NEW DRUG APPROVAL

Brand Name	Voxzogo™
Generic Name	vosoritide
Drug Manufacturer	BioMarin Pharmaceutical Inc.

New Drug Approval

FDA Approval Date: November 19, 2021
Review designation: Priority; Orphan
Type of review: Type 1 - New Molecular Entity; NDA: 214938
Dispensing restriction: Specialty Only, Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Achondroplasia is the most common of the skeletal dysplasias that result in marked short stature (dwarfism). Although its clinical and radiologic phenotype has been described for more than 50 years, there is still a great deal to be learned about the medical issues that arise secondary to this diagnosis, the manner in which these are best diagnosed and addressed, and whether preventive strategies can ameliorate the problems that can compromise the health and well-being of affected individuals. The vast majority of individuals with achondroplasia are diagnosed in early infancy, although prenatal recognition has become more frequent and more accurate. It is critical that diagnosis not be delayed since certain complications can only be prevented through assessment in early infancy. Clinical features include small stature, short limbs and rhizomelic disproportion, macrocephaly, midfacial retrusion, small chest, thoracolumbar kyphosis, Lumbar hyperlordosis, limited elbow extension, short fingers and trident configuration of the hands, hypermobile hips, and knees, bowing of the mesial segment of the legs and hypotonia.

There have been no large population-based studies of the prevalence of achondroplasia and thanatophroic dysplasia in the United States. This study compared data from seven population-based birth defects monitoring programs in the United States. We also present data on the association between older paternal age and these birth defects, which has been described in earlier studies. The prevalence of achondroplasia ranged from 0.36 to 0.60 per 10,000 livebirths (1/27,780–1/16,670 livebirths). The prevalence of thanato-phoric dysplasia ranged from 0.21 to 0.30 per 10,000 livebirths (1/33,330–1/47,620 livebirths). In Texas, fathers that were 25–29, 30–34, 35–39, and ≥40 years of age had significantly increased rates of de novo achondroplasia among their offspring compared with younger fathers. The birth prevalence of achondroplasia in North America ranges from 1:10,000 to 1:30,000. BioMarin estimates there are approximately 3000 individuals 0–18 years of age with achondroplasia in the United States.

Efficacy

The approval of Voxzogo™ was based on one 52-week, multicenter, randomized, double-blind, placebo-controlled, Phase3 study (Study 1) of 121 participants (NCT03197766) and the open-label extension of the Phase 3 study (NCT03424018).Table 1 provides a summary of the Study 1 design.

Table 1. Voxzogo™ Study 1 (NCT03197766): Study Design Summary	
Study Population (N = 121)	• Genetically confirmed achondroplasia • Mean age: 8.7 years (range, 5.1–14.9 years) • 53% male • 71% White/Caucasian; 19% Asian; 5% Black/African American; 6% multiple races • Mean baseline height SDS: –5.13 • **Key exclusion criteria:** ○ Evidence of growth plate closure (proximal tibia, distal femur) or AGV <1.5 cm/yearover 6 months ○ Previous treatment with GH, IGF-1, or anabolic steroids in the previous 6 months ○ Planned or expected limb-lengthening surgery during study period (but may enroll ifsurgery occurred at least 18 months prior to study)
Interventions	• 121 participants were randomized to receive either: ○ Voxzogo™ at a dose of 15 mcg/kg administered SC once daily (n = 60) or ○ Placebo (n = 61)
Endpoints	**Primary endpoint:** Change in AGV (cm/year) at Week 52 **Secondary endpoint:** Height SDS

Study 1 Results:

The results presented in Table 2 show that patients treated with Voxzogo™ experienced an increase in AGV of 1.57 centimeters/year greater than placebo. Results published in Nature in August 2021 show that the AGV benefit was observed by Week 26. The prescribing information states that the improvement in AGV in favor of Voxzogo™ was consistent across sex, age group, Tanner stage, baseline height Z-score, and baseline AGV.

The secondary endpoint of height standard deviation score (SDS) found least squares (LS) mean change from baseline to Week 52 in height SDS was –0.02 in the placebo group and 0.26 in the Voxzogo™ group. The difference in LS mean change from baseline was 0.28 in favor of Voxzogo™ (95% confidence interval [CI] 0.17, 0.39; P <0.0001).

Table 2. Study 1 (NCT03197766) Annualized Growth Velocity (cm/year) at Week 52		
	Placebo (n = 61)	**Voxzogo™ (n = 60)**
Baseline mean AGV (SD)	4.06 (1.20)	4.26 (1.53)
Change from baseline	–0.17	1.40
Difference in change of Voxzogo™–Placebo (95% CI)	1.57 (1.22, 1.93) P <0.0001 for superiority	

Results from Study 1 were published in The Lancet in September 2020 and provide additional information on secondary and exploratory endpoints. There were no significant improvements found in the outcomes of upper to lower body segment proportionality, quality of life, activities of daily living, and frequency and type of medical and surgical intervention. However, it is important to note that the trial only followed patients for 52 weeks; a longer duration is usually required to detect changes in these types of outcomes.

Open-Label Extension Trial Results:

Results from the open-label extension trial were published in Nature in August 2021. The open-label extension followed participants after completion of the original 52-week study (Study 1) for an additional 52 weeks. In children randomized to Voxzogo™, AGV increased from 4.26 centimeters/year at baseline to 5.39 centimeters/year at 52 weeks and 5.52 centimeters/year at Week 104. While the AGV did not continue to increase after the 52-week period, the extension trial demonstrated that the initial improvement in AGV from vosoritide is maintained over time. The open-label extension also switched patients from the placebo group to Voxzogo™ and found an increase in AGV similar to that of the Voxzogo™ arm in the initial 52-week trial. These results substantiate the findings of Study 1.

Safety:

The adverse reactions that occurred in ≥10% of patients treated with Voxzogo™ and at a greater percentage than placebo is injection site erythema, swelling, and urticaria; vomiting; arthralgia; decreased blood pressure; gastroenteritis; diarrhea; dizziness; ear pain; and influenza.

There is a warning in the Voxzogo™ label for transient decreases in blood pressure. The label states that patients with significant cardiac or vascular disease and patients on antihypertensive medications were excluded from participation inthe Voxzogo™ clinical trials. To reduce the risk of a decrease in blood pressure and associated symptoms, the label recommends that the patient should:

- Have adequate food intake prior to Voxzogo™ administration.
- Drink approximately 240–300 mL of fluid in the hour prior to Voxzogo™ administration.

Safety

ADVERSE EVENTS

Voxzogo™ was studied in a 52-week, randomized, double-blind, placebo-controlled trial in 121 subjects with achondroplasia. The subjects' ages ranged from 5.1 to 14.9 years with a mean of 8.7 years. Sixty-four (53%) subjects were male and 57 (47%) were female. Overall, 86 (71%) subjects were White, 23 (19%) were Asian, 5 (4%) were Black or African American, and 7 (6%) were classified as "multiple" races. The demographic and baseline characteristics were balanced between treatment groups. The subjects received either Voxzogo™ 15 mcg/kg, or placebo administered subcutaneously once daily. Table shows adverse reactions that occurred in ≥5% of patients treated with Voxzogo™ and at a percentage greater than placebo.

Table 2: Adverse Reactions that Occurred in ≥5% of Patients Treated with VOXZOGO and at a Percentage Greater than Placebo in Study 1*

Adverse Reaction	Placebo (N=61) n (%)	VOXZOGO (N=60) n (%)
Injection site erythema	42 (69%)	45 (75%)
Injection site swelling	22 (36%)	37 (62%)
Vomiting	12 (20%)	16 (27%)
Injection site urticaria	6 (10%)	15 (25%)
Arthralgia	4 (7%)	9 (15%)
Decreased blood pressure	3 (5%)	8 (13%)
Gastroenteritis[a]	5 (8%)	8 (13%)
Diarrhea	2 (3%)	6 (10%)
Dizziness[b]	2 (3%)	6 (10%)
Ear pain	3 (5%)	6 (10%)
Influenza	3 (5%)	6 (10%)
Fatigue[c]	2 (3%)	5 (8%)
Seasonal allergy	1 (2%)	4 (7%)
Dry skin	0	3 (5%)

Abreviations: N, total number of subjects in the treatment arm; n, number of subjects with the adverse reaction; %, percent of subjects with the adverse reaction.
* Includes adverse reactions occurring more frequently in the vosoritide arm and with a risk difference of ≥5% (i.e., difference of >2 subjects) between treatment arms
[a] Includes the preferred terms: gastroenteritis and gastroenteritis, viral
[b] Includes the preferred terms: dizziness, presyncope, procedural dizziness, vertigo
[c] Includes the preferred terms: fatigue, lethargy, malaise

WARNINGS & PRECAUTIONS

Risk of Low Blood Pressure-

Transient decreases in blood pressure were observed in clinical studies of Voxzogo™. Subjects with significant cardiac or vascular disease and patients on anti-hypertensive medicinal products were excluded from participation in Voxzogo™ clinical trials. To reduce the risk of a decrease in blood pressure and associated symptoms (dizziness, fatigue and/or nausea), instruct patients to be well hydrated and have adequate food intake prior to administration of Voxzogo™.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

In patients with achondroplasia, endochondral bone growth is negatively regulated due to a gain of function mutation in fibroblast growth factor receptor 3 (FGFR3). Binding of vosoritide to natriuretic peptide receptor-B (NPR-B) antagonizes FGFR3 downstream signaling by inhibiting the extracellular signal-regulated kinases 1 and 2 (ERK1/2) in the mitogen-activated protein kinase (MAPK) pathway at the level of rapidly accelerating fibrosarcoma serine/threonine protein kinase (RAF-1). As a result, vosoritide, like CNP, acts as a positive regulator of endochondral bone growth as it promotes chondrocyte proliferation and differentiation.

Dose & Administration

ADULTS

N/A

PEDIATRICS

The recommended dosage of Voxzogo™ is based on the patient's actual body weight. Voxzogo™ is administered by subcutaneous injection once daily.

Table 1: Recommended VOXZOGO Daily Dosage and Injection Volume

Actual Body Weight	Vial Strength for Reconstitution*	Dose	Injection Volume
10-11 kg	0.4 mg	0.24 mg	0.3 mL
12-16 kg	0.56 mg	0.28 mg	0.35 mL
17-21 kg	0.56 mg	0.32 mg	0.4 mL
22-32 kg	0.56 mg	0.4 mg	0.5 mL
33-43 kg	1.2 mg	0.5 mg	0.25 mL
44-59 kg	1.2 mg	0.6 mg	0.3 mL
60-89 kg	1.2 mg	0.7 mg	0.35 mL
≥90 kg	1.2 mg	0.8 mg	0.4 mL

*The concentration of vosoritide in reconstituted 0.4 mg vial and 0.56 mg vial is 0.8 mg/mL. The concentration of vosoritide in reconstituted 1.2 mg vial is 2 mg/mL.

GERIATRICS

N/A

RENAL IMPAIRMENT

No dosage adjustment is needed for patients with eGFR ≥ 60 mL/min/1.73 m^2. Voxzogo™ is not recommended for patients with eGFR < 60 mL/min/1.73 m^2.

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

For injection: 0.4 mg, 0.56 mg, or 1.2 mg lyophilized powder in a single-dose vial for reconstitution.