HAUTE AUTORITÉ DE SANTÉ

NEUROLOGY
New indication
April 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

HIZENTRA, human immunoglobulin

High clinical benefit in the immunomodulator maintenance treatment of chronic inflammatory demyelinating polyneuropathy, but no demonstrated clinical advantage over other immunoglobulins (CLAIRYG, OCTAGAM, PRIVIGEN, TEGELINE)

Main points

- HIZENTRA has now been granted a marketing authorisation in the immunomodulator maintenance treatment of chronic inflammatory demyelinating polyneuropathy (CIDP).
- Intravenous (IV) immunoglobulin (IG) treatment is now well-established and most IV IGs are indicated for this disease. HIZENTRA is the first subcutaneous (SC) immunoglobulin to be indicated in CIDP as maintenance treatment after stabilisation by means of IV IGs.
- In one comparative, double-blind, randomised study versus placebo, the proportion of CIDP relapse over 24 weeks (primary endpoint), was significantly lower with HIZENTRA than with the placebo.

Pre-existing indications*

HIZENTRA has already been granted a marketing authorisation for replacement therapy in patients suffering from primary immune deficiencies, with deficient antibody production, hypogammaglobulinaemia and recurrent bacterial infections in patients suffering from chronic lymphoid leukaemia, multiple myeloma, or in patients in allogenic haematopoietic stem cell pre- and post-transplantation phase.

Therapeutic strategy

- IV IGs represent the first-line treatment for CIDP, along with corticotherapy and plasma exchange.
- The prescription of SC IGs in replacement of IV IGs must take into consideration the patient's clinical situation, access and preservation of the venous approach, practical considerations (caregiver on the one hand and travel constraints on the other), and a joint medical decision with the patients.

  Initial treatment:
  - In the event of mild symptoms with moderate discomfort, monitoring without treatment is recommended.
  - In the event of moderate to severe disability with sensorimotor impairment: IV IGs and corticosteroids are the first-line treatments, the choice being made according to their respective contraindications.
  - In the event of the purely motor form: IV IGs are the treatment of choice as corticosteroids expose patients to neurological aggravation.
  - In the event of failure of IV IGs or corticotherapy, plasma exchanges are used (they thus have a second-line role).

  Once the clinical response is achieved, the following maintenance treatment is recommended:
  - with IV IGs, to continue until maximum efficacy is achieved, then to reduce the dose to the lowest effective maintenance dose;
  - with corticosteroids, to reduce the doses to the minimum effective dose over a 1 to 2-year period;
  - if the response to IGs or corticosteroids is deemed insufficient by the physician and patient, or if the maintenance doses are too high, the addition of an immunomodulator may be considered, though none of these treatments have been validated for CIDP by a randomised controlled study.
- **Role of the medicinal product in the therapeutic strategy**

* This summary does not concern these indications.

HIZENTRA, as a maintenance treatments following stabilisation by IV IGs, is a therapeutic alternative to IV IGs with the same indications (CLAIRYG, OCTAGAM, PRIVIGEN, TEGELINE).

No recommendations have been formulated for the switch from IV IG to SC IG. Considering the lack of direct comparative data versus the other immunoglobulins, the choice of one IG over another in CIDP maintenance treatment after stabilisation by IV IG cannot be specified. This choice is dependent on the patient's characteristics and preference.

Clinical data

- One comparative, double-blind, multi-centre study versus placebo included 172 patients stabilised under IV IG, who were then administered, according to a 1:1:1 randomisation, a placebo, HIZENTRA 0.4 g/kg or HIZENTRA 0.2 g/kg for 24 weeks. The proportion of CIDP relapse (primary endpoint) was significantly lower for the two HIZENTRA groups (32.8% for HIZENTRA 0.4 g/kg and 38.6% for HIZENTRA 0.2 g/kg) than for the placebo group (63.2%), i.e. a significant difference of -30.40 ($p<0.001$) for HIZENTRA 0.4 g/kg and -24.56 ($p=0.007$) for HIZENTRA 0.2 g/kg.
- An additional 48-week extension study, involving 82 patients, failed to show any safety signals relative to the already known safety profile of HIZENTRA.
- One meta-analysis assessed, as primary endpoint, changes in patients' motor strength according to the MRC-SS scale when switching from IV IG to SC IG treatment. No statistically significant difference in this score was detected between IV IGs and SC IGs in CIDP maintenance treatment (4 studies).

Special prescription requirements

- Blood-derived medicinal product
- Medicinal product subject to hospital prescription
- Medical prescription restricted to healthcare professionals with experience in the treatment of immune deficiencies/CIDP with SC IGs
- Medicinal product included in the retrocession list

Benefit of the medicinal product

- The actual clinical benefit* of HIZENTRA is high.
- HIZENTRA does not provide any clinical added value** (CAV V) compared to other immunoglobulins (CLAIRYG, OCTAGAM, PRIVIGEN, TEGELINE).
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 17 April 2019 (CT-17037) 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".