REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Crysvita

10 mg/ml solution for injection – 1 ml x 1 vial;

20 mg/ml solution for injection – 1 ml x 1 vial;

30 mg/ml solution for injection – 1 ml x 1 vial

Burosumab

Therapeutic indication(s)	indicated for the treatment of X-linked hypophosphataemia, in children aged 1 year and over and adolescents with incomplete bone growth
Start/end date of procedure	30.09.2019 - 11.11.2020
Final decision	Rejects inclusion in Annex 1 of the Positive Drug List (PDL) for home treatment of diseases, paid for by the NHIF and in Annex 2 of the PDL for purchase from medical institutions with state and/or municipal participation and under Art. 5 of the Medical Establishments Act..

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Crysvita

Health problem

X-linked hypophosphatemia is a hereditary, progressing disease, caused by mutations in the endopeptidase X-linked gene, leading to a disturbance of the phosphate-regulating system and increased circulating levels of fibroblast growth factor 23 (FGF23). Elevated circulating FGF23 levels reduce renal phosphate reabsorption and reduce the production of active vitamin D, resulting in impaired bone and tooth mineralization. The disease begins in utero, with the first clinical symptoms occurring in early childhood and persisting with age. In children, XLH causes rickets, leading to bone deformities of the lower extremities, requiring corrective surgical interventions, short stature, development of dental abscesses, deformities of the joints and skull. Onset of walking is delayed, the gait changes, children complain from easy fatigability and pain in the bones and joints. These complaints intensify with increasing age.

The diagnosis of hypophosphatemic rickets is based on a combination of clinical, radiological and biochemical disorders.

X-linked hypophosphatemia is characterized by loss of renal phosphate and is the most common form of hereditary rickets. Clinical manifestations vary in severity, their debut is most often in childhood with limb deformities and short stature.

Due to the low frequency of X-linked hypophosphatasia and the variety of clinical manifestations, the diagnosis is often delayed and treatment can be a challenge.

Epidemiological data

The most common form of hypophosphatemic rickets is the X-linked with a frequency of 1:20 000. Based on data from Orphanet, the expected number of patients with hypophosphatemic rickets for the population 0 to 18 years is about 22. The estimated incidence is approximately 0-3 new cases of year, with some of the children born with XLH remaining undiagnosed.

Efficacy data

Efficacy data for Crysvita are based on three ongoing studies, evaluating the efficacy and safety of burosumab, and a retrospective longitudinal skeletal survey in children with hypophosphatemic rickets.

UXO23-CL301 is a randomized, open-label phase 3 study, assessing the efficacy and safety of burosumab versus treatment with oral phosphate and active vitamin D in pediatric patients with hypophosphatemic rickets. Study CL301 showed that treatment with burosumab had

better effect on the primary and secondary endpoints of the study as compared to conventional treatment. Patients treated with burosumab had a greater improvement in mean rickets severity (Rickets Severity Score, RSS) as compared with those receiving conventional treatment with vitamin D and phosphate. The serum phosphate increases in patients treated with burosumab to mean values within or just below the reference intervals.

UXO23-CL201 is a randomized, open-label, phase 2 dose-finding study, investigating the pharmacodynamics, efficacy and safety of the anti-FGF23 antibody burosumab in pediatric patients with hypophosphatemic rickets. The results of the clinical trial CL201 show a reduced mean value for the severity of rickets (Rickets Severity Score, RSS) for both dosing regimens, which indicates an improvement in rickets symptoms compared to the baseline. The improvement is greater for patients who have a higher RSS at the baseline. The results of the study showed that the inhibition of FGF-23 by burosumab results in increased tubular renal phosphate reabsorption and correction of hypophosphatemia in children with hypophosphatemic rickets. Every two weeks dosing provides a more stable increase in the serum phosphate and renal tubular levels phosphate reabsorption as well as a greater decrease in serum ALP compared to every four weeks dosing. The results of CL201 show that treatment with burosumab every two weeks leads to a healing of rickets, as measured by RGI-C, in all children (100%) with more severe disease at baseline.

UXO23-CL205 is an open-label, phase 2 study, evaluating the safety, pharmacodynamics and efficacy of burosumab in children with hypophosphatemic rickets 1 to 4 years old. Data from clinical trial CL205 confirm efficacy results for RSS, as well as the pharmacokinetic parameters observed in CL201 and CL201 in younger children with CKD as well. All patients show eradication of the symptoms of rickets, as calculated by RGI-C at week 40 of the study.

Safety data

The most common adverse events in patients treated with burosumab in clinical trials are fever, cough, joint pain, nausea, inflammation of the nose and throat and pain in the limbs. Of all patients, 45% had reactions at the injection site, with all but one being mild and none considered serious.

Data on comparators

Current treatment of first choice consists of concomitant use of active vitamin D analogues: alfacalcidol or calcitriol and oral phosphate supplements, taken several times a day.

Pharmacoeconomic indicators

Published health technology assessments of governmental institutions intended for the health care systems of other countries

NICE (UK) gives a positive recommendation with a mandatory scheme with confidential access discount. A positive recommendation was also given by TLV (Sweden), G-BA (Germany) and HAS (France).

Applied analysis

The applied pharmacoeconomic methods are cost-effectiveness and cost-benefit analysis. QALY and intermediate outcomes were used as outcome measures (based on data from clinical trials - the severity of rickets and overall impression of radiographic change). The perspective of the analysis is that of the payer institution – the NHIF. The time horizon is lifelong. Both costs and results are discounted with a discount rate of 3.5%. Osteo D is chosen as comparator. Cost-effectiveness analysis uses data from all three clinical trials with Crysvita to reduce the uncertainty of the final results. Cost-benefit analysis covers two hypothetical scenarios - early diagnosis and early initiation of therapy and late diagnosis and/or late start of therapy. Both scenarios are further divided into girls and boys, because of the different age of completion of bone growth. When comparing scores for boys, ICER is significantly higher in the additional scenario with late diagnosis and/or late initiation of Crysvita therapy relative to baseline scenario. In girls, given the shorter treatment period of 2 years, these results are close. A one-way sensitivity analysis of the cost-benefit analysis results was performed. In all scenarios, the new health technology is not cost effective.

Analysis of subgroups

No subgroup analysis was performed.

Costs of the assessed health technology

Treatment costs with Crysvita and treatment costs with the comparator (Osteo D) are included.

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the paying institution - the National Health Insurance Fund. The time horizon is 5 years. The expected number of treated patients in the first year is 8, and in the fifth it is 28. Reimbursement of the health technology will generate additional costs for the payer institution for the first year, which will increase over each following year, not considering risk-sharing agreements and patient access schemes.

Conclusion

Crysvita is an orphan medicine designed for use in a rare disease. Crysvita is recommended as a second-line therapy in children with severe X-linked hypophosphatemia, hypophosphatemic rickets with radiographic evidence of bone disease in children aged 1 year and older and adolescents with incomplete bone growth, refractory to conventional therapy. In the subgroup of patients - children with radiographic data of bone disease aged 1 year and older and adolescents with incomplete bone growth with severe CKD with complications, Crysvita is recommended as the first choice of therapy. The medicinal product is not cost-effective with a threshold of profitability 3 times GDP per capita. Reimbursement of the health technology will generate additional costs for the paying institution.