SUMMARY

iptacopan

FABHALTA 200 mg

hard capsules

First listing

Adopted by the Transparency Committee on 9 October 2024

Summary of opinion

Favourable opinion for reimbursement only in "the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have symptomatic haemolytic anaemia after treatment with a C5 inhibitor for at least 6 months".

Unfavourable opinion for reimbursement in the other situations covered by the MA indication.

Transparency Committee's conclusions

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 occur primarily at night, as a result of a 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 FABHALTA (iptacopan) is a preventive medicinal product.
- The efficacy/adverse effects ratio of FABHALTA (iptacopan) in the treatment of PNH is:
  - High in adult patients with symptomatic haemolytic anaemia after treatment with a C5 inhibitor for at least 6 months;
  - Inadequately established in the treatment of adult patients with haemolytic anaemia who have not had previous treatment with a complement inhibitor, in the absence of robust comparative data versus the currently recommended reference treatment in this population (C5 complement inhibitor), in a context in which a direct comparative study would have been feasible, meaning that it is not possible to exclude the possibility of a loss of opportunity for patients treated with iptacopan rather than a C5 complement inhibitor.
  - Not established in the other clinical situations due to a lack of clinical data.
- There are currently medicinal therapeutic alternatives:
  - ASPAVELI (pegcetacoplan) is a therapeutic alternative in adult patients with persistent haemolytic anaemia after treatment with a C5 inhibitor; the proprietary medicinal product

VOYDEYA (danicopan) is authorised but not available to date (see section 2.2 of the opinion);

- The C5 inhibitors SOLIRIS (eculizumab) and ULTOMIRIS (ravulizumab) are therapeutic alternatives in patients with haemolytic anaemia who have not had previous treatment with a complement inhibitor.

➔ In adult patients with PNH and haemolytic anaemia, FABHALTA (iptacopan):

- Is a second-line treatment, only in patients with symptomatic haemolytic anaemia after treatment with a C5 inhibitor for at least 6 months.
- Has no role in the other clinical situations of the MA, particularly in patients who have not had previous treatment with a complement inhibitor.

➔ Public health benefit

Considering:

- the seriousness of the disease, which is life-threatening due to its complications,
- its low prevalence (orphan disease),
- the partially met medical need,
- the partial response to the identified need only in the event of residual haemolytic anaemia despite treatment with a C5 inhibitor for at least 6 months, given:
  - a demonstrated additional impact in this population only on morbidity and compared to continuation of treatment with a C5 inhibitor, with no demonstration versus ASPAVELI (pegcetacoplan), noting that they were developed concomitantly,
  - the substantial expected impact on the care pathway of these patients due to the methods of administration of iptacopan (oral administration of two doses per day versus SC administration of two infusions per week with storage in the refrigerator for pegcetacoplan), although this has not been demonstrated to date,
  - the lack of evidence of an additional impact on morbidity and mortality or on quality of life compared to the current reference treatment using a C5 inhibitor in patients who have not had previous treatment with a complement inhibitor,

FABHALTA (iptacopan) is likely to have an additional impact on public health only in patients with residual symptomatic haemolytic anaemia after treatment with a C5 inhibitor for at least 6 months.

Considering all of these elements, the Committee deems that the clinical benefit of FABHALTA 200 mg (iptacopan) hard capsules is:

- **substantial only in "the treatment of adult patients with PNH who have symptomatic haemolytic anaemia after treatment with a C5 inhibitor for at least 6 months";**
- **insufficient to justify public funding in view of the available alternatives in the other MA situations.**

The Committee issues the following opinions:

- **A favourable opinion for inclusion of FABHALTA 200 mg (iptacopan) hard capsules in both the list of covered drugs for outpatients and the list of covered drugs for inpatients approved for use only within the scope retained and at the MA dosages.**
- **An unfavourable opinion for inclusion of FABHALTA 200 mg (iptacopan) hard capsules in both the list of covered drugs for outpatients and the list of covered drugs for inpatients approved for use in the other situations covered by the MA indication.**

Clinical Added Value

Considering:

- evidence of the superiority of iptacopan versus continuation of a C5 inhibitor (ravulizumab or eculizumab) after 24 weeks of treatment, in terms of increase in haemoglobin levels, reduction in transfusion needs and reduction in episodes of haemolysis, in adult patients with PNH who have residual haemolytic anaemia after treatment with a C5 inhibitor for at least 6 months,
- the clinical relevance of these endpoints and the high effect size observed for haemoglobin levels and transfusion needs, which seems more modest for reduction of episodes of haemolysis (annualised rate of clinical breakthrough haemolysis of 0.07 versus 0.67) in a context where the history of episodes was not known,

and despite:

- a possible overestimation of the benefit observed, as it cannot be ruled out that some patients in the control group were not receiving optimised treatment with a C5 inhibitor in accordance with French practice,
- the absence of comparative data beyond 24 weeks in a context of chronic disease with potentially lifelong treatment, in order to be able to assess maintenance of the benefits and safety profile of iptacopan in the long term, along with its impact on the incidence of thrombotic events, the leading cause of death in patients,
- the absence of a demonstrated benefit on patients' quality of life,
- the absence of robust comparative data versus pegcetacoplan, a treatment already available as second-line therapy after a C5 inhibitor, in particular the absence of a direct comparison, which would nonetheless have been justified on the date of the present assessment given their concomitant development; to date, it cannot be assumed that there is a lower risk of serious haemolysis with iptacopan than with pegcetacoplan, in view of their similar mechanisms of action,

the Committee deems that FABHALTA 200 mg (iptacopan) hard capsules provides a moderate clinical added value (CAV III) in the treatment of adult patients with PNH who have symptomatic haemolytic anaemia after treatment with a C5 inhibitor for at least 6 months, in the same way as ASPAVELI (pegcetacoplan).