OPINION ON MEDICINAL PRODUCTS

burosumab

CRYSVITA 10 mg, 20 mg and 30 mg,

solution for injection

First assessment

Adopted by the Transparency Committee on 18 January 2023

SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement for:

- the treatment of FGF23-related hypophosphataemia in children and adolescents aged from 1 year to 17 years and in adults with oncogenic osteomalacia associated with phosphaturic mesenchymal tumours not eligible for curative excision or which may not be localised.

Therapeutic improvement?

Therapeutic improvement in the care pathway.

Role in therapeutic strategy?

The definitive curative treatment is complete tumour excision which makes it possible normalise biological and clinical signs. However, some tumours remain undetectable or are not resectable. In these scenarios, a symptomatic treatment with oral phosphate and vitamin D analogue supplementation several times daily may be envisaged.

Role of the medicinal product

CRYSVITA (burosumab) is a first-line treatment of patients with oncogenic osteomalacia associated with phosphaturic mesenchymal tumours with high serum FGF23 levels linked with a non-operable, or partially operated, or non-localised tumour, with persisting clinic signs of chronic hypophosphataemia.

After the titration period, follow-up must include regular fasting blood phosphate measurements, every 6 months.

For patients with stage 3 chronic kidney failure (GFR <60ml/min) and particularly for patients over 60 years of age, especially those having vascular risk factors, the blood phosphate level must be monitored once the titration period has passed. The blood phosphate level must be measured midway between 2 injections, at least twice yearly, to detect hyperphosphataemia. In the event of the onset of hyperphosphataemia, it may be necessary to discontinue treatment and/or reduce the dose. It is recommended to assess kidney function once a year in patients without kidney failure at treatment initiation (GFR ≥ 60ml/min).

To monitor osteomalacia progression, bone mineral density (BMD) must be measured one year after treatment initiation, and subsequently every two years until a plateau is obtained. This plateau concept is not applicable to postmenopausal women, for whom a decrease in BMD may be due to causes other than osteomalacia. Total alkaline phosphatase must be measured twice yearly as long as they are above normal.

Long-term follow-up of burosumab treatment is essential to assess the benefits and potential risks associated with long-term treatment.

In the absence of a comparative study versus recommended symptomatic treatments based on phosphate and vitamin D analogues, it is not possible to rank the treatments in relation to each other. However, this symptomatic treatment, unlike CRYSVITA (burosumab), does not target the underlying mechanism of the disease, i.e. FGF23 overproduction, causing hypophosphataemia, and requires multiple daily doses with a night-time dose often required. Furthermore, this symptomatic treatment is not without adverse events.

Committee's conclusions

Clinical Benefit

- High fibroblast growth factor 23 (FGF23)-related oncogenic osteomalacia is a rare disease characterised by hypophosphataemia due to kidney phosphate reabsorption disorder. In TIO, a mesenchymal tumour, generally benign and small in size, secretes massive amounts of FGF23. Combined phosphate and 1,25-dihydroxy-vitamin D (calcitriol) deficiencies induce bone matrix demineralisation and severe osteomalacia, with a significant impact on patients' quality of life.
- The proprietary medicinal product CRYSVITA (burosumab) is a curative medicinal product.
- The efficacy/adverse effect ratio of CRYSVITA (burosumab) is significant.
- Alternative medicinal therapies are available (see Section 5).
- CRYSVITA (burosumab) is a first-line treatment of patients with oncogenic osteomalacia associated with phosphaturic mesenchymal tumours with high serum FGF23 levels linked with a non-operable, or partially operated, or non-localised tumour, with persisting clinic signs of chronic hypophosphataemia.

Public health benefit

Considering:

- the severity of the disease and its rare nature,
- the insufficiently met medical need,
- that CRYSVITA (burosumab) is likely to provide a partial response to the identified need:
  - with an expected but undemonstrated additional impact on morbidity, quality of life and the care and life pathway, with improvement observed on blood phosphate levels and excess osteoids based on non-comparative data, with a favourable safety profile,
  - the lack of evidence of an additional impact on mortality in the absence of furnished data,

CRYSVITA (burosumab) is not likely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the actual clinical benefit of CRYSVITA (burosumab) is significant in the extension of the marketing authorisation indication.

The Committee approves inclusion in the list of proprietary medicinal products qualifying for reimbursement under social security and in the list of proprietary products approved for community use for the extension of indication and at the dosages of the marketing authorisation.

Recommended reimbursement rate: 65%

Clinical Added Value

Considering:

- the observation of the efficacy of burosumab, which inhibits FGF23 activity, in a non-comparative study after 48 weeks of treatment on a biological primary outcome measure deemed to be acceptable in this disease (proportion of patients reaching mean serum phosphate levels greater than 2.5 mg/dl (0.81 mmol/l) assessed midway through the administration cycles of 50% (7 patients) (95%CI [26.8; 73.2]) as well as the effects on variation from the inclusion of excess osteoid, based on iliac crest bone biopsies from adult patients previously treated for approximately 10 years with an off-label recommended symptomatic treatment in this disease, with dose and adverse effect constraints limiting its use,
- the safety profile of burosumab, monoclonal antibody, which appears to be acceptable, with nonetheless limited follow-up in clinical studies and a lack of clinical data on children in this indication; some clinical findings on children being however available for X-linked hypophosphataemia, another indication of burosumab,
- the medical need for a treatment in this disease,

and despite:

- uncertainties around the efficacy of burosumab particularly on osteomalacia, considering the clinical data available and the limited follow-up of use,

the Transparency Committee deems that CRYSVITA (burosumab) provides minor clinical added value (CAV IV) in the therapeutic strategy of FGF23-related hypophosphataemia in children and adolescents aged from 1 year to 17 years and in adults with oncogenic osteomalacia associated with phosphaturic mesenchymal tumours ineligible for curative excision or which may not be localised.