EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 August 2021
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment report designation

Voxzogo (modified recombinant human C-type natriuretic peptide)
Treatment of achondroplasia
EU/3/12/1094

Sponsor: Biomarin International Limited

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

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Table of contents

1. Product and administrative information

Product	
Designated active substance	Modified recombinant human C-type natriuretic peptide
Other name	Modified recombinant human C-type natriuretic peptide
International Non-Proprietary Name	Vosoritide
Tradename	Voxzogo
Orphan condition	Treatment of achondroplasia
Sponsor's details:	Biomarin International Limited Shanbally Co. Cork Ringaskiddy P43 R298 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	BioMarin Europe Ltd.
COMP opinion	06 December 2012
EC decision	24 January 2013
EC registration number	EU/3/12/1094
Post-designation procedural history	
Transfer of sponsorship	Transfer from BioMarin Europe Ltd. to Biomarin International Limited – EC decision of 12 February 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Martina Weise / Andrea Laslop
Applicant	Biomarin International Limited
Application submission	23 July2020
Procedure start	13 August 2020
Procedure number	EMA/H/C/5475/0000
Invented name	Voxzogo
Proposed therapeutic indication	Treatment of achondroplasia Further information on Voxzogo can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Voxzogo
CHMP opinion	24 June 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Ingeborg Barisic
Sponsor's report submission	05 February 2021
COMP discussion	14-17 June 2021
COMP opinion (adoption via written procedure)	25 June 2021

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2012 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing vosoritide was considered justified based on pre-clinical studies showing chondrocyte proliferation and differentiation leading to widening of the growth plates and skeletal growth;
- the condition is chronically debilitating due to manifestations such as otolaryngeal system dysfunction, and rhizomelic short stature, thoracolumbar kyphosis, spinal stenosis, and foramen magnum stenosis and life-threatening with approximately 10 years shorter life expectancy compared to the general population;
- the condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment 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

Achondroplasia is an autosomal dominant form of dwarfism, associated with activating mutations in the Fibroblast Growth Factor Receptor 3 (FGFR3) gene. This mutation results in defects in long bone growth resulting in short stature and other skeletal deformities described below.

The most common mutation (p.G380R) is linked to a region in the transmembrane domain of FGFR3 of approximately 98% of achondroplasia patients and leads to ligand-dependent hyperactivation of the receptor by increasing the residence time of the receptor on the membrane thereby contributing to increased signalling (Laederich et al, 2010; Monsonego-Ornan et al, 2000; Bonaventure et al, 1996). Increased FGFR3-mediated signalling inhibits differentiation of the growth plate chondrocytes of long bones and select intramembranous bones leading to short stature, narrowing of the spinal canal (foramen magnum), spinal stenosis and recurrent ear infections.

The approved therapeutic indication "Voxzogo is indicated for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing." falls within the scope of the designated orphan condition "Treatment of Achondroplasia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Among the most serious and fatal consequences of achondroplasia are respiratory disorders that lead to increased mortality among infants. Studies have reported up to a 6-fold higher mortality among infants <1 year of age compared to the general population in recent decades (Simmons et al, 2014; Hecht et al, 1987). Among age groups the standardized mortality ratio (mortality of disease population compared to healthy population within the age group) was highest among infants age 0 to 4 years, with deaths most frequently attributed to sudden infant death related to respiratory complications. Overall survival and the average life expectancy have been reported to be decreased by up to 10 years compared to healthy populations.

The skeletal growth abnormalities from achondroplasia also result in significant respiratory complications, most notably a high prevalence of sleep disordered breathing.

Neurologic complications associated with spinal stenosis also persist throughout life. Lumbosacral spine stenosis with resulting intermittent spinal claudication or overt stenosis (with asymmetric lower extremity strength, gait changes, and bladder or bowel incontinence) has been found to develop in older children and adults (Pauli et al, 1998). Approximately 36% of patients with lumbar stenosis require decompression surgery (Okenfuss et al, 2020).

Musculoskeletal impairments arising from disproportionate limb-to-trunk ratios result in limited reach and range of motion, mobility, and impaired independent self-care, lumbosacral lordosis with subsequent back pain and muscle fatigue (Ireland et al, 2014).

Otolaryngology complications are also frequently present. Achondroplasia is also associated with long term psychosocial consequences.

The condition is therefore associated with both chronically debilitating and life-threatening aspects.

Number of people affected or at risk

At the time of designation, the prevalence (P) was agreed to be approximately 0.4 per 10,000.

For this review the prevalence was presented to the COMP to remain less than 5 per 10,000. Based on the European literature (Table 1) the prevalence ranges from 0.08 to 0.48 per 10,000.

These estimates have been derived also by using the formula P=I*D (incidence * duration). Incidence was calculated using the reported birth prevalence multiplied by the number of country-specific live births. Duration was calculated as the mean years of survival for individuals with achondroplasia (59.6 years), using data from Wynn et al, 2007. Complete point prevalence is the appropriate measure for achondroplasia since it is an inborn error lasting for life. As such, complete point prevalence was defined as the total number of prevalent achondroplasia cases in a predefined population, divided by the sample size of the predefined population, multiplied by 10,000. For both country-specific live births and population, 2019 data were used as it represents the most recent year of complete data reporting for both measures.

The sponsor considers the recently published study from the EUROCAT registry (Coi et al., 2019) to represent the highest quality of evidence for the prevalence of achondroplasia in Europe, reporting a birth prevalence of 0.31 per 10,000 affected live births, which predicts a complete point prevalence of

0.18 per 10,000 in 2019. All other point prevalence estimates based on European literature range from 0.08 to 0.48 per 10,000.

Achondroplasia prevalence as reported in the dossier:

Table 1: Summary Prevalence of Achondroplasia-Affected Individuals in the European Community

Country [Region], (Author, Year)	Reported achondroplasia birth prevalence (per 10,000)	Number of live births per country in 2019[b]	Number of predicted affected new births in 2019 ("Incidence")[c]	Estimated number of living affected achondroplasia population ("Prevalence")[d]	Total population per country in 2019[e]	Estimated achondroplasia complete point prevalence in 2019 (per 10,000)[f]
EUROCAT registries (28 registries/17 countries)a (Coi et al., 2019)	0.31	4,864,563	151	8,988	513,471,676	0.18
Denmark (Kallen et al., 1993)	0.61	61,167	4	222	5,806,081	0.38
Italy (Camera and Mastroiacovo, 1988)	0.37	61,167	1	47	5,806,081	0.08
Italy (Kallen et al., 1993)	0.34	753,578	23	1,392	67,012,883	0.21
Scotland [Edinburgh] (Gardner, 1977)	0.23	753,578	48	2,874	67,012,883	0.43
Sweden (Kallen et al., 1993)	0.16	420,170	15	905	60,359,546	0.15
Spain, [16/17 regions] (Martinez-Frias et al., 1991)	0.25	420,170	14	851	60,359,546	0.14
France, [Strasbourg and Departement du Bas-Rhin]	0.64	420,170	16	927	60,359,546	0.15

(Stoll et al., 1989)						
France (Kallen et al., 1993)	0.31	420,170	15	920	60,359,547	0.15
Denmark [Fyn] (Andersen Jr and Hauge, 1989)	0.13	49,863	1	68	5,424,800	0.13
Italy (Camera, 1980)	0.19	357,924	9	533	46,937,060	0.11
Italy (Orioli et al., 1995)	0.36	114,523	2	109	10,230,185	0.11
Sweden [Uppsala] (Gustavson & Jorulf, 1975)	0.68	114,523	8	461	10,230,185	0.45
UK [Manchester] (Harris & Patton, 1971)	0.63	712,699	54	3,209	66,647,112	0.48
UK (Sokal et al., 2014)	0.76	712,699	45	2,658	66,647,112	0.40
European Region totalg	0.31	4,864,563	151	8,988	513,471,676	**0.18**
Europe excluding UKg	0.31	4,151,864	129	7,671	446,824,564	**0.17**

[a]EUROCAT included countries [registries]: Austria [Styria]; Belgium [Antwerp]; Croatia [Zagreb]; Denmark [Odense]; France [Paris, Isle de Reunion, Auvergne, French West Indies, Brittany]; Germany [Saxony Anhalt]; Ireland [Cork & Kerry, South East Ireland]; Italy [Emilia Romagna, Tuscany]; Malta; Netherlands [Northern]; Norway; Poland [Wielkopolska]; Portugal [South]; Spain [Basque Country, Valencia]; Switzerland [Vaud]; UK [Wales, South West England, Northern England, Thames Valley, Wessex] Ukraine [OMNI-net].
[b] Source: All countries except Scotland: Eurostat https://ec.europa.eu/eurostat/databrowser/view/tps00204/default/table?lang=en (data for 2019). Europe total uses Eurostat estimate for European Union 28 countries (2013-2020); Accessed 30th September 2020. Scotland: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/vital-events-reference-tables/2019/list-of-data-tables; Accessed 30th September 2020.
[c] Incidence (I) = Birth prevalence X number of country-specific live births per 10,000.
[d] Prevalence (P) = Incidence (I) X Duration (D), where duration is average life expectancy of achondroplasia population at 59.6 years from Wynn et al., 2007
[e]Source: All countries except Scotland: https://ec.europa.eu/eurostat/databrowser/view/tps00204/default/table?lang=en. (data for 2019). Europe total uses Eurostat estimate for European Union 28 countries (2013-2020); Accessed 30th September 2020. Scotland: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population/population-estimates/mid-year-population-estimates/mid-2019; Accessed 30th September 2020.
[f] Complete Point Prevalence = Estimated living affected population (prevalence) divided by total country-specific population x 10,000

[9] European total (with and without UK) calculated uses birth prevalence from Coi et al 2019 and population sources as described above

The COMP agreed that not much has changed since the orphan designation and that a prevalence of 0.4 in 10,000 is still suitable.

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

No medicinal products are authorised in the EU for this condition.

Current treatments are mainly limited to surgical interventions, including cervicomedullary decompression for foramen magnum stenosis and laminectomy surgery for spinal canal stenosis, and medical devices such as thoracolumbar braces to help ameliorate the kyphosis (Shirley, 2009).

However, there is no established therapy that improves growth as well as body proportionality while also decreasing the burden of complications (Kubota et al, 2020).

Significant benefit

Not applicable, since there are no satisfactory methods currently authorised in the EU for treatment of patients with achondroplasia.

4. COMP position adopted on 25 June 2021

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of achondroplasia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.4 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 manifestations such as hypotonia, otolaryngeal system dysfunction, and rhizomelic short stature, thoracolumbar kyphosis, spinal stenosis, and foramen magnum stenosis and life-threatening with approximately 10 years shorter life expectancy;
- there is, at present, no satisfactory method of 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 Voxzogo, modified recombinant human C-type natriuretic peptide, vosoritide for treatment of achondroplasia (EU/3/12/1094) is not removed from the Community Register of Orphan Medicinal Products.