HAUTE AUTORITÉ DE SANTÉ

HAEMATOLOGY
New indication
April 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

FERRIPROX (deferiprone), iron chelator

High clinical benefit combined with deferoxamine (DESFERAL) in thalassaemia major, when monotherapy with a different iron chelator is ineffective, or when iron overload is life-threatening, and minor clinical added value compared to deferoxamine monotherapy.

Insufficient clinical benefit combined with deferasirox (EXJADE) to justify its reimbursement for this same indication.

Main points

- FERRIPROX has been granted marketing authorisation in combination with another iron chelator in the treatment of thalassaemia major, when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction.
- For this indication, the superiority of the FERRIPROX/deferoxamine (FERRIPROX/DESFERAL) combination compared to deferoxamine (DESFERAL) monotherapy has been demonstrated in cardiac iron overload, though not for long-term survival due to a lack of robust data.
- The clinical benefit of the FERRIPROX/deferasirox (FERRIPROX/EXJADE) combination has not been established, due to insufficient clinical data to document its efficacy and safety and due to the contraindication of EXJADE in combination with other iron chelators.

Pre-existing indication*

FERRIPROX has already been granted marketing authorisation for the treatment of iron overload in monotherapy in patients with thalassaemia major, when current chelation therapy is contraindicated or inadequate.

Therapeutic strategy

- Management of blood transfusion-related iron overload is based on the prescription of iron chelators. Iron chelator treatment is initiated after 10 to 20 transfusions, or once ferritinaemia exceeds 1,000 µg/l. Three chelators are currently available, two of which have been granted marketing authorisation for first-line treatment:
  - DESFERAL (deferoxamine), administered by injection,is available from non-hospital and hospital pharmacies and is used in multiple indications
  - and EXJADE (deferasirox), administered orally, indicated in patients over the age of 6 years suffering from thalassaemia, receiving frequent transfusions (≥7 ml/kg/month of concentrated red cells) and presenting with post-transfusional iron overload.
- If deferoxamine is contraindicated or inappropriate, two oral alternatives are available:
  - deferiprone (FERRIPROX), indicated for patients with thalassaemia major,
  - deferasirox (EXJADE), indicated for patients aged between 2 and 5 years, receiving frequent blood transfusions and for adults and children over the age of 2 years, receiving infrequent blood transfusions (<7 ml/kg/month of concentrated red cells).
- In the event of persistent iron overload during monotherapy, the following are recommended: increase chelator dose or administration frequency, change of chelator, combination of two chelators.

* This summary does not cover this indication.

- For the prevention or treatment of the consequences of life-threatening iron overload (cardiac overload in particular), continuously administered deferoxamine is recommended, along with the deferiprone / deferoxamine (FERRIPROX/DESFERAL) combination, with a view to increasing treatment intensity.
- Concerning the combination of two chelators during treatment intensification, the most commonly used regimens combine deferiprone (FERRIPROX) administered every day at a standard dose, with deferoxamine (DESFERAL) at variable frequency and dosage. The deferiprone/deferoxamine combination can be used to intensify the chelator treatment. This combination is proposed, in particular, in the event of major myocardial iron overload detected by MRI. A FERRIPROX/DESFERAL combination may be proposed for patients with moderate to severe cardiac iron overload, or in the event of cardiac dysfunction.

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

  The FERRIPROX/deferoxamine (DESFERAL) combination is a second-line or later treatment, indicated in patients requiring chelation intensification: when monotherapy with another iron chelator (deferoxamine or deferasirox) is ineffective, or when the prevention or treatment of the consequences of life-threatening iron overload (in particular cardiac overload) justifies a rapid and effective solution.

  The FERRIPROX/deferasirox (EXJADE) combination has no role in the therapeutic chelation intensification strategy in patients presenting with thalassaemia major, considering the insufficient clinical data required to document its efficacy and safety in this indication, along with its contraindication in combination with other iron chelators, mentioned in the EXJADE SPC.

Clinical data

- Deferiprone/deferoxamine (FERRIPROX-DESFERAL) combination
  A randomised double-blind study compared the deferiprone/deferoxamine combination to deferoxamine monotherapy, over a 12-month period, in 65 adult patients suffering from thalassaemia major, all of whom had been pretreated with deferoxamine.
  After 12 months of treatment, and compared to inclusion, the myocardial T2* value by MRI (main endpoint) had improved to a greater extent in the deferiprone/deferoxamine group than in the deferoxamine alone group (10% variation difference between the groups; p=0.02). An absolute difference of +6 ms in myocardial T2* (from 11.7 ms to 17.7 ms) was thus observed in the group receiving the bitherapy, and of +3.3 ms (from 12.4 ms to 15.7 ms) in the deferoxamine monotherapy group.
  No new serious adverse events concerning the deferiprone-deferoxamine combination were reported, relative to the known safety profiles for these two chelators. For information, the use of FERRIPROX is associated with a serious risk of agranulocytosis and of more or less severe neutropenia.
- Deferiprone-deferasirox (FERRIPROX-EXJADE) combination
  One observational, non-comparative single-centre study evaluated the deferiprone-deferasirox combination in 15 patients intolerant to deferoxamine, or for whom deferoxamine treatment was no longer indicated.
  After 24 months of treatment, and relative to inclusion, a decrease in serum ferritin (581 µg/l *versus* 103 µg/l) was observed, along with a +2.8 ms difference in myocardial T2* value (36.9 ms *versus* 34.1 ms) and a +11.9 ms in hepatic T2* value (30.5 ms *versus* 18.6 ms).
  Very little information is available concerning the safety of this combination. There is currently a divergence between the SPC of FERRIPROX and that of EXJADE, the latter contraindicating the combination of EXJADE with any other chelator failing sufficient safety evaluation.

Special prescription requirements

- Medicinal product subject to initial half-yearly hospital prescription.
- Prescription reserved for haematology specialists or physicians with expertise in blood disorders.

Benefit of the medicinal product

- The actual clinical benefit* of FERRIPROX is:
  - high, in combination with DESFERAL (deferoxamine),
  - insufficient to justify its reimbursement in combination with EXJADE (deferasirox).

- FERRIPROX, in combination with deferoxamine, offers minor clinical added value** (CAV IV) over deferoxamine monotherapy in the treatment of thalassaemia major, when monotherapy with another iron chelator is ineffective, or when the prevention or treatment of the consequences of life-threatening iron overload (in particular cardiac overload) justifies a rapid and effective solution.
- Approved for hospital treatment, within a restricted scope, only when combined with deferoxamine (DESFERAL)

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This document was drafted on the basis of the Transparency Committee opinion dated 04 April 2018 (CT-16067) available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) is its benefit particularly on the basis of its clinical performances and the severity of the disease 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) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement"