MINISTRY
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PHARMACOCLINICAL PROTOCOL FOR THE USE OF BUROSUMAB IN THE TREATMENT OF X-LINKED HYPOPHOSPHATEMIC RICKETS IN CHILDREN 1 YEAR OF AGE AND OLDER AND ADOLESCENTS WITH A GROWING SKELETON IN THE NATIONAL HEALTH SYSTEM

Approved by the Permanent Pharmacy Commission

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All the experts have made a conflict of interest declaration

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1. INTRODUCTION

X-linked hypophosphatemic rickets or X-linked hypophosphatemia (HLX) is the most common form of hereditary rickets. It is a rare, debilitating chronic disease, with deformations at the bone level that represents approximately 80% of cases of hereditary hypophosphatemic rickets, with a prevalence that ranges from 1.51- 4.8/100.000[1,2,3] and an incidence of 3.9/100,000 live births[3].

HLX is a disease with an X-linked dominant inheritance pattern caused by pathogenic variants in the *Phosphate-regulating gene with homologies to endopeptidases on the X chromosome* (*PHEX*) and it is expressed in osteocytes. Although the pathogenesis of HLX is not fully understood, animal studies indicate that loss of function by *PHEX* increases the secretion of fibroblast growth factor 23 (FGF-23)[4]. There is evidence that FGF-23 is physiologically regulated at the transcriptional and post-translational levels and excess FGF-23 is produced when these regulatory networks are altered, although the mechanism by which excess FGF-23 is produced in HLX is not yet fully clear[5].

FGF-23 works by decreasing the production of proteins related to phosphate reabsorption at the renal level through the Na/P cotransporter in the proximal tubule. In addition, it acts by reducing the production of 1,25-OH vitamin D. As a consequence of these pathogenic variants, FGF-23 levels remain elevated, resulting in reduced renal phosphorus reabsorption, deficient synthesis of active vitamin D and abnormal bone mineralisation[6].

Although clinical manifestations can vary widely even in individuals from the same family[7], HLX usually presents with hypophosphatemia, stunted growth with short stature and rickets, with skeletal findings and dental anomalies (predisposition to spontaneous dental abscesses). Age-adjusted reference values indicate that hypophosphataemia and decreased renal phosphorus reabsorption is accompanied by normal serum calcium values, normal to slightly elevated parathyroid hormone (PTH) values, characteristically elevated alkaline phosphatase activity in children, especially during periods of rapid growth, and normal or slightly reduced plasma calcitriol values[8].

The current treatment in children with HLX is primarily based on the use of oral phosphates and 1-alpha-hydroxylated vitamin D derivatives, as well as addressing the associated complications. Patients usually develop clinical symptoms during the first or second year of life. Early treatment with oral phosphate supplements and active vitamin D can correct or ameliorate the symptoms of rickets, limit the formation of dental abscesses and, in some cases, can prevent progressive growth failure. However, a proportion of patients treated at optimal doses do not benefit and/or are associated with adverse effects (e.g. hyperparathyroidism, renal lithiasis and nephrocalcinosis). Up to two thirds of HLX patients require lower limb surgery to correct severe bowing, tibial torsion or pathological fractures[8]. However, where possible, therapeutic goals should be achieved with a minimal amount of surgery. It is recommended surgery be avoided during childhood, however, some severe bone deformities may require a surgical approach because they are irreversible once the growth phase is over and may cause chronic pain.

Burosumab is a recombinant human monoclonal antibody that binds to FGF-23 and it has been granted orphan drug designation and conditional marketing authorisation for the treatment of HLX in children and adolescents based on the results of two phase 2 studies, one of which was considered the pivotal study, and the other a supportive study[9]. Results are now available from a confirmatory phase 3, randomised, open-label study to evaluate the efficacy and safety of burosumab versus standard therapy (oral phosphate and active vitamin D) in paediatric patients (1-12 years) with HLX[10]. The primary efficacy endpoint was change from baseline in the radiographic global impression of change (RGI-C) scale after 40 weeks of treatment. The RGI-C is a 7-point ordinal scale with scores -3 (severe worsening), -2 (moderate worsening), -1 (minimal worsening), 0 (no change), +1 (minimal healing), +2 (substantial healing), +3 (complete healing). The change in the score on the rickets severity scale (RSS)[a] was measured as a secondary variable, the total assigned score varies between 0 (no rickets) and 10 (severe rickets). The EMA indicates that the total score in HLX does not normally exceed 4 points[11]. Based on the results obtained from the pivotal trial where burosumab showed greater benefit in patients with RSS ≥ 2, this value was considered as the inclusion criterion in the phase 3 trial.

[a] RSS: without rickets (RSS of 0), mild (RSS of 0.5 to 1.0), moderate (RSS of 1.5 to 2.0), and severe (RSS of 2.5 or more).

In the phase 3 trial in paediatric patients aged 1-12 years with HLX, burosumab-treated patients had better RGI-C scores at week 40 versus conventional treatment with a statistically significant difference of 1.13 points [95% CI 0.83 to 1.45], which was maintained at week 64. Improvements were also seen with burosumab over conventional treatment in RSS at week 64, mean change -1.2 [95% CI -1.6 to -0.8][10].

While the results are favorable, there are several uncertainties:

- HLX is a chronic disease, but no efficacy and safety data on the long-term use of burosumab are available at this time. Although a 10-year prospective observational study is under way.
- Controlled data demonstrate that burosumab has an effect on correcting bone defects, but the magnitude of the effect and its clinical relevance are difficult to interpret and it is unclear how it could affect the progression of bone disease in adults and quality of life.
- The clinical trials and extension studies in the indication evaluated in this protocol have included patients up to 12 years of age.
- No comparative data are available in patients with RSS < 2.

2. TREATMENT OBJECTIVE

The aim of treatment should focus on minimising the clinical consequences of the disease by achieving normal phosphate levels, improving growth velocity, resolving skeletal abnormalities and related symptoms such as pain in children from one year of age and growing adolescents with radiographic evidence of bone disease. At the same time, the development of complications such as secondary or tertiary hyperparathyroidism, hypercalciuria, hypercalcaemia, renal lithiasis and nephrocalcinosis should also be monitored.

3. PATIENT SELECTION CRITERIA

Patients with X-linked hypophosphatemic rickets who **meet all the following criteria** are considered candidates for commencing treatment with burosumab:

1. Patients from one year of age and growing adolescents with a confirmed diagnosis of HLX.
2. Have been treated with oral phosphate and active vitamin D for at least the previous 12 months, at appropriate doses, in specialist reference centres.
3. Present radiographic evidence of bone disease and total RSS score ≥2.
4. Epiphyseal closure has not occurred

Initiation of therapy should be carefully considered in patients with[b]:

1. Tanner Stage ≥4
2. Height > 50th percentile by sex and age
3. Growth hormone use in the previous 12 months
4. Plasma parathyroid hormone >180 pg/mL
5. Hypocalcaemia (less than 8.5 mg/dl for total calcium and less than 4 mg/dl for ionic calcium) or hypercalcaemia
6. Nephrocalcinosis grade 4
7. Scheduled orthopaedic surgery

Treatment with burosumab should not be initiated in:

1. Patients with severe renal impairment or end-stage renal disease
2. Patients with fasting serum phosphate levels above normal age-adjusted reference values due to the risk of hyperphosphatemia
3. Patients who are simultaneously receiving oral phosphate or active vitamin D analogues

4. GENERAL CONSIDERATIONS FOR TREATMENT WITH BUROSUMAB

The recommendations included in the summary of product characteristics[12] should be taken into account. The recommended starting dose is 0.8 mg/kg body weight administered every 2 weeks subcutaneously. Doses should be rounded to the nearest 10 mg. The maximum dose is 90 mg.

[b] Populations excluded from the clinical trials. No data are available.

Oral phosphate and active vitamin D analogues (e.g. calcitriol) should be stopped one week before starting treatment. Replacement or supplemental vitamin D treatment with inactive forms may be initiated or continued in accordance with local guidelines as long as serum calcium and phosphate levels are monitored. At baseline, the fasting serum phosphate concentration should be below age-adjusted reference values.

After initiating the treatment with burosumab, fasting serum phosphate concentration should be determined every 2 weeks for the first month of treatment, every 4 weeks for the next 2 months of treatment, and as appropriate thereafter.

The fasting serum phosphate concentration should also be determined 4 weeks after any dose adjustment. If the fasting serum phosphate concentration is within the age-adjusted reference values, the same dose should be maintained.

In order to reduce the risk of ectopic mineralisation, it is recommended that the fasting serum phosphate concentration be at the lower limit of the normal age-adjusted reference values.

Dose increase

If the fasting serum phosphate concentration is below the age-adjusted reference values, the dose may be increased in increments of 0.4 mg/kg to a maximum dose of 2.0 mg/kg (maximum dose of 90 mg). The fasting serum phosphate concentration should be determined 4 weeks after the dose adjustment. The dose of burosumab should not be adjusted more frequently than every 4 weeks.

Dose decrease

If the fasting serum phosphate concentration is above the age-adjusted reference values, the next dose should be discontinued and the fasting serum phosphate concentration should be re-determined after 4 weeks. The patient should have fasting serum phosphate below age-adjusted reference values for restarting burosumab at half of the previous dose, rounding the amount as described above.

Missed dose or late administration

To avoid skipping doses, treatments may be given within 3 days before or after the scheduled treatment date. If the patient skips a dose, burosumab should be resumed at the prescribed dose as soon as possible.

Special populations

Renal impairment

No studies have been conducted with burosumab in patients with renal impairment. Burosumab should not be administered to patients with severe or end-stage renal disease.

Paediatric population

The safety and efficacy of burosumab in children under 1 year of age have not been established. No data are available.

Method of administration.

Burosumab should be injected subcutaneously into 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 needs to be administered on a given day, the total volume of the medicinal product should be divided and administered over two or more different injection sites. The injection site should be rotated and carefully monitored for signs of possible reactions.

Concomitant administration of burosumab with oral phosphate or active vitamin D analogues **is contraindicated** as this may increase the risk of hyperphosphataemia and hypercalcaemia.

Caution should be exercised when combining burosumab with calcimimetics, as co-administration has not been studied and could theoretically worsen hypocalcaemia.

5. OUTCOME VARIABLES (BASED ON OBJECTIVES INCLUDED IN THE PAYMENT-BY-RESULTS AGREEMENT)

Patients will be considered responders if they meet the following objectives:

- ✓ At one year of treatment reduction in the overall RSS score ≥ 1 point from baseline

- ✓ Maintenance in the second year of treatment and annually thereafter of the level of reduction in the RSS score obtained in the first year.

Patients who do not meet the above therapeutic objectives will be considered non-responders and their treatment will be discontinued. In addition, treatment will be discontinued when the epiphyseal closure that determines the end of the patient's growth occurs.

6. EVALUATION AND MONITORING

The doctor responsible for the patient in each of the stages of the process must register the following information in VALTERMED.

General patient details (to be collected in VALTERMED before starting treatment to carry out the evaluation):

- NHS Code[c]
- CIP/CITE code[c]:
- NIF/NIE[c]
- Health Card No.[c]
- Medical Record No.:
- Sex[d]:
- Date of birth[d]:

BASELINE DATA (MANDATORY)

Disease characterisation at the beginning of treatment (mandatory)

- Date of diagnosis of HLX:
- HLX confirmation: by genetic diagnosis (pathogenic variant in the *PHEX* gene in haemizygosis in males or heterozygosis in females): yes/no
- Family history: yes/no
- Radiological evidence of rickets: RSS ≥2: yes/no
- Other radiological skeletal findings: yes/no Type:
- Dental abnormalities: yes/no

Clinical/biochemical data/scales at start of treatment (mandatory, except for those marked with an asterisk which are optional)

Age:

[c] It is mandatory to fill in at least one of these fields.

[d] Mandatory fields.

- Epiphyseal closure at the beginning of treatment (by conventional simple radiography): yes/no
- Height (cm) : z-score : percentile :
- Weight (kg):
- Tanner Stage:
- Date of analysis:
  - Fasting serum levels at baseline
    - Phosphorous[e] (mg/dl):
    - Alkaline phosphatase[f] (U/L):
    - Parathyroid hormone[g] (pg/ml):
    - 25(OH)D[h] (ng/ml):
    - Total calcium (mg/dl):
    - Serum creatinine:
  - Baseline fasting urinary levels
    - Tubular reabsorption of phosphate (TRP)
    - Renal phosphate threshold (TmP/GFR)*
    - Calcium/creatinine ratio
  - Basal glomerular filtration rate (ml/min/1.73 m_2)*:
  - Nephrocalcinosis (renal ultrasound): yes/no degree:
- Valuation scales
  - Scale measurement date:
  - Baseline RGI-C score*
  - 6MWT*:
  - Baseline RSS score:

- **<u>Previous treatment received prior to initiation of treatment (OPTIONAL)</u>**
  - Oral phosphate (elemental phosphorus dosage kg/day): Duration ≥12 consecutive months: yes/no
  - Start Date: End Date:
  - Active vitamin D analogues (dose): Duration ≥12 consecutive months: yes/no
  - Start date: End date:
  - Growth hormone: yes/no Start date: End Date:

[e] In infants and children, normal plasma phosphate values are between 4 and 6.5 mg/dl (1.3 to 2.2 mmol/L), and in adults between 2.5 and 4.5 mg/dl (0.6 to 1.4 mmol/L). Adolescents have intermediate values[13.] Values <3mg/dL are associated with HLX although infants and young children may present with higher values.

[f] Normal values vary with age

[g] Normal PTH values in children and adolescents: 15-60 pg/ml, note that the values may vary depending on the method used. Evidence of hyperparathyroidism, PTH levels 2.5 x ULN

[h] Values above the lower limit of normal ≥16 ng/mL are associated with HLX

No response (unsatisfactory/intolerance/) Indicate date of last administration

- **Patient coming from use under Medicinal Products in Special Situations (mandatory)**: (yes/no)

Prior to starting treatment, it must be ensured that the patient meets the clinical conditions for administration in accordance with reimbursement criteria and the payment by results agreement.

Burosumab administration (MANDATORY)

- Start date of treatment (first administration).
- Dose[i]:
- Dose modification: Date: Reason: (fasting serum phosphate below adjusted reference values/fasting serum phosphate above age-adjusted reference values)
- Definitive discontinuation of treatment: yes/no
  Reason for discontinuation (Serious adverse effects/Intolerance/Non-responder/epiphyseal closure, other)
  Date of last administration:

Burosumab administration (OPTIONAL)

- Temporary interruptions to treatment**:** (yes/no)
  Interruption/restart date:
  Reason:
  - Adverse effects (not including definitive discontinuation of treatment)
  -Other

Concomitant treatments (OPTIONAL)

- Concomitant pathology-related treatment**:**

Start date: End date of treatment:

Follow-up monitoring[12] (MANDATORY)

- Fasting serum phosphorus (mg/dl), day 15: day 30: Day 60: Day 90:
- Nephrocalcinosis (renal ultrasound), day 180: yes/no Degree:
- Serum alkaline phosphatase (U/L), day 180:

[i] The recommended starting dose is 0.8 mg/kg body weight administered every 2 weeks. Doses should be rounded to the nearest 10 mg. The maximum dose is 90 mg.

- Serum parathyroid hormone (pg/ml), day 180:
- Total serum calcium (mg/dl), day 180:
- Serum creatinine, day 180:
- Calcium/creatinine ratio, day 90: day 180: day 270: day 360:
- TRP, day 90: day 180: day 270: day 360:
- TmP/GFR*:

Evaluation of response 12 months after treatment initiation (mandatory, except for those marked with an asterisk)

- Scale measurement date:
  - RSS Score Reduction: ≥1 point (yes/no)
  - RGI-C score*
  - 6MWT*
  - Height (cm): z-score: percentile:
  - Weight (kg):
  - Fasting serum phosphorus (mg/dl):
  - Nephrocalcinosis (renal ultrasound): yes/no Degree:
  - Other:

Evaluation of the annual response following the evaluation of the first year after the start of the treatment (mandatory, except for those marked with an asterisk which are optional)

Minimum mandatory criterion maintain response after 12 months of treatment

- Scale measurement date:
  - RSS score
  - Maintenance/improvement over previous year: (yes/no)
  - RGI-C score*:
  - 6MWT*
  - Height (cm) : z-score : percentile :
  - Weight (kg)
  - Fasting serum phosphorus (mg/dl):
  - Nephrocalcinosis (renal ultrasound): yes/no degree:

Safety (optional): continuous safety monitoring will be performed and recorded whenever relevant in VALTERMED, specifically for serious adverse events

leading to definitive discontinuation of treatment. In particular, the following must be recorded:

1. Occurrence of ectopic mineralization due to hyperphosphatemia: yes/no
2. Occurrence of nephrocalcinosis: yes/no
3. Worsening of existing nephrocalcinosis: yes/no
4. Drug hypersensitivity/intolerance: yes/no
5. Hypercalcaemia: yes/no
6. Hypocalcaemia: yes/no
7. Secondary hyperparathyroidism: yes/no
8. Other:

In addition, all suspected adverse reactions will be reported through the appropriate regional pharmacovigilance centre (www.notificaram.es).

7. BIBLIOGRAPHY

1 Hawley S, Shaw NJ, Delmestri A, Prieto-Alhambra D, Cooper C, et al. Prevalence and Mortality of Individuals With X-Linked Hypophosphatemia: A United Kingdom Real-World Data Analysis. J Clin Endocrinol Metab. 2020 Mar 1;105(3):e871–8.

2 Rafaelsen S, Johansson S, Ræder H, Bjerknes R. Hereditary hypophosphatemia in Norway: a retrospective population-based study of genotypes, phenotypes, and treatment complications. Eur J Endocrinol. 2016;174(2):125–136.

3 Beck-Nielsen SS, Brock-Jacobsen B, Gram J, Brixen K, Jensen TK. Incidence and prevalence of nutritional and hereditary rickets in southern Denmark. Eur J Endocrinol. 2009;160(3):491–497.

4 Liu S, Guo R, Simpson LG, Xiao ZS, Burnham CE, Quarles LD. Regulation of fibroblastic growth factor 23 expression but not degradation by PHEX. J Biol Chem. 2003 Sept 26;278(39):37419-26

5 Kinoshita Y, Fukumoto S. X-Linked Hypophosphatemia and FGF23-Related Hypophosphatemic Diseases: Prospect for New Treatment. Endocr Rev. 2018 Jun 1;39(3):274-291.

6 Sharkey MS, Grunseich K, Carpenter TO. Contemporary Medical and Surgical Management of X-linked Hypophosphatemic Rickets. J Am Acad Orthop Surg. 2015 Jul;23(7):433-42.

7 Vahed LK, Arianpur A, Esmaeili M. The frequency of clinical manifestations of hypophosphatemic rickets in patients with therapeutic strategies. Clin Pract. 2018 May 10;8(2):1072. doi: 10.4081/cp.2018.1072. PMID: 30069302; PMCID: PMC6047480.

8 Haffner D, Emma F, Eastwood DM, Duplan MB, Bacchetta J, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 2019 Jul;15(7):435-455.

9 Informe de Posicionamiento Terapéutico de burosumab (Crysvita) en el tratamiento del raquitismo hipofosfatémico ligado al cromosoma X. 3/02/2020, updated 14/04/2020. Pending publication.

10 Imel EA, Glorieux FH, Whyte MP, Munns CF, Ward LM, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. Lancet. 2019 Jun 15;393(10189):2416-2427. doi: 10.1016/S0140-6736(19)30654-3. Epub 2019 May 16. Erratum in: Lancet. 2019 Jul 13;394(10193):120. PMID: 31104833; PMCID: PMC7179969.

11 The European Medicines Agency. European Public Assessment Report. Burosumab (Crysvita®). Available on: https://www.ema.europa.eu/en/documents/assessment-report/crysvita-epar-public-assessment-report_en.pdf [consulted: 08/12/2020]

12 Burosumab summary of product characteristics (Crysvita®). Available on: https://cima.aemps.es/cima/pdfs/es/ft/1171262001/FT_1171262001.pdf [consulted: 08/12/2020]

13 Santos F et al. In: García Nieto VM, Rodríguez Iturbe B, Santos F, editores. Nefrología Pediátrica. Aula Médica. 2006. p 161-179