Seirbhís Sláinte Níos Fearr á Forbairt | Building a Better Health Service

BUROSUMAB (Crysvita®) PROTOCOL FOR THE TREATMENT OF X-LINKED HYPOPHOSPHATAEMIA

This document is intended for use by healthcare professionals only.

While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgment or specialist consultation.

Burosumab (Crysvita®) for the treatment of X-Linked Hypophosphataemia

Brand Name: Crysvita® solution for injection.

Formulation and Composition:

- Crysvita® 10 mg solution for injection. Each vial contains 10 mg of burosumab in 1 ml solution.

- Crysvita® 20 mg solution for injection. Each vial contains 20 mg of burosumab in 1 ml solution.

- Crysvita® 30 mg solution for injection. Each vial contains 30 mg of burosumab in 1 ml solution.

Ex-Manufacturer Price (Ex VAT):

- Crysvita® 10 mg solution for injection: €3,385.54 per vial.

- Crysvita® 20 mg solution for injection: €6,770.75 per vial.

- Crysvita® 30 mg solution for injection: €10,156.29 per vial.

Alternative Price in Place: Yes, Commercial in Confidence agreement in place. Please contact the company for pricing information.

Licensed Indication: Crysvita® is indicated for the treatment of X-linked hypophosphataemia (XLH), in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults.

HSE Approved Indications: The HSE has approved the use of burosumab (Crysvita®) for the treatment of X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons subject to the commercial in confidence agreement approved with the Manufacturing Authorisation Holder.

Eligibility Criteria:

Inclusion:

1. Patient is aged greater than one year
2. Patient has confirmed diagnosis of XLH and has radiographic evidence of disease
3. Patient is accessing treatment subject to the commercial in confidence agreement approved with the Manufacturing Authorisation Holder (MAH).
4. Patient must attend for medical appointments and investigations as determined by the clinical team.

Exclusion:

1. Hypersensitivity to the active ingredient or excipients
2. Concurrent administration with oral phosphate or active Vitamin D analogues
3. Fasting serum phosphate above the normal range for age due to risk of hyperphosphataemia
4. Patients with severe renal impairment or end stage renal disease

Method of Administration: Subcutaneous injection.

Burosumab should be injected in the arm, abdomen, buttock or thigh.

The maximum volume of medicinal product per injection site is 1.5 ml. If more than 1.5 ml is required on a given dosing day, the total volume of medicinal product must be split and administered at two or more different injection sites. Injections sites should be rotated and carefully monitored for signs of potential reactions.

Dose:

The treatment plan must be initiated by a Consultant Endocrinologist experienced in the management of metabolic bone diseases in paediatric, adolescent, or transitional age patients.

Dosing in Children and Adolescents aged 1 to 17 years:

The recommended starting dose[1,2,3] is 0.4mg/kg to 0.8 mg/kg of body weight given every two weeks.

Doses should be rounded nearest 10mg. The maximum recommended dose is 90mg or 2mg/kg.

After initiation of treatment with burosumab, fasting serum phosphate should be measured every 2 weeks for the first month of treatment, every 4 weeks for the following 2 months and thereafter as appropriate. If fasting serum phosphate is within the reference range for age, the same dose should be maintained. Fasting for the purpose of this protocol is defined as 4 hours since last oral intake.

Dose increases

If fasting serum phosphate is below the reference range for age, the dose may be increased stepwise by 0.4 mg/kg up to a maximum dose of 2.0 mg/kg (maximum dose of 90 mg). Fasting serum phosphate should be measured 4 weeks after dose adjustment.

Dose decreases

If fasting serum phosphate is above the reference range for age, the next dose should be withheld and the fasting serum phosphate reassessed within 4 weeks. The patient must have fasting serum phosphate below the reference range for age to restart burosumab at half of the previous dose, rounding the amount as described above.

[1] Haffner, D., Emma, F., Eastwood, D.M. *et al.* Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat Rev Nephrol* **15,** 435–455 (2019). https://doi.org/10.1038/s41581-019-0152-5.

[2] Padidela R, Cheung MS, Saraff V, Dharmaraj P. Clinical guidelines for burosumab in the treatment of XLH in children and adolescents: British paediatric and adolescent bone group recommendations. *Endocr Connect*. 2020;9(10):1051-1056. doi:10.1530/EC-20-0291

[3] Medicines.ie. *Summary of Product Characteristics: Crysvita solution for subcutaneous injection.* Available online from: https://www.medicines.ie/medicines/crysvita-solution-for-subcutaneous-injection-34946/spc . Accessed 20 April 2021.

Missed or delayed doses:

Treatments may be administered 3 days either side of the scheduled treatment date if needed for practical reasons. If a patient misses a dose, burosumab should be resumed as soon as possible at the prescribed dose.

Dose conversion at age 18 years: In adolescents with evidence of continued bone growth at 18 years of age, conversion to the adult dose and dosing regimen may be considered although continuation at paediatric levels is acceptable if puberty is delayed for age.

Refer to the Summary of Product Characteristics for further information (available from: https://www.medicines.ie/medicines/crysvita-solution-for-subcutaneous-injection-34946/spc).

Interval assessment:

Duration of treatment: Information on long term efficacy of this medicinal product is not yet available. The need for continuation of therapy should be reviewed regularly and considered on an individual basis depending on the patient's clinical presentation and response to the therapy. If treatment is tolerated and there are no adverse effects, treatment should continue until there is radiological evidence of cessation of skeletal growth (see *Stopping Criteria* section below).

Burosumab is intended for long-term treatment. A decision to continue the therapy should be made at least annually based on assessment of response.

Stopping Criteria:

Treatment should be discontinued if:

- burosumab therapy is not tolerated

  OR

- Radiological evidence of epiphyseal fusion indicating cessation of skeletal growth. A bone age is recommended once height velocity is <2cm/year^2.

  OR

- Lack of clinical evidence of response.

Additional Information

The information listed is not exhaustive; please refer to the Summary of Product Characteristics for full details on prescribing information. Available online from: https://www.medicines.ie/medicines/crysvita-solution-for-subcutaneous-injection-34946/spc .

Special warnings and precautions for use:

- Ectopic mineralisation Ectopic mineralisation, as manifested by nephrocalcinosis, has been observed in patients with XLH treated with oral phosphate and active vitamin D analogues; these medicinal products should be stopped at least 1 week prior to initiating burosumab treatment. Monitoring for signs and symptoms of nephrocalcinosis is recommended, see ***Monitoring*** section below for further information.

- Hyperphosphataemia: Levels of fasting serum phosphates should be monitored due to the risk of hyperphosphatemia. To decrease the risk for ectopic mineralisation, it is recommended that fasting serum phosphate is targeted in the lower end of the normal reference range for age. Dose interruption and/or dose reduction may be required. Periodic measurement of post prandial serum phosphate is advised.

- Serum parathyroid hormone: Increases in serum parathyroid hormone have been observed in some XLH patients during treatment with burosumab. Periodic measurement of serum parathyroid hormone is advised (see ***Monitoring*** section below).

- Injection site reactions: Administration of burosumab may result in local injection site reactions. Administration should be interrupted in any patient experiencing severe injection site reactions and appropriate medical therapy administered.

- Hypersensitivity: Burosumab must be discontinued if serious hypersensitivity reactions occur and appropriate medical treatment should be initiated.

Drug-Drug Interactions

- Concurrent administration of burosumab with oral phosphate and active vitamin D analogues is contraindicated as it may cause an increased risk of hyperphosphatemia and hypercalcaemia.

- Caution should be exercised when combining burosumab with calcimimetic medicinal products (i.e. agents that mimic the effect of calcium on tissues by activating the calcium receptor). Co-administration of these medicinal products has not been studied in clinical trials and could potentially exacerbate hypocalcaemia.

Pregnancy and Breastfeeding

See the Summary of Product Characteristics for information on the use of burosumab in pregnancy and breastfeeding (available from: https://www.medicines.ie/medicines/crysvita-solution-for-subcutaneous-injection-34946/spc).

Adverse Drug Reactions

▼Burosumab (Crysvita®) is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie .

The most common (>10%) adverse drug reactions reported in paediatric patients treated for up to 64 weeks during clinical trials were: injection site reactions (56%), cough (56%), headache (50%), pyrexia (43%), pain in

extremity (40%), vomiting (39%), tooth abscess (35%), vitamin D decreased (32%), diarrhoea (25%), rash (24%), nausea (15%), constipation (11%), dental caries (11%) and myalgia (11%).

See the Summary of Product Characteristics for full list of adverse drug reactions (available from: https://www.medicines.ie/medicines/crysvita-solution-for-subcutaneous-injection-34946/spc).

Monitoring:

Baseline tests:

- Phosphate-regulating endopeptidase homolog, X-linked (PHEX) mutation or variant of uncertain significance in either the patient or in a directly related family member with appropriate X-linked inheritance.
- Radiographic evidence of rickets.
- Monitor for signs and symptoms of nephrocalcinosis, by renal ultrasound.
- Plasma Alkaline Phosphatase, Calcium, Parathyroid hormone (PTH), Creatinine, and FGF23 levels.
- Urine calcium and phosphate.

Regular tests:

- Tubular maximum reabsorption of phosphate per glomerular filtration rate (TmP/GFR) every 3-6 months depending on age and dose modifications.
- Vitamin D and 1,25 Dihydroxy vitamin D serum levels every 6 months.
- After initiation of treatment with burosumab, fasting serum phosphate should be measured every 2 weeks for the first month of treatment, every 4 weeks for the following 2 months and thereafter as appropriate. Fasting serum phosphate should also be measured 4 weeks after any dose adjustment. If fasting serum phosphate is within the reference range for age, the same dose should be maintained.
- Plasma levels of Alkaline Phosphatase, Calcium, Parathyroid hormone (PTH), Creatinine, and FGF23 levels every 6 months (every 3 months for children 1-2 years) or as indicated.
- Urine calcium:creatinine ratio every 3-6 months depending on age and dose modifications.
- Monitor for signs and symptoms of nephrocalcinosis, e.g. by renal ultrasonography, at least annually.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.