VOXZOGO®
(vosoritide) for injection

The first and only targeted FDA-approved therapy to increase linear growth in pediatric patients with achondroplasia aged 5 years and up with open growth plates[1]

Transient decreases in blood pressure were observed in clinical studies. To reduce the risk of a decrease in blood pressure and associated symptoms (dizziness, fatigue, and/or nausea), patients should be well fed and hydrated in the hour prior to VOXZOGO® (vosoritide) administration.

The efficacy and safety of VOXZOGO were evaluated in patients with achondroplasia aged 5 to 15 years[1,2]

Observational study

- ≥6-month period
- Baseline standing heights collected

VOXZOGO 52-week study

- Double-blind, randomized, placebo-controlled
- N=121
- Duration: 52 weeks
- 15 µg/kg administered subcutaneously daily

Open-label extension trial

- All patients who completed the 52-week trial opted to receive VOXZOGO in the open-label extension trial
- N=119

Primary efficacy endpoint: Change from baseline in annualized growth velocity (AGV) at Week 52 compared to placebo

Indication and Important Safety Information

VOXZOGO® (vosoritide) is indicated to increase linear growth in pediatric patients with achondroplasia 5 years of age and older with open growth plates.

Warnings and Precautions for Risk of Low Blood Pressure

Transient decreases in blood pressure were observed in clinical studies. Patients 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), patients should be well hydrated, have adequate food intake, and drink approximately 8-10 ounces of fluid in the hour prior to VOXZOGO administration.

Please see Important Safety Information throughout as well as the full Prescribing Information.

Statistically significant improvement in annualized growth velocity (AGV) was seen in patients aged 5 to 15 years[1,2]

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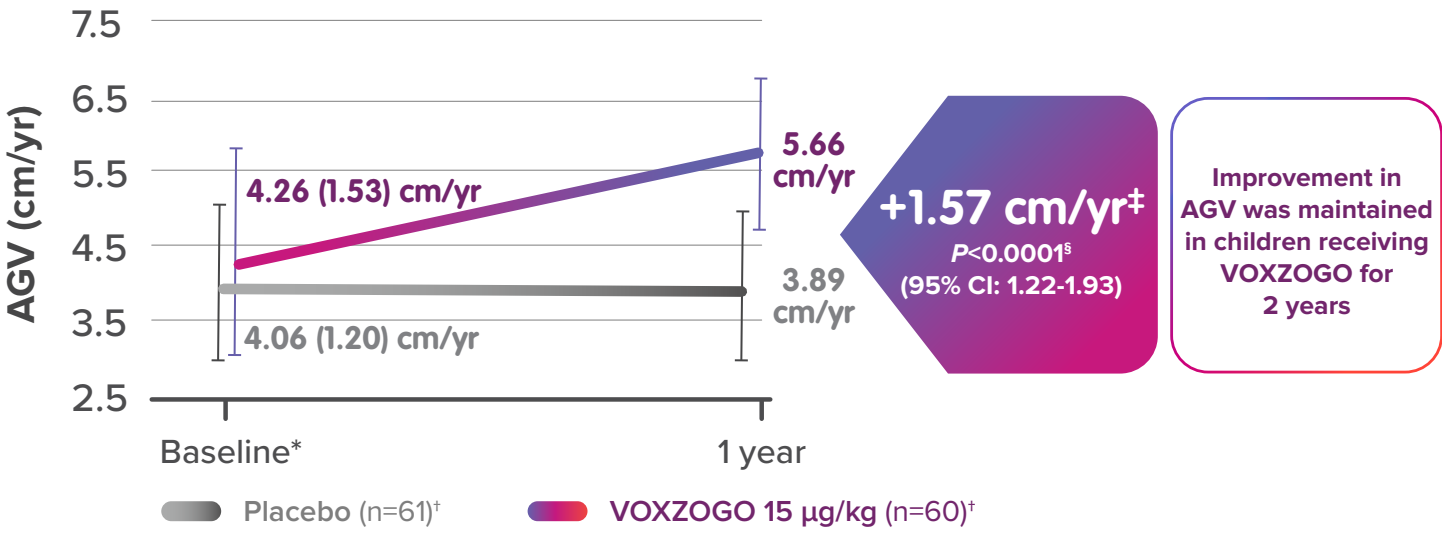
Mean (SD) AGV results from a placebo-controlled clinical trial



SD, standard deviation.
*LS means were estimated from the ANCOVA (analysis of covariance) model, which included treatment, stratum defined by sex and Tanner stage, baseline age, baseline AGV, and baseline height Z-score.
†All randomized subjects. Two patients in the VOXZOGO group discontinued from the study before Week 52. The values for these 2 patients were imputed assuming baseline growth rate for the period with missing data.
‡Baseline AGV was based on standing height at least 6 months prior to enrollment into the study.
§Two-sided *P* value <0.0001 for superiority.

VOXZOGO improved height standard-deviation score (Z-score) compared to placebo[1]

Height Z-score
+0.28
Statistically significant difference at 1 year vs placebo
***P*<0.0001 (95% CI: 0.17-0.39)**

Change from baseline at Week 52 in height Z-score
–0.02 in the **placebo** group
+0.26 in the **VOXZOGO** group

Warnings and Precautions for Risk of Low Blood Pressure (cont'd)

Eight (13%) of 60 patients treated with VOXZOGO had a total of 11 events of transient decrease in blood pressure, compared to 3 (5%) of 61 patients on placebo, over a 52-week treatment period. The median time to onset from injection was 31 (18 to 120) minutes, with resolution within 31 (5 to 90) minutes in VOXZOGO-treated subjects. Two out of 60 (3%) VOXZOGO-treated patients each had one symptomatic episode of decreased blood pressure with vomiting and/or dizziness compared to 0 of 61 (0%) patients on placebo.

Please see Important Safety Information throughout as well as the full Prescribing Information.

VOXZOGO safety was evaluated in children with achondroplasia aged 5 to 15 years[1]

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Adverse reactions that occurred in ≥5% of patients treated with VOXZOGO and at a rate greater than placebo in Study 1*

Adverse Reaction	Placebo (n=61)	VOXZOGO (n=60)
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‡	5 (8%)	8 (13%)
Diarrhea	2 (3%)	6 (10%)
Dizziness§	2 (3%)	6 (10%)
Ear pain	3 (5%)	6 (10%)
Influenza	3 (5%)	6 (10%)
Fatigue‖	2 (3%)	5 (8%)
Seasonal allergy	1 (2%)	4 (7%)
Dry skin	0 (0%)	3 (5%)

*Includes adverse reactions occurring more frequently in the VOXZOGO arm and with a risk difference of ≥5% (ie, difference of >2 subjects) between treatment arms.
†Injection site reactions occurring more frequently in VOXZOGO-treated subjects than placebo.
‡Includes the preferred terms: gastroenteritis and gastroenteritis, viral.
§Includes the preferred terms: dizziness, presyncope, procedural dizziness, and vertigo.
‖Includes the preferred terms: fatigue, lethargy, and malaise.

8 of 60 (13%) patients on VOXZOGO experienced a transient decrease in blood pressure compared to 3 of 61 (5%) on placebo[1]

Decreases in blood pressure were identified during periods of frequent vital sign monitoring.

- **Median onset:** 31 minutes (range, 18-120 minutes)
- **Median resolution:** 31 minutes (range, 5-90 minutes)

- 2 (3%) patients treated with VOXZOGO each had one symptomatic episode of blood pressure with vomiting and/or dizziness compared to 0 patients on placebo
- Patients with significant cardiac or vascular disease and patients on antihypertensive medicinal products were excluded from participation in VOXZOGO clinical trials

97% of children on VOXZOGO (58/60) remained on treatment during the 1-year clinical trial[1,2]

One patient discontinued after 2 days due to pain from injections and one after 6 days due to fear of needles.

Indication and Important Safety Information

VOXZOGO® (vosoritide) is indicated to increase linear growth in pediatric patients with achondroplasia 5 years of age and older with open growth plates.

- 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).

Warnings and Precautions for Risk of Low Blood Pressure

Transient decreases in blood pressure were observed in clinical studies. Patients 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), patients should be well hydrated, have adequate food intake, and drink approximately 8-10 ounces of fluid in the hour prior to VOXZOGO administration.

Eight (13%) of 60 patients treated with VOXZOGO had a total of 11 events of transient decrease in blood pressure, compared to 3 (5%) of 61 patients on placebo, over a 52-week treatment period. The median time to onset from injection was 31 (18 to 120) minutes, with resolution within 31 (5 to 90) minutes in VOXZOGO-treated subjects. Two out of 60 (3%) VOXZOGO-treated patients each had one symptomatic episode of decreased blood pressure with vomiting and/or dizziness compared to 0 of 61 (0%) patients on placebo.

Adverse Reactions:

Adverse reactions that occurred in ≥5% of patients treated with VOXZOGO and at a rate greater than that of placebo in the phase 3 study are injection site reactions (including erythema, swelling, urticaria, pain, bruising, pruritus, hemorrhage, discoloration, and induration), vomiting, arthralgia, decrease in blood pressure, gastroenteritis, diarrhea, dizziness, ear pain, influenza, fatigue, seasonal allergy, and dry skin.

Injection site reactions: Injection site reactions occurred in 51 (85%) subjects receiving VOXZOGO and 50 (82%) subjects receiving placebo over a 52-week period of treatment. Patients receiving VOXZOGO experienced a total of 6983 events of injection site reactions, while patients receiving placebo experienced a total of 1776 events of injection site reactions, over a 52-week period, representing 120.4 events per patient/year exposure and 29.2 events per patient/year exposure, respectively. Two patients in the VOXZOGO arm discontinued treatment due to adverse events of pain and anxiety with injections.

Administration and Monitoring:

VOXZOGO is administered as a daily subcutaneous injection. Prior to use, instruct caregivers on proper preparation and administration of VOXZOGO, and ensure caregivers have demonstrated the ability to perform a subcutaneous injection.

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

Special Populations:

- Safety and effectiveness of VOXZOGO in pediatric patients with achondroplasia below the age of 5 years have not been established.
- There are no available data on the use of VOXZOGO in pregnant women, or data on the presence of VOXZOGO in human milk, the effects on the breastfed infant, or the effects on milk production.
- The influence of renal impairment on the pharmacokinetics of VOXZOGO has not been evaluated. 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.

You may report side effects to the FDA at **1-800-FDA-1088** or **www.fda.gov/medwatch**. You may also report side effects to BioMarin at **1-866-906-6100**.

Please see additional safety information in the full Prescribing Information.

References: 1. VOXZOGO [package insert]. Novato, CA: BioMarin Pharmaceutical Inc; 2021. **2.** Savarirayan R, Tofts L, Irving M, et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. *Lancet*. 2020;396(10252):684-692. doi:10.1016/S0140-6736(20)31541-5

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BIOMARIN®