19 February 2018
EMA/51018/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Crysvita (recombinant human monoclonal IgG1 antibody for fibroblast growth factor 23)
Treatment of hypophosphataemic rickets
EU/3/14/1351(EMA/OD/133/14)
Sponsor: Kyowa Kirin Limited - United Kingdom

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substance	Recombinant human monoclonal IgG1 antibody for fibroblast growth factor 23
International Non-Proprietary Name	Burosumab
Initial orphan indication	Treatment of X-linked hypophosphataemia
Amended orphan indication	Treatment of hypophosphataemic rickets
Pharmaceutical form	Solution for injection
Route of administration	Subcutaneous use
Pharmaco-therapeutic group (ATC Code)	Drugs affecting bone structure and mineralization, other drugs affecting bone structure and mineralization (M05BX)
Sponsor's details:	Kyowa Kirin Limited Galabank Business Park Galashiels TD1 1QH United Kingdom
Orphan medicinal product designation procedural history	
Sponsor/applicant	Kyowa Kirin Limited - United Kingdom
COMP opinion date	4 September 2014
EC decision date	15 October 2014
EC registration number	EU/3/14/1351
Post-designation procedural history	
Transfer of sponsorship	Transfer from NDA Group AB to Kyowa Kirin Limited EC decision of 1 August 2016
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	K. Dunder, R. J. Hemmings
Applicant	Kyowa Kirin Limited
Application submission date	30 November 2016
Procedure start date	23 December 2016
Procedure number	EMEA/H/C/004275/0000
Invented name	Crysvita
Therapeutic indication	Treatment of X-linked hypophosphataemia Further information on Crysvita can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	14 December 2017
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	V. Tillmann /.I. Barisic
Expert	No experts were appointed by the COMP for this application
Sponsor's report submission date	7 August 2017
COMP discussion and adoption of list of questions	30-31 October 2017
Sponsor responses to the list of questions	20 November 2017
COMP opinion date	15 January 2018

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2014 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing recombinant human monoclonal IgG1 antibody for fibroblast growth factor 23 was considered justified based on pre-clinical in vivo and clinical data in patients with the condition;
- the condition is chronically debilitating due to inadequate mineralization which results in soft bones and consequential bone deformities, and once the patients become weight bearing, it leads to the characteristic genu varum, genu valgum, tibial torsion, as well as rickets changes in metaphyses of the bones, especially notable in the wrists and knees on x-ray;
- the condition was estimated to be affecting between 0.002 to 0.04 per 10,000 persons in the European Union, at the time the application was made;
- there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The condition submitted by the sponsor is for X-linked hypophosphataemia (XLH). At the time of the initial designation this condition was well established in the literature.

The disorder is reportedly linked to a mutation of the phosphate regulating gene homologous to endopeptidases on the X chromosome. This gene is believed to encode for fibroblast growth factor 23 (FGF-23) which is expressed in bone.

The gene defect leads to impaired proximal renal tubular reabsorption of phosphate due to reduced expression of sodium-phosphate (TRP), due to reduced expression of sodium-phosphate co-transporters on the apical surface of the proximal renal tubule cells. Elevated FGF-23 levels cause the abnormal modulation of the vitamin D axis.

The mutations inhibit FGF-23 inactivation, thus causing increased levels of free FGF-23 in the plasma and thereby causing hyperphosphaturia. There is also a loss of the conversion of 25(OH)-vitamin (Calcidiol) conversion to its active form 1,25(OH)-vitamin D. FGF-23 seems to play a central role on this axis through its phosphoturic effects and its autocrine action on osteoblasts, thus modulating bone mineralisation.

Clinical features of XLH presents itself in the first years of life and can include short stature, reduced growth rate and bone deformity (*Eur J Orthop Surg Traumatol (2015) 25:221-226*).

FGF23 has been found to be related to a number of hereditable and acquired phosphate wasting disorders which the literature has been consolidating these disorders under the term of hypophosphtaemic rickets since the designation in 2014. Genetic disorders include X- linked dominant hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, hypophosphatemic rickets associated with McCune–Albright syndrome and Linear sebaceous nevus syndrome. Acquired disorders include tumour induced osteomalacia.

Hypophosphatemic rickets is a genetic disorder and the X-linked inheritance (XLI) is the most frequent form of transmission, accounting for about 80 % of the familial cases of hypophosphatemia. The remaining 20 % of familial HR patients belong to the HR autosomal dominant and to the hereditary HR with calciuria types (*Eur J Orthop Surg, Traumatol, February 2015, Volume 25, Issue 2, pp 221–226*).

Furthermore the autosomal dominant hyposphatemic rickets (ADHR) patients have clinical and biochemical findings similar to those of X-linked dominant hypophosphataemic rickets patients. The autosomal forms show variable and incomplete penetrance with variable symptomatology and biochemical findings depending on the age at presentation. Patients who manifest the disease in their childhood develop short stature, rickets, bone pain, lower extremity deformities, and dental abscess. Some of the children have spontaneous resolution of symptoms during adulthood (*Bone Research (2013) 2: 120-132*).

Autosomal-recessive hypophosphatemic rickets (ARHR), is a rare disorder that is recently recognized (Eur J Orthop Surg, Traumatol, February 2015, Volume 25, Issue 2, pp 221–226). Clinical and biochemical findings of the affected individuals are similar to ADHR and XLH. Clinical features include rickets, skeletal deformities, dental defects, and affected individuals develop sclerotic bone lesions and enthesopathies. The clinical presentation of ARHR is not found at birth. Affected individuals present signs of rickets/osteomalacia later during childhood and even in adulthood.

In view of the grouping of the different forms of the condition linked with either a dysfunction of fibroblast growth factor 23 or a similarity in phosphate wasting signs and symptoms the COMP was of the opinion that the original condition could be broadened from X-linked hyphosphataemia to hypophosphataemic rickets. This was to include the autosomal forms and acquired forms described in review articles on hypophosphataemic rickets.

The approved therapeutic indication “treatment of X-linked hypophosphataemia (XLH) in children and adolescents aged 1 to <18 years” falls within the scope of the amended orphan indication “treatment of hypophosphataemic rickets”.

Intention to diagnose, prevent or treat

Based on the positive CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

Clinical manifestations vary in severity, but patients most commonly present in childhood with bowing deformities of the legs. Progressive bowing, antero-medial rotational torsion of tibiae, and short stature represent the predominant skeletal outcomes in growing children. Osteomalacia (accumulation of unmineralized osteoid) is characteristic of hypophosphataemic rickets.

The patients present with growth retardation and disproportionately short stature and limb deformities which appear after the ages of 1 or 2 years. In adulthood, the disease is associated with osteomalacia, musculoskeletal pain/stiffness and dental abscesses.

When rickets is quickly and properly treated, there is a rapid improvement of the symptomatology, although treatment requires careful and frequent laboratory evaluation. Short stature may persist into

adult age. After 20 years of age, the treatment may become less aggressive and patients may be treated only with calcitriol. (Endocrine Connections (2014) 3, R13–R30). Identification of the causative mutation in patients with hypophosphatemic rickets may be useful to confirm the diagnosis and probably for prognosis. (Curr Opin Endocrinol Diabetes Obes 2012, 19:460–467)

Number of people affected or at risk

The sponsor has provided a prevalence calculation which covers more recent publications than what was submitted at the time of designation, and information from the UK's NIHR (RUDY) database. Below please find the table submitted by the sponsor of the publications used.

Table 1.

Country	Incidence or prevalence (as stated in the publication)	Referenced by	Source reference	Limitation(s)
Prevalence and incidence				
Denmark France	Incidence of 3.9 per 100,000 (0-0.9 years) Prevalence of 4.8 per 100,000 (0-14.9 years), corresponding to 1:21,000	(Beck-Nielsen et al. 2009) (Beck-Nielsen et al. 2010a) (Gjorup et al. 2011) (Beck-Nielsen et al. 2012) (Beck-Nielsen et al. 2013) (Nielsen et al. 2014) (Shanbhogue et al. 2015) (Che et al. 2016)	(Beck-Nielsen et al. 2009)	Incidence is in children only (0-0.9 years Prevalence is in children only under 15 years Ethnic Danish children only Southern Denmark only, Southern Jutland County excluded. Small national population.
Incidence				
Germany Greece Italy	Incidence of 1:20,000	(Freudlsperger et al. 2013) (Papadopoulou et al. 2013) (Capelli et al. 2015)	Unreferenced	Unreferenced/Source is unclear.
Portugal and Spain	Incidence of 1 in 20,000	(Morey et al. 2011)	(Tenenhouse 1999)	Source is unreferenced.
France	Approximately 1 in 20,000 births.	(Lempicki et al. 2017)	(Endo et al. 2015)	Study in Japan only.
Prevalence				
Germany Latvia	Prevalence of 1 in 20,000 births	(Kienitz et al. 2011) (Mukane et al. 2015)	Unreferenced	Source is unreferenced/unclear.
Greece	Approximate prevalence of 1 in 20,000	(Yavropoulou et al. 2010)	(Brame et al. 2004)	No source of prevalence indicated in (Brame et al. 2004).
Italy	Prevalence of 1/20,000	(Capelli et al. 2015)	(Albright et al. 1937)	Author references Albright 1937 as the source of prevalence. Prevalence is not stated in Albright 1937.
Germany	Prevalence of 1/20,000	(Anthonissen et al. 2014)	(Carpenter 1997) (Rasmussen et al. 1994)	No further back-referencing has been undertaken for this citation.
Norway	Prevalence of approximately 1 in 60 000 Norwegian children under 18 years old.	(Rafaelsen et al. 2016)	(Rafaelsen et al. 2016)	Norway population only, in children under 18 years

The condition is reported to be present in many of the EU Member States, the incidence however, seem to vary between the European countries. In Denmark it is reported as 3.9 in 100,000, in the UK as 3 in 100,000, and in Sweden as 5 in 100,000. This translates to an incidence of ~1 in 20,000.

The data supports that the prevalence is stable and similar across Europe. Life expectancy for these patients is normal. Indeed if *rickets is quickly and properly treated, there is a rapid improvement of the symptomatology, although treatment requires careful and frequent laboratory evaluation* (Eur J Orthop Surg Traumatol (2015) 25:221-226). The same publications states: "*After 20 years of age, the treatment may become less aggressive and patients may be treated only with calcitriol.*"

The sponsor proposes that the prevalence is 0.48 in 10,000 in Europe.

Another approach to the test the proposed prevalence is the following: If the incidence of the condition is around the same in most Member States namely 1 in 20,000 and there is 5.1 million live births in the European Union this corresponds to 250 children born with the condition. If life expectancy is taken to be ~80 years this would correspond to around 20,000 individuals or a prevalence of 0.5 in 10,000 in Europe.

The sponsor's proposal of 0.48 in 10,000 is acceptable for the population with *X-linked Hyphosphataemia*. The remaining 20 % of familial HR patients belong to the HR autosomal dominant and to the hereditary HR with calciuria types (Eur J Orthop Surg, Traumatol, February 2015, Volume 25, Issue 2, pp 221–226). As the COMP asked the sponsor to expand the condition to *Hypophosphataemic rickets* which includes the autosomal forms described in the literature the

prevalence slightly increased. The sponsor amended the prevalence accordingly to 0.6 in 10,000 to account for the additional forms described in the literature.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are no products authorised for the treatment of this condition. Calcitriol or alfacalcidol and phosphate supplementation are used from the time of diagnosis until growth is complete. Current outcomes of this therapy are still not optimal, and therapies targeting the pathophysiology of the disease, i.e. FGF23 excess, are desirable. (Endocrine Connections (2014) 3, R13–R30) There are no specific guidelines for the management or treatment of patients with this condition in Europe. Gudielines have been pubished in the US in 2011 for X-linked hypophosphataemia (*J Bone Miner Res. 2011 July ; 26(7): 1381–1388.)*. This guideline recommends *combining active vitamin D metabolites with a balanced dose of phosphate asa the mainstay of therapy.*

In a recent publication in the Lancet in 2014 (*Lancet 2014;383:1665-76*) a treatment algorithm divides the treatment by parathyroid hormone levels. If parathyroid hormone levels are elevated and Vitamin D levels are low, the vitamin D deficiency should be treated. The article highlights that in this setting the treatment is with a vitamin D preparation ergocalciferol or cholecalciferol. If the Vitamin D levels are not low the physician should retake the history and consider a vitamin D pathway defect.

Significant benefit

Not applicable.

4. COMP position adopted on 15 January 2018

The Committee for Orphan Medicinal Products (COMP) considered that the designated orphan condition, X-linked hypophosphataemia, should be renamed as “hypophosphataemic rickets” (hereinafter referred to as “the condition”).

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of hypophosphataemic rickets was estimated to remain below 5 in 10,000 and was concluded to be 0.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to inadequate mineralization which results in soft bones and consequential bone deformities, and once the patients become weight bearing, it leads to the characteristic genu varum, genu valgum, tibial torsion, as well as rickets changes in metaphyses of the bones, especially notable in the wrists and knees on x-ray;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Crysvita, burosumab, recombinant human monoclonal IgG1 antibody for fibroblast growth factor 23, EU/3/14/1351 for treatment of hypophosphataemic rickets is not removed from the Community Register of Orphan Medicinal Products.