HAUTE AUTORITÉ DE SANTÉ

HAEMATOLOGY
New medicinal product
December 2016

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

KOVALTRY (octocog alfa), antihaemophilic factor (factor VIII)

Substantial clinical benefit but no clinical benefit demonstrated by comparison with other coagulation factor VIII products in the treatment and prophylaxis of bleeding in patients with haemophilia A

Main points

- KOVALTRY is a recombinant FVIII indicated in the treatment and prophylaxis of bleeding in patients with haemophilia A.
- It is similar to KOGENATE, which it is intended to replace on the market. They both contain the same recombinant FVIII protein.
- In the course of clinical trials in previously treated patients, no case of FVIII inhibitor antibodies, thromboembolic event or anaphylactic reaction was reported.
- In children with severe, previously untreated, haemophilia A, the interim data from the ongoing study report a risk of development of inhibitors at the upper limit of what is expected in this population. However, these data must be interpreted carefully given the small number evaluated and the interim nature of the results.

Therapeutic use

- The first-line treatment for haemophilia A is replacement therapy involving the administration of coagulation factor VIII concentrates. They may be administered:
  - in the prevention of bleeding: as primary prophylaxis in children with severe haemophilia aged under 2 years and before the occurrence of a second haemarthrosis, as secondary prophylaxis (long-term or intermittent) after the occurrence of a second haemarthrosis, or during surgery or invasive procedures (depending on the severity and the risk of bleeding expected),
  - as curative treatment ("on demand" treatment) when bleeding occurs that cannot be controlled by local haemostatic measures or is not suitable for treatment with desmopressin or tranexamic acid.
- In children with severe haemophilia, prophylactic treatment is the reference treatment, the main disadvantage of which is its therapeutic weight.
- **Role of the proprietary medicinal product in the therapeutic strategy**
  Considering the clinical data available and the current uncertainties about the risk of inhibitors in patients with severe haemophilia not previously treated, KOVALTRY is:
  - a first-line treatment in patients with previously treated haemophilia A and in patients with minor or moderate, previously untreated, haemophilia A;
  - a last-resort treatment in patients with severe, previously untreated, haemophilia A.

Clinical data

Previously treated patients

- KOVALTRY has been evaluated in three non-comparative studies in patients with severe haemophilia A: two 12-month studies in patients aged ≥ 12 years (LEOPOLD I and LEOPOLD II) and one 6-month study in children aged < 12 years having cumulated at least 50 cumulative days of treatment (LEOPOLD Kids part A).
  A total of 204 patients were included: 153 aged ≥ 12 years, 26 between 6 and 12 years, and 25 aged < 6 years. Of the population ≥ 12 years, 140 patients had been treated for at least 12 months.
- In long-term prophylaxis, KOVALTRY has demonstrated its efficacy in prevention of bleeding with dosing regimens of 2 to 3 injections per week. In adults and adolescents (LEOPOLD I), the mean annual bleed rate (ABR) was 3.8±5.2 (primary endpoint) with a mean annualised spontaneous bleeding rate of 2.5±3.5 (0.0-3.9). The ABR was similar during the additional year of follow-up (extension phase).
- In the paediatric population (LEOPOLD Kids), the mean annualised bleeding rate 48 hours post-injection (primary endpoint) was 2.0 ±2.9 and for the entire study was 3.8±5.0.
- In the LEOPOLD I and II studies, the response to treatment of intercurrent bleeding on prophylaxis was judged as good or excellent by the caregiver in at least 80% of cases (98% in children <6 years). For adults and adolescents treated on demand (LEOPOLD II), the response to treatment was judged as good or excellent in 68% of cases and moderate for around 30%. KOVALTRY has not been evaluated in on-demand treatment in children aged < 12 years.
- In prevention of bleeding in case of major surgery (n= 10) or minor surgery (n=20), the surgeon judged the haemostatic control to be good or excellent in all cases.
- There have been no reported cases of anti-factor VIII inhibitors or thromboembolic events in studies in previously treated patients. The safety profile seems to conform to what is expected and known for other FVIIIs and is similar in children and adults.

Previously untreated patients

- A study is ongoing (LEOPOLD Kids - Part B) to evaluate KOVALTRY in children under 6 years of age with severe, previously untreated, haemophilia.
- On 31 June 2016, 21 children were included (25 to 50 expected), including 12 who had reached at least 50 days of exposure. To date, 38% of children have developed inhibitors, 4 (19%) at a high titre and 4 (19%) at a low titre, i.e. a risk at the upper limit of what is expected in this population. However, these data must be interpreted carefully given the small number evaluated and the interim nature of the results.

Special prescribing conditions

- Initial 6-month hospital prescription.

Benefit of the medicinal product

- The actual benefit* of KOVALTRY is substantial.
- KOVALTRY does not provide clinical added value** (CAV V, non-existent) by comparison with the other coagulation factor VIII products available.
- Recommends inclusion on the list of reimbursable products for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 14 December 2016 (CT-15274) and is available at **www.has-sante.fr**

* The actual benefit (AB) of a proprietary 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 AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means “no clinical added value”.