FERINJECT (ferric carboxymaltose), iron preparation

**Main points**

- FERINJECT has an MA for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The clinical data obtained in adults with symptomatic heart failure with reduced left ventricular ejection fraction and iron deficiency (defined in the study as: serum ferritin < 100 µg/l or serum ferritin between 100 and 299 µg/l and transferrin saturation < 20%), with or without anaemia, do not modify its high clinical benefit in the MA indication and the absence of clinical added value compared to other injectable iron preparations.

- In symptomatic heart failure with reduced left ventricular ejection fraction, it is a first-line treatment in the event of iron deficiency with or without anaemia, defined as serum ferritin < 15 µg/l (WHO definition) or assumed due to serum ferritin < 100 µg/l and transferrin saturation < 20% in a context of biological inflammatory syndrome. Long-term treatment is not recommended in these patients.

- In adults with symptomatic heart failure with reduced left ventricular ejection fraction and serum ferritin between 100 and 299 µg/l and transferrin saturation < 20%, it is not recommended.

- All causes of iron deficiency and all curable or reversible causes of inflammation must be investigated before treating iron deficiency with iron supplementation.

**Therapeutic strategy**

- All causes of iron deficiency and all curable or reversible causes of inflammation must be investigated before treating iron deficiency with iron supplementation. The diagnosis of iron deficiency must be based on appropriate laboratory tests.

- Oral iron preparations have not demonstrated their efficacy in the treatment of iron deficiency in patients with heart failure.

- The use of injectable iron preparations is proposed on the basis of studies conducted with ferric carboxymaltose in patients with serum ferritin < 100 µg/l or serum ferritin between 100 µg/l and 299 µg/l and transferrin saturation < 20%, with or without anaemia, on the basis of functional criteria. However, a robust demonstration of efficacy on hospitalisations and cardiovascular deaths is required in order to make a strong recommendation concerning the use of injectable iron in heart failure patients. Although they are accepted by learned societies in the field of cardiology, these serum ferritin thresholds are not validated by scientific data with a high level of evidence.

- **Role of the medicinal product in the therapeutic strategy**

  FERINJECT is a first-line treatment in adults with symptomatic heart failure with reduced left ventricular ejection fraction combined with iron deficiency, with or without anaemia. This iron deficiency can be confirmed by serum ferritin < 15 µg/l (WHO definition of iron deficiency) and assumed by serum ferritin < 100 µg/l and transferrin saturation < 20% in a context of biological inflammatory syndrome.

  Given the absence of a clearly established serum ferritin threshold value to diagnose absolute iron deficiency in the event of inflammation related to heart failure, of morbidity and mortality data (hospitalisations, cardiovascular deaths) and of long-term safety data, long-term treatment is not recommended in these patients.

  In the event of serum ferritin between 100 and 299 µg/l and transferrin saturation < 20%, in the absence of conclusive data concerning functional clinical criteria and morbidity and mortality (hospitalisations and...
cardiovascular deaths), and in terms of long-term safety (risk of iron overload), injectable iron supplementation is not recommended.

Clinical data

- Ferric carboxymaltose solution for injection has been evaluated in three studies (two placebo-controlled studies and one study versus standard of care) in adults with symptomatic heart failure with reduced left ventricular ejection fraction and serum ferritin < 100 µg/l or serum ferritin between 100 and 299 µg/l and transferrin saturation < 20%, with or without anaemia. The results demonstrated the modest effects of ferric carboxymaltose solution for injection compared to placebo on Patient Global Assessment score, heart failure severity and the 6-minute walk test, and a non clinically relevant effect compared to standard of care for peak oxygen uptake during exercise (VO₂ max).
- No efficacy of ferric carboxymaltose for injection has been demonstrated in terms of reduction of hospitalisations and cardiovascular deaths. Ferric carboxymaltose has not been compared with other injectable irons.
- These studies do not enable differentiation between the efficacy of ferric carboxymaltose in patients with established iron deficiency (serum ferritin < 15 µg/l) and its efficacy in patients with serum ferritin between 15 and 99 µg/l with transferrin saturation < 20% (iron deficiency possible in the event of inflammatory syndrome, or in patients with serum ferritin between 100 and 299 µg/l and transferrin saturation < 20% (iron deficiency doubtful). Randomisation was not stratified on the basis of this criterion and the great majority of patients (around 90%) had serum ferritin < 100 µg/l with a median of 40 to 50 µg/l.
- No long-term efficacy and safety (risk of iron overload) data are available.

Special prescription requirements

- Medicinal product for hospital use only

Benefit of the medicinal product

- The clinical data for FERINJECT in heart failure do not modify the Committee’s previous opinions in terms of actual clinical benefit (high) clinical added value (absence compared to other injectable irons) for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.

HAS

This document was drafted on the basis of the Transparency Committee opinion dated 20 February 2019 (CT-16716) available at www.has-sante.fr

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to “no clinical added value”) denotes a “lack of clinical improvement”.

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