OPINION RELATIVE TO MEDICINAL PRODUCTS

ravulizumab

ULTOMIRIS 100 mg/ml

Concentrate for solution for infusion, 300 mg/3 ml and 1,100 mg/11 ml vials

New indication

Adopted by the Transparency Committee on 29 June 2022

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SUMMARY

The legally binding text is the original French opinion version

- **Paroxysmal nocturnal haemoglobinuria**
- **Sector: Hospital**

Key points

Favourable opinion for reimbursement of ULTOMIRIS (ravulizumab) in the treatment of paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH):

– in patients with haemolysis with clinical symptom(s) indicative of high disease activity;
– in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.

What therapeutic improvement?

Therapeutic improvement in the management of paroxysmal nocturnal haemoglobinuria (PNH) in children.

Role in the care pathway?

In children, the treatment of paroxysmal nocturnal haemoglobinuria is currently based on eculizumab (SOLIRIS) to prevent haemolysis, 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 validated indication in PNH in children. Although it has an MA in children and adults without a history of transfusions, eculizumab has not been evaluated by the Committee in these populations.

Bone marrow transplantation is currently the only treatment that can cure PNH but is only indicated in the event of associated severe aplastic anaemia 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.

In the paediatric population with PNH, considering the frequent link with aplastic anaemia, and the better prognosis of this procedure in children and young adults, bone marrow transplantation should be favoured in patients aged < 18 years with severe aplastic anaemia or myelodysplastic syndrome. In the event of severe aplastic anaemia associated with a PNH clone and the absence of a possible allogeneic bone marrow transplant, immunosuppressive therapy with antilymphocyte serum combined with ciclosporin should be favoured (PNDS).

Role of the medicinal product in the care pathway

ULTOMIRIS (ravulizumab) is a complement inhibitor that has demonstrated non-inferior efficacy to that of SOLIRIS (eculizumab) in terms of control of haemolysis and need for transfusions, in adult patients naïve to complement inhibitor treatment and as a switch from eculizumab (SOLIRIS) in clinically stable patients treated for at least 6 months.

To date, there is no demonstrated benefit of ULTOMIRIS (ravulizumab) compared to SOLIRIS (eculizumab) in terms of efficacy and safety, particularly for the risk of thromboembolic events, a major cause of death in paroxysmal nocturnal haemoglobinuria.

In children and adolescents, the results of the pharmacokinetic and pharmacodynamic study conducted in this population with ravulizumab suggest a comparable efficacy and safety profile to that described in adults.

The administration regimen for ULTOMIRIS (ravulizumab) offers the advantage of a long interval between doses, with an infusion every 8 weeks. An improvement in the care conditions for patients is therefore expected with ULTOMIRIS (ravulizumab), although its benefit in terms of improving quality of life remains to be confirmed.

Considering these elements, the Committee deems that ULTOMIRIS (ravulizumab) is a first-line treatment in the management of paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria:

- in complement inhibitor naïve patients,
- as a switch from eculizumab (SOLIRIS) in clinically stable patients treated for at least 6 months.

The Committee reiterates that ravulizumab (ULTOMIRIS) has no marketing authorisation in patients not having responded to eculizumab.

Insofar as ULTOMIRIS (ravulizumab) is a complement protein C5 inhibitor that increases the patient's predisposition to meningococcal infection or septicaemia due to its mechanism of action, the Transparency Commission 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, and/or prophylactic antibiotic therapy, in accordance with the 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.

The use of this medicinal product in pregnant or breast-feeding women must comply with the SPC (http://lecrat.fr/).

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 disease can affect people of all ages, but it particularly affects young adults (median of around 30-40 years). It is rare in children under 15 years of age.
- ULTOMIRIS (ravulizumab) is a preventive treatment for haemolysis.
- The efficacy/adverse effects ratio is high.
- There is currently a medicinal therapeutic alternative, eculizumab (another complement inhibitor).
- This is a first-line treatment in paediatric patients with a body weight of 10 kg or above naïve to complement inhibitor treatment or as a switch from eculizumab (SOLIRIS) in clinically stable patients treated for at least 6 months.

Public health benefit

Considering:

- the seriousness of the disease, which can be life-threatening due to its complications,
- its very low prevalence in children and adolescents,
- the partially met medical need,
- the partial response to the identified need, with an impact on morbidity and mortality that remains to be demonstrated in the paediatric population (pharmacokinetic and pharmacodynamic study conducted in children and adolescents for which the results suggest an impact of ravulizumab on morbidity and mortality similar to that described in adults),
- the expected impact on the organisation of care and the expected improvement of the patient's care pathway, due to the administration conditions for the medicinal product (reduced frequency of administration with infusions every 8 weeks), but the absence of demonstration of an improvement in quality of life,

ULTOMIRIS (ravulizumab) is unlikely to have a public health benefit.

Considering all these elements, the Committee deems that the clinical benefit of ULTOMIRIS (ravulizumab) is substantial in the treatment of paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH):

- in patients with haemolysis with clinical symptom(s) indicative of high disease activity;
- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the treatment of paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH) and at the MA dosages.

Clinical Added Value

Considering:

- very limited data in children and adolescents in paroxysmal nocturnal haemoglobinuria (PNH) based on the results of a non-comparative study having included 13 patients aged 9 to 17 years and pharmacokinetic and pharmacodynamic data from this study; but supported by results suggesting a similar clinical response to treatment with ravulizumab between the adult and paediatric populations and by data previously obtained in adults in PNH and in adults and children in aHUS,
- a short-term safety profile globally similar to that observed in adults, but with uncertainties with respect to long-term safety,
- the medical need partially met by eculizumab (SOLIRIS),
- the administration conditions for the medicinal product (reduced frequency of administration with infusions every 8 weeks),

the Transparency Committee considers that, as in adults, ULTOMIRIS (ravulizumab) provides **a minor clinical added value (CAV IV) compared to SOLIRIS (eculizumab)** in the treatment of paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH):

- in patients with haemolysis with clinical symptom(s) indicative of high disease activity;
- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.