HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New medicinal product
January 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

CRYSVITA (burosumab), drug affecting bone mineralisation in the treatment of X-linked hypophosphataemia

High clinical benefit and moderate clinical added value compared to conventional therapy in the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons, with severe forms refractory to conventional therapy or complicated severe forms.

Main points

- CRYSVITA has a marketing authorisation in the treatment of X-linked hypophosphataemia.
- Its efficacy is greater than that of conventional therapy with respect to improvement of a radiographic criterion after 40 weeks of treatment, in a population of patients with severe disease not responding to conventional therapy.
- No data are available concerning its efficacy on growth and dental development.
- The data relating to improvement of quality life cannot be analysed.
- Uncertainties remain concerning the long-term safety of this monoclonal antibody.

Therapeutic strategy

- The objectives of treatment for X-linked hypophosphataemia are to ensure optimal bone and dental mineralisation, promote growth and limit pain and bone deformities, as well as to reduce alkaline phosphatase (ALP) levels to as close as possible to the upper limit of normal for age and to maintain urine calcium and parathormone (PTH) levels within the normal range. In the event of residual lower limb deformities at the end of growth or that threaten the joints, corrective orthopaedic surgery is proposed. The prevention of dental manifestations by means of scrupulous oral and dental hygiene, and, if necessary, specific treatment in a reference centre, should be implemented. The first-line treatment consists in the concomitant administration of active vitamin D analogues: UNALFA (alfacalcidol) or ROCALTROL (calcitriol) and oral phosphate supplements, as several doses per day.
- This treatment is begun as early as possible and continued until the end of growth, at least. Treatment is adjusted every three months. A treatment duration of 1 year appears to be appropriate to assess the efficacy, safety and compliance with treatment.
- **Role of the medicinal product in the therapeutic strategy**
  CRYSVITA, as monotherapy, is a treatment for X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons, with:
  - severe forms refractory to conventional therapy (as second-line therapy),
  - or complicated severe forms (as first-line therapy), for which the conventional treatment with vitamin D analogues and phosphate supplements would, theoretically, not be optimal and would be liable to result in a loss of opportunity for the patient. Complications that may warrant immediate treatment with burosumab include, in particular, tooth abscess, craniostenosis, growth delayed by more than 2 standard deviations or nephrocalcinosis.
  The role in patients considered to be responders to conventional therapies is not known, due to a lack of data.
- Oral phosphate and vitamin D analogues should be discontinued one week prior to initiation of treatment. Fasting serum phosphate concentrations should be below the reference range for age at the time of treatment initiation.
  The optimal duration of CRYSVITA treatment cannot be determined. In any case, in accordance with the marketing authorisation, treatment is scheduled to be maintained until the end of growth.

- Decisions with respect to the initiation or discontinuation of CRYSVITA treatment should be taken during multidisciplinary review meetings in reference centres with expertise in rare calcium and phosphorus metabolism diseases.

Clinical data

- A randomised, open-label phase III study, with blind assessment with respect to the treatment allocated and the patient examined, compared the efficacy and safety of burosumab (not combined with conventional therapy) with the conventional medical therapy, i.e., oral phosphate supplements and active vitamin D analogues, in 61 patients aged 1 to 12 years (including 26 children aged < 5 years). The patients' growth was impaired. The patients had a deformity of the tibia (83.6%), femur (80.3%), and/or bowed gait (57%), a history of tooth abscess for 34% of patients. All the patients had been treated with oral phosphate and active vitamin D derivatives before inclusion in the study, for an average of 3.8 years (3.09). All the patients had rickets at inclusion. The patients included had severe disease and conventional therapy had failed. Following 40 weeks of treatment, the mean total RGI-C score (primary endpoint, score ranging from -3: severe worsening of rickets to +3: complete healing of rickets) was 1.92 (0.110) in the burosumab group and 0.77 (0.107) in the active control group, i.e., a statistically significant difference of +1.14 95% CI [+0.83, +1.45] in favour of the burosumab group, p<0.0001.
- The mean exposure duration in the 2 groups was a little more than 11 months. A total of 59% of patients in the burosumab group and 13% of patients in the control group had adverse events judged by the investigators to be at least possibly related to the treatment. The most common adverse events in the burosumab group were related to the subcutaneous administration of the medicinal product. Nine patients (31%) in the burosumab group and three patients (9%) in the control group had hypersensitivity-type adverse events related to the treatment, none of which were considered to be serious. The children included in the study do not appear to have developed anti-burosumab antibodies.

Special prescription requirements

- Medicinal product subject to hospital prescription.
- Prescription reserved for paediatric, endocrinology, diabetes and nutrition, nephrology or rheumatology specialists.

Benefit of the medicinal product

- The actual clinical benefit* of CRYSVITA is:
  - high in the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons, with severe forms refractory to conventional therapy or complicated severe forms.
  - insufficient to justify public funding cover in the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons, with severe forms refractory to conventional therapy or complicated severe forms.
- CRYSVITA provides moderate clinical added value** (CAV III) compared to conventional therapy.
- Favourable opinion for hospital use in patients for whom the actual clinical benefit is high.

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This document was drafted on the basis of the Transparency Committee opinion dated 23 January 2018 (CT-16912) 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".