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HAEMATOLOGY
New medicinal product
July 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

HEMLIBRA (emicizumab), haemostatic

High clinical benefit for the prophylaxis of bleeding episodes in congenital haemophilia A with high-titer anti-factor VIII inhibitor and significant clinical added value over FEIBA and NOVOSEVEN

Insufficient clinical benefit to justify its reimbursement for the prophylaxis of bleeding episodes in congenital haemophilia A without high-titer anti-factor VIII inhibitor

Main points

- HEMLIBRA has been granted a marketing authorisation for the prevention of bleeding episodes in patients with haemophilia A who have developed an anti-factor VIII inhibitor.
- This monoclonal antibody mimics FVIII activity. It is administered via a once-weekly subcutaneous (SC) injection.
- The clinical data, even though the level of evidence is sub-optimal, suggest that the efficacy of HEMLIBRA is greater than prophylaxis with bypassing agents (FEIBA and NOVOSEVEN). It is expected to offer a major quality of life benefit for patients by comparison to these treatments.
- The SPC must be consulted for the interpretation of coagulation tests (interference with HEMLIBRA) and in the event of concomitant administration of a bypassing agent (interaction with FEIBA), considering the risks of thrombotic microangiopathy and thromboembolic events.

Therapeutic strategy

The development of an anti-FVIII inhibitor following replacement therapy using FVIII concentrates is the most serious complication of haemophilia A treatment. The choice between the various options must be discussed on a per case basis by physicians with specialist knowledge of haemophilia and will be governed by numerous factors. The decision is based, in particular, on the type of inhibitor. In schematic terms, we can distinguish “high-titer” from “low-titer” patients according to their response to the injection of factor VIII concentrates. The management of patients with haemophilia A with an inhibitor is primarily based on two strategies:

- **Inhibitor eradication via an immune tolerance induction (ITI) protocol**: frequent injections of high-dose FVIII for several months, or even years, in order to be able to effectively re-administer FVIII. No alternative treatment is as effective as the use of FVIII in haemophilia A patients without inhibitor. Inhibitor eradication is thus always the first-line option for most patients with inhibitor.
- **Bleeding treatment or prophylaxis by means of bypassing agents** (NOVOSEVEN activated coagulation factor VII concentrate, or FEIBA activated prothrombin complex): in some patients, repeated haemorrhages while ITI is in progress, has failed, or cannot be implemented, may justify the initiation of prophylaxis by bypassing agent.
- The use of FVIII remains primarily reserved for the treatment of bleeding in some patients with inhibitor. Maintenance of FVIII prophylaxis may be considered in some of these patients with a low-titer inhibitor.

Role of the medicinal product in the therapeutic strategy

- HEMLIBRA is a first-line treatment for patients with congenital haemophilia A with a high-titer inhibitor for which long-term prophylaxis appears to be the most appropriate therapeutic option. HEMLIBRA thus represents an alternative to bypassing agents (FEIBA and NOVOSEVEN) in this population of high-titer patients, particularly in the event of ITI failure. HEMLIBRA could also be proposed for certain high-titer patients, as an alternative to ITI, which currently represents the first-line treatment when an inhibitor has been diagnosed. Contrary to ITI, HEMLIBRA is not intended to eradicate the inhibitors. The benefit of implementing HEMLIBRA prophylaxis rather than ITI must be assessed on a per case basis, according in particular to the chances of ITI success, the patient’s

profile and his/her wishes. To date, no studies have compared these two strategies, particularly in terms of impact on joint prognosis.

- HEMLIBRA has not be assessed in low-titer patients, or in patients undergoing ITI.
- Moreover, no clinical data are available to justify the use of HEMLIBRA in patients in a state of immune tolerance and receiving effective long-term FVIII prophylaxis.
- Beyond its prophylactic efficacy, the main benefit of HEMLIBRA resides in its method of administration (weekly subcutaneous injection), less constraining than available alternatives (multiple IV infusions per week, or even daily). The routine and long-term use of HEMLIBRA raises several uncertainties: management of intercurrent bleeding or traumatic events, of urgent or scheduled surgical procedures. The interaction between HEMLIBRA and FEIBA, causing FEIBA to only be considered as a last resort, should particularly make the management of intercurrent bleeding more difficult.
- HEMLIBRA interferes with some routine coagulation tests, thus presenting a risk of interpretation errors in the event of urgent management by non-specialist clinicians. The SPC must be consulted for the interpretation of coagulation tests and in the event of concomitant administration of a bypassing agent, considering the risks of thrombotic microangiopathy and thromboembolic events.
- HEMLIBRA should not be systematically prescribed: great care must be taken in patients with thrombotic risk (in particular patients with coronary risk or with atrial fibrillation), patients over the age of 65 and those not prone to bleeding. Patients who could best benefit from HEMLIBRA are those who bleed very frequently and young children with severe haemophilia, in the presence of a high-titer inhibitor. In adults, who are most frequently treated on-demand rather than by long-term prophylaxis, the haemorrhagic profile and thrombotic risk must be taken into account before considering such a treatment.

Clinical data

Two studies included patients, most of whom suffered from a severe form of haemophilia and with an historic inhibitor peak greater than 5 UB/ml.

- An initial open-label study included 109 teenagers and adults aged between 12 and 75 years, previously treated with a bypassing agent (BPA) and for half of whom ITI treatment had failed. Patients received HEMLIBRA prophylaxis (arms A and C), or were treated on-demand with BPA (arm B). The primary objective was to compare the annual bleeding rate (ABR) requiring treatment between arm A and arm B, after 24 weeks of treatment.
- At 24 weeks, the ABR was lower in patients receiving HEMLIBRA prophylaxis (n=35) than in patients treated on-demand with BPA (n=18): 2.9 CI95% [1.69; 5.02] versus 23.3 CI95% [12.33; 43.89], R=0.13 CI95% [0.057; 0.277]. Nearly 63% (n=22/35) of patients receiving HEMLIBRA did not bleed during this period. These results were supported by all the secondary endpoints analysed according to a predefined ranked procedure.
- The sequential analysis plan included intra-individual comparisons in arm C receiving HEMLIBRA, the intermediate results of an observational study having been used as historical control. The comparisons suggest a distinctly lower annual bleeding rate with HEMLIBRA compared to prior prophylaxis with BPA (FEIBA or NOVOSEVEN).
- A second open-label, single-arm study assessed HEMLIBRA in patients under the age of 12 years, in particular those awaiting an ITI protocol. The available data are descriptive and derived from an intermediate analysis not specified in the protocol. Approximately ¾ of the 60 patients included at this date were receiving prophylactic treatment prior to inclusion, primarily by BPA (89%) and had already undergone an ITI protocol.
- The efficacy of HEMLIBRA was assessed in patients treated for at least 12 months at the same dose, i.e. 23 children (median duration: 38 weeks). Over this period, 20 patients (87.0%) reported no bleeding requiring treatment. Concerning patients coming from the observational study and who then received HEMLIBRA for at least 12 weeks (n=13), the treated annual bleeding rate was of 0.2 versus 17.2 in the observational study (prophylactic BPA for 12 patients and on-demand for 1 patient). Few data are currently available for patients under the age of 2 years.
- The most frequent adverse effects were injection site reactions (19%), headaches (15%) and arthralgia (10%). The most serious adverse effects were thrombotic microangiopathy (1.6% of patients; n=3/189) and thromboembolic events (2 cases reported in adults). These serious events all occurred when a cumulative average dose of FEIBA greater than 100 U/kg/24 hours had been administered. The risk of interaction between FEIBA and HEMLIBRA, potentially causing severe thrombotic events, has been included in the SPC warnings. The use of NOVOSEVEN is thus recommended to treat bleeding under HEMLIBRA. Pharmacokinetic analyses suggest the occurrence of anti-emicizumab inhibitor in two patients during the follow-up period.
- As in the vast majority of developments in haemophilia, one of the primary limitations of available studies resides in their open-label nature, leading to a non-quantifiable bias when assessing the partially subjective endpoints. Thus, the differences observed between groups in the HAVEN studies were probably overestimated.
- The only data comparing HEMLIBRA prophylaxis to bypassing agent prophylaxis have a low level of evidence; estimation of the relative efficacy of these treatments is thus probably biased.
- It is regrettable that the pivotal studies, particularly those conducted on young children, failed to assess the change in orthopaedic status, considering that one of the main objectives of prophylaxis is to preserve joint function.

Special prescription requirements

- Medicinal product subject to hospital prescription

Benefit of the medicinal product

- The actual clinical benefit* of HEMLIBRA is:
  - high in the prophylaxis of haemorrhagic episodes, exclusively in patients suffering from congenital haemophilia A who have developed a high-titer anti-factor VIII inhibitor,
  - insufficient to justify public funding cover in all other clinical situations.
- HEMLIBRA provides a major improvement in actual clinical benefit (IACB II) relative to bypassing agents (FEIBA and NOVOSEVEN) in the management of patients suffering from congenital haemophilia A and having developed a high-titer anti-factor VIII inhibitor.
- Approval for hospital management within a restricted scope.

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This document was drafted on the basis of the Transparency Committee opinion dated 11 July 2018 (CT-16921) 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 improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"