HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
16 FEBRUARY 2022

The legally binding text is the original French opinion version

pegcetacoplan
ASPAVELI 1,080 mg solution for infusion

First assessment

Key points

Favourable opinion for reimbursement in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months, only in the event of haemoglobin levels <10.5 g/dL.

Unfavourable opinion for reimbursement in the other clinical situations of the MA.

What therapeutic improvement?

Therapeutic improvement in management of the disease.

Role in the care pathway?

The treatment of paroxysmal nocturnal haemoglobinuria (PNH) is currently based on eculizumab (SOLIRIS), blood transfusions in the event of severe anaemia and other symptomatic treatments without a validated indication in the treatment of PNH, such as anticoagulants.

Eculizumab (SOLIRIS), a complement inhibitor, is the only medicinal treatment with a reimbursed indication in PNH. This medicinal product is only reimbursed in adults with a history of transfusions. Although it has an MA in children and adults without a history of transfusions, eculizumab is not reimbursed in these populations, since the pharmaceutical company has not applied for its inclusion in the list.

Bone marrow transplantation is currently the only treatment that can cure PNH but is only indicated in the event of associated severe bone marrow failure or myelodysplastic syndrome due to the complexity and risks associated with this procedure. If eculizumab treatment fails, allogeneic haematopoietic stem cell transplantation can sometimes be envisaged but these cases are very rare. In patients who have not responded to eculizumab treatment and who are not eligible for transplant, management is based on transfusions alone.

It should be noted that ravulizumab (ULTOMIRIS) has been granted an MA in adult patients with PNH who are complement inhibitor treatment-naïve or in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months. Ravulizumab has no marketing authorisation in patients not having responded to eculizumab. To date, ravulizumab is not yet available on the French market in the absence of publication of a reimbursement rate and price in the French Official Journal, despite having received a favourable opinion for reimbursement from the Transparency Committee in September 2020.

Role of ASPAVELI (pegcetacoplan) in the care pathway:

Considering demonstration of the superiority of treatment with pegcetacoplan compared to the continuation of eculizumab in terms of increase in haemoglobin after 16 weeks, with a substantial effect size, in a restricted MA population, i.e. PNH patients who are anaemic, with Hb levels <10.5 g/dL despite treatment with eculizumab for at least 3 months, transfusion-dependent or otherwise, ASPAVELI (pegcetacoplan) is a second-line treatment in adult patients who are anaemic after treatment with a C5 inhibitor for at least 3 months, only in the event of haemoglobin levels <10.5 g/dL.

However, ASPAVELI (pegcetacoplan) has no role in the treatment of PNH in other clinical situations, due to a lack of data.

Its administration as a subcutaneous infusion makes home infusion and self-administration possible for patients who have tolerated treatment well in specialised treatment centres.

It should be noted that episodes of haemolysis that were serious and/or led to treatment discontinuation have been reported following the switch from eculizumab to pegcetacoplan. The severity of these episodes may be partially explained by the expansion of the PNH clone under C3 inhibitor treatment, according to expert opinion. Close monitoring with respect to this risk is therefore necessary in clinical practice.

Finally, insofar as ASPAVELI (pegcetacoplan) is a complement protein C3 inhibitor that increases the patient's predisposition to meningococcal infection or septicaemia due to its mechanism of action, the Transparency Committee reiterates that its prescription must be combined with vaccination against meningococcal infections using the ACYW conjugated tetravalent vaccine and the serogroup B invasive meningococcal infection vaccine, in accordance with the current SPC and subject to the opinion of the French High Council for Public Health (HCSP).

The Summary of Product Characteristics (SPC) and the Risk Management Plan (RMP) must be complied with.

This medicinal product is not recommended during pregnancy and in women of childbearing potential not using contraception (see SPC).

Special recommendations

Given the specificities of treatment of this rare disease, the Committee recommends that decisions to initiate or discontinue pegcetacoplan treatment be taken after a documented proposal resulting from a multidisciplinary team meeting within a reference or expert centre for the treatment of PNH. Regular follow-up of patients within one of these centres is essential to ensure the efficacy of treatment and monitor its safety, with particularly close monitoring in terms of the risk of the occurrence of episodes of haemolysis and thrombotic events.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Paroxysmal nocturnal haemoglobinuria (PNH) is a rare (orphan disease) and serious condition caused by an acquired clonal mutation affecting all the haematopoietic cell lines. The disease is polymorphous but is usually manifested (90% of patients) by haemolysis due to the sensitivity of red blood cells to the haemolytic action of the complement. Episodes of haemolysis with haemoglobinuria primarily occur at night, as a result of the reduction in blood pH. The disease course is variable and can be life-threatening due to its complications: thromboembolic events (responsible for 40 to 67% of deaths), haemorrhages, infections, kidney and bone marrow failure.

◗ The proprietary medicinal product ASPAVELI (pegcetacoplan) is a preventive medicinal product.

◗ The efficacy/adverse effects ratio of ASPAVELI (pegcetacoplan) in the treatment of PNH in adult patients with anaemia following C5 inhibitor treatment for at least 3 months is:

- high only in the event of haemoglobin levels <10.5 g/dL, in view of the available data and the inclusion criteria for the PEGASUS study,
- not established in the other clinical situations due to a lack of clinical data.

◗ There are few therapeutic alternatives in adult patients with anaemia following C5 inhibitor treatment for at least 3 months (see section 05 of the opinion):

- in the event of Hb levels <10.5 g/dL: RBC transfusions may be proposed.
- in other clinical situations: the continuation of SOLIRIS (eculizumab), and ULTOMIRIS (ravulizumab)

◗ In adult patients with anaemia following C5 inhibitor treatment for at least 3 months**,** ASPAVELI (pegcetacoplan) is a second-line treatment, only in the event of Hb levels <10.5 g/dL.
ASPAVELI (pegcetacoplan) has no role in the treatment of PNH in other clinical situations.

Public health impact

Considering:

- the seriousness of the disease, which can be life-threatening due to its complications,
- its low prevalence (orphan disease),
- the partially met medical need,
- the additional partial response to the identified need only in the event of haemoglobin levels <10.5 g/dL, with:
    - an additional impact demonstrated on morbidity only (haemoglobin levels),
    - the lack of demonstrated impact on quality of life in the absence of robust data,
- the lack of demonstrated impact on the organisation of care and the patient's life pathway, in the absence of data,

ASPAVELI (pegcetacoplan) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that, in the treatment of PNH in adult patients with anaemia following C5 inhibitor treatment for at least 3 months, the clinical benefit of ASPAVELI (pegcetacoplan) is:
- Substantial, only in the event of haemoglobin levels <10.5 g/dL.
- Insufficient in the other clinical situations of the MA.

The Committee issues the following opinions:

- **a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months, only in the event of haemoglobin levels <10.5 g/dL.**
- **an unfavourable opinion for public funding cover in the other MA situations.**

- **Recommended reimbursement rate: 65%**

Clinical Added Value

Within the scope of sufficient clinical benefit: adult patients who have anaemia with haemoglobin levels <10.5 g/dL after treatment with a C5 inhibitor for at least 3 months

Considering:

- demonstration of the superiority of ASPAVELI (pegcetacoplan) compared to the continuation of eculizumab in terms of the improvement in haemoglobin levels after 16 weeks in patients with haemoglobin levels <10.5 g/dL after treatment with a stable dose of eculizumab for at least the previous 3 months,
- the substantial effect size demonstrated for this relevant endpoint, with a difference of +3.84 g/dL in favour of pegcetacoplan,

And despite:

- the absence of any available superiority analysis with respect to the need for transfusions given the discontinuation of the ranked analysis before this endpoint, with only non-inferiority having been demonstrated for this endpoint,
- the absence of long-term comparative data, in particular enabling assessment of the impact of pegcetacoplan in comparison with eculizumab on the occurrence of thrombotic events, the leading cause of death in these patients,
- the more frequent occurrence of serious haemolysis (4.9% vs 2.6% during the randomised period) or haemolysis having led to treatment discontinuation (7.3% vs 0) in the pegcetacoplan group after switching from eculizumab to pegcetacoplan,
- the absence of a demonstrated benefit on patients' quality of life,

the Transparency Committee considers that **ASPAVELI (pegcetacoplan) provides a moderate clinical added value (CAV III) in the therapeutic strategy for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months, only in the event of haemoglobin levels <10.5 g/dL.**