HAUTE AUTORITÉ DE SANTÉ

HAEMATOLOGY
New medicinal product
February 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

REFIXIA (nonacog beta pegol), antihaemophilic factor (factor IX)

Insufficient clinical benefit to justify its reimbursement in haemophilia B due to uncertainties as to the long-term consequences of the accumulation of PEG in tissue

Main points

- REFIXIA has MA in the treatment and prevention of bleeding episodes in patients over 12 years with haemophilia B**.**
- It is a factor IX with half-life extended by conjugation with a 40 kD polyethylene-glycol (PEG) molecule. The FIX with half-life extension already on the market do not contain PEG.
- In the current state of knowledge, we cannot rule out the potential long-term risks related to the accumulation of PEG molecules in tissue, especially in the plexus choroideus.

Therapeutic strategy

- The first-line treatment for haemophilia B is replacement treatment and is based on administration of clotting factor IX (FIX) concentrates. They can be administered:
  - curatively, “on demand”, on occurrence of a bleeding event that cannot be controlled by local haemostatic methods or cannot be treated with tranexamic acid,
  - to prevent bleeding: in primary prophylaxis in children with severe haemophilia before the age of two years, and before onset of the second haemarthrosis, in secondary prophylaxis (long-term or periodic) after onset of the second haemarthrosis or in the event of surgery or invasive procedures (according to severity and the expected risk of bleeding).
- Long-term prophylaxis is the conventional treatment in children with severe haemophilia. There is no consensus as to the role of prophylaxis in adults.

- **Role of the medicinal product in the therapeutic strategy**
  No study has compared REFIXIA to the other two FIX concentrates with extended half-life already available (ALPROLIX and IDELVION).
  As this FIX concentrate contains PEG, it poses difficulties for routine FIX testing, as with the other FIX (interferences with reagents), which is all the more preoccupying in an emergency situation.
  REFIXIA does not have a role in the treatment and prevention of bleeding episodes in patients with haemophilia B.

Clinical data

- REFIXIA was mainly evaluated in two phase III, non-comparative studies having included previously treated patients from age 12 with a moderate to severe form of haemophilia B.
- REFIXIA has demonstrated its efficacy for the long-term prevention of bleeding at the dose of 40 IU/kg once a week over 52 weeks. In the patients aged 13 to 65 evaluated (n=26), the annualised median rate of bleeding was 1.04 CI95% [0.00; 4.01]. The data suggest that the 40 U/kg posology proposed in prophylaxis in the SPC could be excessive for many patients.
- In treatment on demand, the overall rate of success of REFIXIA for treating bleeding was 95% (n=135/143 bleeding episodes), with 98% of bleeding episodes treated with one or two injections. Minor or moderate bleeding episodes were treated with 40 IU/kg of REFIXIA, and severe episodes with 80 IU/kg.
- In the study having evaluated REFIXIA during major surgery, haemostatic efficacy was considered to be excellent or good for all surgeries evaluated (n=13). Two patients required transfusion in the global surgical period.

- None of these studies compared the efficacy or safety of REFIXIA to that of another factor IX, whether conventional or with long half-life. The efficacy of REFIXIA seems to be at least comparable (expert opinion).
- No inhibitor antibodies or thromboembolic events were observed in clinical studies having included 115 previously treated patients having totalled up to 174 days' exposure to REFIXIA (78% of them were exposed for at least 50 days and 42% at least 100 days). One case of severe hypersensitivity attributed to REFIXIA was reported during a first injection.
- REFIXIA is the first FIX containing a 40 kDa PEG particle, and therefore the only FIX for which there is uncertainty as to the potential toxicity of PEG deposits in the body, especially in the plexus choroideus, after several years' treatment. Although this risk is particularly preoccupying for the youngest children, at an early stage in their development, we cannot fully rule out a risk for children over the age of 12 (ongoing neurogenesis), or for adults. The uncertainties as to the long-term impact of these deposits, especially as REFIXIA is a high-dose, long-term treatment, led the EMA to refuse MA in children under the age of 13.

Special prescription requirements

- Medicinal product subject to initial six-month hospital prescription.

Benefit of the medicinal product

- The actual clinical benefit* of REFIXIA is insufficient.
- Not approved for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 31 January 2018 (CT-16400) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of 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"