tolerated. The development of dyskeratosis of the face, mouth ulcers and, especially, ulcers on the ankles (related to the cumulative total hydroxyurea dose), which are very painful and resistant to all symptomatic treatments, are formal indications for discontinuation of treatment. The same is true in the event of absence of control of polyglobulia, high platelet counts or even hyperleukocytosis, despite increasing doses of the medicinal product. In this event, splenomegaly, which had generally disappeared following normalisation of the blood count, may recur.

As second-line therapy, following the failure of hydroxyurea, pipobroman (VERCYTE) and ruxolitinib (JAKAVI) are the two recommended alternatives with an MA. The choice of treatment should be made based on the patient's profile.

Ruxolitinib is primarily indicated in patients resistant or intolerant to hydroxyurea with splenomegaly.

Pipobroman may be preferentially used in elderly patients, in these situations of intolerance or resistance. It generally enables normalisation of the blood count. It is recommended that this medicinal product be avoided in young patients, since it is an alkylator with a leukaemogenic potential.

The NNCN 2020 American guidelines and the ESMO 2015 European guidelines, as well as the ELN 2018 guidelines, cite interferon-α (including in its PEGylated form) as one of the alternatives to hydroxyurea for first and second-line treatment when a cytoreductive treatment needs to be initiated, particularly in the youngest patients and/or when a pregnancy is planned.

Role of the medicinal product in the care pathway

Considering:

- the numerous methodological limitations (modification of the objective, non-inferiority threshold and primary endpoint during the study) of the open-label, randomised phase 3 PROUD-PV study, having evaluated the efficacy and safety of ropeginterferon alfa-2b,
- the results of this study, which did not enable a conclusion to be reached concerning the non-inferiority of ropeginterferon alfa-2b compared to hydroxyurea (clinically relevant comparator) for the primary endpoint (complete haematological response after 12 months defined by the achievement of 3 laboratory criteria and a normal spleen size),
- the limited experience in view of the disease progression time,
- the lack of a predefined statistical hypothesis in the analysis plan for the CONTINUATION-PV study, not enabling a conclusion to be reached with respect to the effect size or role of BESREMI in the care pathway,

the Transparency Committee considers that, on the basis of currently available data, BESREMI (ropeginterferon alfa-2b) has no role in the care pathway for polycythaemia vera without symptomatic splenomegaly.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Polycythaemia vera causes short-term complications (thrombosis) and long-term complications (conversion to acute leukaemia or myelofibrosis), which can be life-threatening.

◗ BESREMI (ropeginterferon alfa-2b) is a curative treatment.

◗ In the absence of data of acceptable methodological quality providing evidence of its non-inferiority for a clinically relevant endpoint compared to hydroxyurea (clinically relevant comparator) and given its short-term safety profile and uncertainties with respect to its long-term safety, the efficacy/adverse effects ratio of BESREMI (ropeginterferon alfa-2b) has not currently been adequately established.

◗ There are alternatives. For the first-line treatment of adults with polycythaemia vera, there is a therapeutic alternative: hydroxyurea, which has an MA, and interferon alfa (off-label). In second-line therapy, i.e. in patients resistant or intolerant to hydroxyurea, the alternatives are ruxolitinib (JAKAVI), pipobroman (VERCYTE) and interferon alfa (off-label).

◗ BESREMI (ropeginterferon alfa-2b) has no role in the care pathway for polycythaemia vera (see section 08).

Public health impact

Considering:

- the seriousness of the disease. Polycythaemia vera (PV) is a serious and incapacitating chronic disease, that can be complicated by thromboembolic events, in particular, and is liable to progress to myelofibrosis or acute leukaemia,
- its incidence and prevalence (rare disease). PV has an estimated annual incidence of around 1/36,000 to 1/100,000 and a prevalence of 1/3,300 (Orphanet),
- the partially met medical need,
- the lack of response to the identified need, in the absence of demonstration of an additional impact on morbidity and mortality (non-inferiority not demonstrated compared to hydroxyurea) and on quality of life.
- the lack of expected impact on the organisation of care,

BESREMI (ropeginterferon alfa-2b) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of BESREMI (ropeginterferon alfa-2b) is insufficient to justify public funding cover in the MA indication in view of the available alternatives.

The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the MA indication and dosages.