PDL DRUG REVIEW

Proprietary Name: Voxzogo®
Common Name: vosoritide
PDL Category: Achondroplasia Treatments

Summary

Pharmacology/Usage: Vosoritide, the active ingredient of Voxzogo®, is a human C type natriuretic peptide (CNP) analog, a 39 amino acid peptide. 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.

In animal models with open growth plates, vosoritide administration resulted in the promotion of chondrocyte proliferation and differentiation that led to a widening of the growth plate and subsequent increase in skeletal growth.

Indication: To increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses. This indication is approved under accelerated approval based on an improvement in annualized growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. The safety and efficacy of use in the pediatric population younger than 5 years of age have not been established.

Dosage Form: Lyophilized powder for reconstitution in a single-dose vial for Injection: 0.4mg, 0.56mg, or 1.2mg.

Recommended Dosage: To reduce the risk of low blood pressure and its associated signs and symptoms, instruct the caregiver and patient that the patient should:

- Have adequate food intake prior to Voxzogo® administration
- Drink about 240-300ml of fluid in the hour prior to Voxzogo® administration.

The recommended dose is based on the patient's actual body weight, and to be administered by subcutaneous (SC) injection once daily. Refer to the prescribing information for additional information on the dose and injection volume. Inject at the same time each day. Caregivers may inject Voxzogo® SC after proper training by a healthcare professional on the preparation and administration of Voxzogo®. Rotate the sites of injection, with the recommended injection sites being the front middle of the thighs, the lower part of the abdomen at least 2 inches away from the navel, top of the buttocks or the back of the upper arms. The same injection area should not be used on two consecutive days. If a dose is missed, it can be administered within 12 hours of the scheduled time of

administration. Beyond 12 hours, skip the missed dose and administer the next daily dose per the usual dosing schedule.

Monitor and assess patient body weight, growth, and physical development regularly every 3-6 months. Adjust the dosage per the patient's actual body weight. Permanently discontinue Voxzogo® upon confirmation of no further growth potential, indicated by closure of epiphyses.

The influence of renal impairment on the pharmacokinetics of Voxzogo® has not been evaluated. While no dosage adjustment is needed for patients with eGFR ≥60ml/min/1.73m^2, Voxzogo® is not recommended for patients with eGFR <60ml/min/1.73m^2.

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Voxzogo®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included injection site erythema (6%), injection site swelling (26%), vomiting (7%), injection site urticaria (15%), arthralgia (8%), decreased blood pressure (8%), gastroenteritis (5%), diarrhea (7%), dizziness (7%), ear pain (5%), influenza (5%), fatigue (5%), seasonal allergy (5%), and dry skin (5%).

Transient decreases in blood pressure were observed in clinical studies of Voxzogo®. Subjects with significant cardiac or vascular disease and patients on anti-hypertensive 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: There are no contraindications listed with this product.

Manufacturer: BioMarin Pharmaceutical Inc.

Analysis: The safety and efficacy of Voxzogo® were assessed in one multicenter, randomized, double-blind, placebo-controlled study of 52 weeks in duration that included patients with genetically confirmed achondroplasia (N=121) who were randomized to either Voxzogo® or placebo. The 52-week placebo-controlled study was followed by an open-label treatment extension study period in which all subjects received Voxzogo®. Baseline standing height, weight Z-score, body mass index (BMI) Z-score, and upper to lower body ratio were collected for at least 6 months prior to randomization.

The included patients age ranged from 5.1 to 14.9 years, with a mean of 8.7 years. Most were male (53%) and white (71%). The subjects had a mean baseline height standard deviation score (SDS) of -5.13. The primary efficacy endpoint was the change from baseline in annualized growth velocity (AGV) at week 52 compared with placebo. Results suggested that treatment with Voxzogo® for 52 weeks resulted in a treatment difference in the change from baseline in AGV of 1.57 cm/year after 52 weeks of treatment. Results can be seen in the table below, which was adapted from the prescribing information.

	Placebo (N=61)	Voxzogo® 15mcg/kg QD (N=60)
Baseline mean	4.06	4.26
Change from baseline	-0.17	1.40
Difference in change of Voxzogo® minus placebo	1.57 (p<0.0001)	

The least square (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 (p<0.0001) in favor of Voxzogo®.

The LS mean change from baseline to week 52 in upper to lower body segment ratio was -0.02 in the placebo group and -0.03 in the Voxzogo® group. The difference in LS mean change from baseline was -0.01 (p=0.5).

After the 52 week double-blind, placebo-controlled trial, 58 subjects initially randomized to Voxzogo® enrolled into an open-label extension. Among the subjects who had 2 years of follow-up since randomization, the improvement in AGV was maintained.

Place in Therapy: Voxzogo® is indicated to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses. This indication is approved under accelerated approval based on an improvement in annualized growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). To reduce the risk of low blood pressure and its associated signs and symptoms, the patient should have adequate food intake prior to administration and drink about 240-300ml of fluid in the hour prior to administration. The safety and efficacy of Voxzogo® were assessed in a multicenter randomized, double-blind, placebo controlled study that included pediatric patients (mean age of 8.7 years) with genetically-confirmed achondroplasia. Voxzogo® treatment for 52 weeks resulted in a treatment difference in the change from baseline in AGV of 1.57 cm/year (p<0.0001)

It is recommended that Voxzogo® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred**

References

[1] Voxzogo [package insert]. Novato, CA: BioMarin Pharmaceutical Inc; 2021.

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