HAUTE AUTORITÉ DE SANTÉ

INFECTIOUS DISEASE
New indication
December 2017

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

HYQVIA (normal human immunoglobulin), multi-purpose immunoglobulin combined with recombinant human hyaluronidase

Insufficient clinical benefit to justify its reimbursement for children and adolescents (< 18 years) for replacement therapy for primary immunodeficiency

Main points

- HYQVIA has been granted a marketing authorisation for children and adolescents (aged from 0 to 18 years) for replacement therapy for primary immunodeficiency.
- It differs from other immunoglobulins by its lower administration frequency: a single injection every 3 to 4 weeks, whereas other subcutaneous immunoglobulins have a weekly administration schedule.
- Its observed efficacy is similar to that of other immunoglobulins, but not demonstrated failing a comparative study versus other normal human immunoglobulins.
- In children, uncertainties concerning the impact of recombinant human hyaluronidase on fertility and the lack of follow-up on safety (not more than 3.3 years of exposure), although the treatment would be prescribed on a long-term basis, mean that HYQVIA cannot be assigned a role in the therapeutic strategy, while therapeutic alternatives that are equally effective and do not involve this uncertainty are available.

Pre-existing indications*

HYQVIA has also been granted a marketing authorisation for replacement therapy for adults suffering from primary immune deficiency with defective antibody production and for adults suffering from chronic lymphoid leukaemia or multiple myeloma with hypogammaglobulinaemia and recurrent bacterial infections.

Therapeutic strategy

The benefit of human immunoglobulin replacement therapy for humoral deficiency is established.
In children, this treatment concerns all genetic immune deficiency varieties responsible for IgG deficiency and/or an agammaglobulinemia antibody production defect; IgG and IgA deficiency with hyper IgM; hypogammaglobulinemia and/or isolated antibody production deficiency or arising in cases of primary T-cell immune deficiencies.
Ig therapy may also be recommended for immune deficiencies in one or more IgG subclasses whether associated with an IgA deficiency or not, in cases of repeated infections. Multi-purpose human Ig are administered either intravenously every 3 or 4 weeks (in a hospital setting), or subcutaneously each week. Intravenous administration may be replaced by subcutaneous administration.
HYQVIA is an immunoglobulin having the specific feature of being co-administered with recombinant human hyaluronidase and therefore enables monthly SC administration at a single site (compared to IV Ig administrated at one site on a monthly basis and compared to SC Ig administered at multiple sites on a weekly basis). To date, little safety data feedback is available, in particular uncertainties remain on the safety of chronic use of hyaluronidase: in the short term on changes in skin appearance (according to expert opinion) and in the long term on fertility.

Role of the medicinal product in the therapeutic strategy

Given:

* This summary does not concern these indications.

- the lack of comparative data versus other normal human immunoglobulins having the same indications and used via the IV or SC route;
- the lack of follow-up, particularly in respect of the safety associated with subcutaneous administration of recombinant human hyaluronidase (not more than 3.3 years of exposure) even though the treatment would be subject to long-term prescription
- uncertainties concerning the impact of recombinant human hyaluronidase on fertility, particularly in children;
- and the existence of therapeutic alternatives, that are equally effective and do not involve this uncertainty in respect of safety,

HYQVIA has no role in the therapeutic strategy for primary immune deficiencies in children.

Clinical data

- The efficacy of normal human immunoglobulin, with the successive administration of hyaluronidase followed by Ig by the SC route, has essentially been assessed on the basis of a post-hoc subgroup analysis of patients aged under 18 years included in a study and subsequently in its extension phase. The annual rate of severe acute bacterial infections, the primary endpoint, was 0.08 per patient-year (upper limit of the 99% confidence interval: 0.20), significantly lower than the predefined threshold of 1 in the protocol ($p<0.0001$). The median residual IgG count, regardless of the infusion frequency in question, was between 10 and 16 g/L; it was greater than the reference threshold of 8 g/L deemed to be the target value for immune replacement therapy. These data should be interpreted with caution due to the inherent limitations of this type of comparison (before/after), particularly as the patients had all been pretreated with Ig via the IV route for at least 3 months in phase 1 of the study.
- In this study, no serious adverse effects were reported in patients aged under 18 years. No patients developed neutralising antibodies targeted against recombinant human hyaluronidase (rHuPH20). Three patients (3/24 or 12.5%) transiently developed non-neutralising anti-rHUPH20 antibodies. No correlation was found between the development of anti-rHuPH20 antibodies and efficacy or safety.
- In a prospective phase II/III study in the United States, discontinued prematurely, and a study on 1526 patients receiving hyaluronidase for various treatments, anti-rHuPH20 antibodies were detected; none of these were neutralising, there was no impact on the pharmacokinetics or efficacy of the medicinal product or on endogenous hyaluronidase.
- Limited data are available on the long-term impact of anti-rHUPH20 antibody development. The lack of follow-up in respect of the safety associated with the long-term subcutaneous administration of recombinant human hyaluronidase remains a major concern, particularly for the paediatric population.
- There is a risk of antibodies targeting human hyaluronidase cross-reacting with endogenous PH20, known to develop in adult male testicles, the epididymis and semen. The clinical effect on embryos. foetuses or humans is not known. Data on fertility disorders are very limited and anti-rHuPH20 antibody screening is not included in male and female fertility disorder investigation tests.

Special prescription requirements

- Medicinal product subject to hospital prescription

Benefit of the medicinal product

- The actual clinical benefit* of HYQVIA is insufficient to justify public funding cover for children and adolescents (aged from 0 to 18 years) for replacement therapy for primary immune deficiencies.
- Not approved for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 6 December 2017 (CT-16113)
available at **www.has-sante.fr**

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