SUMMARY

ravulizumab

ULTOMIRIS 300 mg/3 ml and 1100 mg/11 ml,

concentrate for solution for infusion

Reassessment

Adopted by the Transparency Committee on 26 April 2023

The legally binding text is the original French opinion version

Key points

Favourable opinion for maintenance of reimbursement in the “treatment of atypical haemolytic uremic syndrome (aHUS)”.

Role in the care pathway?

ULTOMIRIS (ravulizumab) is a first-line therapy in the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab (SOLIRIS) for at least 3 months and have evidence of response to eculizumab. However, in the absence of a direct comparison with eculizumab, the role of ravulizumab cannot be determined compared to this medicinal product.

The Committee highlights that ULTOMIRIS (ravulizumab) has no marketing authorisation in patients not having responded to eculizumab, or in children with a body weight of under 10 kg, in contrast with SOLIRIS (eculizumab), which has an MA from 5 kg.

ULTOMIRIS (ravulizumab) is a complement protein C5 inhibitor that, due to this mechanism of action, increases the patient’s predisposition to infections caused by encapsulated bacteria, in particular meningococcal infection/septicaemia (Neisseria meningitidis). Consequently, 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 current vaccination schedule guidance.

The Committee recommends that prophylactic antibiotic therapy be implemented for all patients requiring ravulizumab, as for eculizumab, in accordance with the 2021 French national diagnostic and care protocol (PNDS): long-term prophylactic antibiotic therapy with full-dose phenoxymethylpenicillin as two doses per day (or macrolides in the event of allergy) from the start

of treatment, to be continued throughout treatment and for 60 days following its discontinuation (until normalisation of CH50 in children). Vaccination of close relatives may be discussed in transplant patients, in whom a weak or nil vaccine response is possible.

Committee's conclusions

Clinical benefit

- Atypical haemolytic uremic syndrome (aHUS) is a very rare genetic or acquired disease leading to the absence of alternative complement pathway regulation in 60% of cases. It is a very severe disease that can result in serious complications affecting various organs due to complement-mediated thrombotic microangiopathy, particularly in the kidneys, with progression to end-stage kidney disease. Atypical HUS can be life-threatening in the short term. It also significantly impairs the quality of life of patients and their families.
- ULTOMIRIS 300 mg (ravulizumab) concentrate for solution for infusion is a curative medicinal product.
- The efficacy/adverse effects ratio is high.
- This medicinal product is a first-line therapy in the treatment of atypical haemolytic uremic syndrome (aHUS) in adults and children with a body weight of 10 kg or above who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab. However, in the absence of a comparison with eculizumab, the role of ravulizumab cannot be determined compared to this medicinal product (see chapter 08 Role in the care pathway).
- There is currently a medicinal therapeutic alternative, eculizumab (another complement inhibitor).

- **Public health benefit:**

Given:

- the seriousness of the disease, which is life-threatening due to its complications,
- its very low prevalence,
- the partially met medical need,
- the lack of additional response to the identified partially met medical need, due to the absence of robust comparative data versus eculizumab enabling assessment of the additional impact of ravulizumab on morbidity and mortality,
- the expected impact on the organisation of care and the patient's care or life pathway, of having access to a treatment making it possible to increase the interval between infusions compared to eculizumab (every 8 weeks or every 4 weeks for children weighing from 10 to under 20 kg, instead of every 2 weeks),
- the lack of robust evidence of an impact on quality of life,

ULTOMIRIS 300 mg (ravulizumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ULTOMIRIS 300 mg/3 ml and 1,100 mg/11 ml (ravulizumab) concentrate for solution for infusion becomes substantial in the MA indication.

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indication and at the MA dosages.

Clinical added value

Considering:

- the partially met medical need in a disease that is life-threatening in the absence of treatment,
- the potential, but not demonstrated, benefit in terms of patients' quality of life and care pathway, of having access to a treatment making it possible to increase the interval between infusions compared to eculizumab (every 8 weeks or every 4 weeks for children weighing from 10 to under 20 kg, instead of every 2 weeks),
- the clinical responses obtained with ravulizumab for a clinically relevant endpoint, complete response in terms of thrombotic microangiopathy (TMA), and the maintenance of these responses up to week 104, in patients naïve to complement inhibitor treatment (60% adult responders and 18/20 responders in the children/adolescents),
- maintenance of LDH and haemoglobin levels up to week 104 in children/adolescents treated with ravulizumab having previously responded to at least 3 months of treatment with eculizumab,

but considering:

- the low level of evidence of ravulizumab's efficacy demonstration of based on two non-comparative clinical studies and including a small number of patients,
- the absence of direct comparative between ravulizumab and eculizumab, another complement C5 inhibitor considered to be the reference first-line treatment for the last ten years,
- persistent uncertainties with respect to the long-term efficacy and safety,

the Transparency Committee deems that ULTOMIRIS (ravulizumab) continues to provide no clinical added value (CAV V) compared to current management in the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS), which includes SOLIRIS (eculizumab), who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.