Rare disease
Sectors: Retail and hospital

HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
2 JUNE 2021

The legally binding text is the original French opinion version

burosumab
CRYSVITA 10 mg solution for injection
CRYSVITA 20 mg solution for injection
CRYSVITA 30 mg solution for injection

New indication

Key points

Favourable opinion for reimbursement only in the treatment of X-linked hypophosphataemia in severe forms refractory to conventional treatment or complicated severe forms in adolescents with radiographic evidence of bone disease in whom bone growth is complete, and in adults, and in paediatric patients and adolescents having started treatment with CRYSVITA (burosumab) during the bone growth period and for whom treatment needs to be continued beyond this period.

Unfavourable opinion for reimbursement in the other clinical situations.

What therapeutic improvement?

Therapeutic improvement in the management of the condition.

Role in the care pathway?

Oral supplementation with phosphorus and vitamin D analogues several times per day to compensate for the consequences of hypophosphataemia is the "conventional" recommended treatment for X-linked hypophosphataemia according to the French national diagnostic and care protocol (PNDS) established in March 2018. The proprietary medicinal products concerned are used off-label. This treatment is restrictive since it requires multiple doses with, in particular, a night-time dose often necessary, and it exposes patients to a risk of complications, such as ectopic mineralisation, manifested by nephrocalcinosis. This treatment is begun as early as possible after diagnosis of the disease and continued until the end of growth, at least. A treatment duration of 1 year appears to be appropriate to assess the efficacy, safety and compliance with conventional treatment (expert opinion). This treatment can be continued into adulthood, but the relevance of continuing treatment should be assessed at the transition consultation. In fact, in adults, the conventional treatment has not been assessed in controlled, randomised studies, is not routinely administered to all adults with XLH and can cause adverse effects such as nephrocalcinosis, which can result in renal failure, one of the most severe complications reported in the disease. The conventional treatment therefore has limited efficacy in adults with XLH.

The proprietary medicinal product CRYSVITA (burosumab), as monotherapy, had an MA from 2018 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**. In its opinion of 23 January 2019, the Transparency Committee considered that its role in the care pathway concerned patients 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.

Role of the medicinal product in the care pathway

Considering:

- the results of the UX023-CL303 phase 3, randomised, double-blind, placebo-controlled study, having demonstrated the efficacy of burosumab in terms of normalisation of serum phosphate (laboratory endpoint) in adult patients who had mostly been previously treated with the conventional therapy for a number of years before adulthood, with conventional therapy having been stopped before inclusion in the study, and the majority of whom had a *PHEX* mutation (95.5% of patients),
- the limited efficacy of conventional treatment based on phosphate derivatives and vitamin D, which is not routinely used in the population concerned by the indication extension, with constraints related to taking the treatment and adverse effects limiting its use,
- the data previously assessed by the Committee having established, with a good level of evidence, the efficacy and safety of use of burosumab in children 1 year of age and older and adolescents with growing skeletons (see Committee opinion dated 23/01/2019),

The Transparency Committee considers that CRYSVITA (burosumab), as monotherapy, is a:

- first-line treatment for complicated severe forms, particularly in patients with a *PHEX* mutation, 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, in adolescents whose in whom bone growth is complete and in adults,
- a second-line treatment in adolescents whose bone growth is complete and in adults refractory to conventional therapy.

Finally, when the treatment is effective and was initiated during childhood or in adolescents with growing skeletons, CRYSVITA should be maintained when treatment needs to be continued beyond this period.

However, uncertainties remain concerning the long-term efficacy and safety of CRYSVITA (burosumab). The optimal treatment duration for CRYSVITA (burosumab) is not currently known.

The Transparency Committee reiterates that the administration of burosumab has not been assessed in asymptomatic patients (i.e. worst pain score < 4), nor in patients aged over 66 years, pregnant women or patients with impaired renal function.

Special recommendations

As in its inclusion opinion dated 23/01/2019 in children 1 year of age and older and adolescents with growing skeletons, considering the complexity of management of this rare disease, the Committee recommends that:

- the first two injections be administered in a hospital setting,
- decisions with respect to the initiation or discontinuation of CRYSVITA (burosumab) treatment should be taken after a documented proposal resulting from a multidisciplinary team (MDT) meeting in reference and expert centres for rare calcium and phosphorus metabolism diseases, or rare kidney diseases.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ X-linked hypophosphataemia (XLH) is a rare, disabling disease, with a significant social impact in childhood and adolescence, which may continue into adulthood.

◗ The proprietary medicinal product CRYSVITA (burosumab) is a curative medicinal product.

◗ The efficacy/adverse effects ratio of CRYSVITA (burosumab) is high.

◗ There are therapeutic alternatives, which have a non-optimal efficacy and a safety profile limiting their use in XLH forms in adolescents whose bone growth is complete and in adults with complicated severe forms.

◗ CRYSVITA (burosumab), as monotherapy, is a:
- first-line treatment for complicated severe forms, particularly in patients with a *PHEX* mutation, 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, in adolescents whose in whom bone growth is complete and in adults,
- a second-line treatment in adolescents whose bone growth is complete and in adults refractory to conventional therapy.

Finally, when the treatment is effective and was initiated during childhood or in adolescents with growing skeletons, CRYSVITA should be maintained when treatment needs to be continued beyond this period.

Public health impact

Considering:
- the seriousness of the disease and its prevalence/incidence,
- the unmet medical need to have access to an effective and well-tolerated treatment for X-linked hypophosphataemia,
- the partial response to the identified need (superiority to placebo for a laboratory endpoint, non-demonstrative result for pain and functional endpoints, exploratory result for osteomalacia), with the absence of demonstration of an additional impact on morbidity and mortality or quality of life, safety that appears to be acceptable with experience limited to 3 years,
- the absence of data relative to an additional impact on the organisation of care,

CRYSVITA (burosumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of CRYSVITA (burosumab) is:
- **substantial in the treatment of X-linked hypophosphataemia in severe forms refractory to conventional treatment or complicated severe forms**
  - **in adolescents with radiographic evidence of bone disease in whom bone growth is complete, and in adults,**
  - **and in paediatric patients and adolescents having started treatment with CRYSVITA (burosumab) during the bone growth period and for whom treatment needs to be continued beyond this period.**

and
- **insufficient to justify its public funding cover in all other clinical situations.**

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indication extension, i.e.:

- **in the treatment of X-linked hypophosphataemia in adolescents with radiographic evidence of bone disease in whom bone growth is complete and in adults with severe forms refractory to conventional treatment or complicated severe forms,**
- **and in paediatric patients and adolescents having started treatment with CRYSVITA (burosumab) during the bone growth period and for whom treatment needs to be continued beyond this period.**

and at the MA dosages.

And an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the other situations.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:

- **the demonstrated superiority of burosumab in a phase 3, controlled, randomised, double-blind, placebo-controlled study, after 24 weeks of treatment for a laboratory primary endpoint judged to be acceptable in this disease (mean serum phosphate above the lower limit of normal, measured in the middle of each administration cycle: 92.6% versus 7.6% of patients in favour of the group treated with burosumab, $p < 0.0001$), in adult patients, the majority of whom had a *PHEX* mutation (95.5%),**
- **the comparison with placebo deemed to be acceptable given the limited efficacy of conventional treatment based on phosphate derivatives and vitamin D, which is not routinely used in the population concerned by the indication extension, with constraints related to taking the treatment and adverse effects limiting its use,**
- **the results of a non-comparative study conducted in adult patients previously treated with conventional therapy suggesting an effect of burosumab on osteomalacia in patients for whom bone biopsies were performed,**
- **the safety profile of burosumab, a monoclonal antibody, which appears to be acceptable, with, however, experience limited to a maximum of 3 years in clinical studies, and**
- **the medical need to have access to treatment in this disease,**

and despite:

- **results on secondary clinical pain and functional endpoints, which are difficult to interpret,**
- **more robust evidence of the efficacy of burosumab in children aged from 1 to 12 years,**

the Transparency Committee considers that CRYSVITA (burosumab) provides a minor clinical added value (CAV IV) in the care pathway for the treatment of X-linked hypophosphataemia in adolescents with radiographic evidence of bone disease in whom bone growth is complete, and in adults.