

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VOXZOGO safely and effectively. See full prescribing information for VOXZOGO.

VOXZOGO (vosoritide) for injection, for subcutaneous use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

VOXZOGO is a C type natriuretic peptide (CNP) analog 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). (1)

DOSAGE AND ADMINISTRATION

- Ensure adequate food and fluid intake prior to administration. (2.1)
- Recommended dosage is based on patient's weight. Administer subcutaneously once daily. (2.2)
- Reconstitute prior to use. The injection volume is based on both patient's weight and concentration of reconstituted VOXZOGO. (2.2)
- Monitor growth and adjust dosage according to body weight. Permanently discontinue upon closure of epiphyses. (2.3)
- See full prescribing information for preparation and administration instructions. (2.4)

DOSAGE FORMS AND STRENGTHS

For injection: 0.4 mg, 0.56 mg, or 1.2 mg lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Risk of Low Blood Pressure: Transient decreases in blood pressure have been reported. (5.1)

ADVERSE REACTIONS

Most common adverse reactions (>10%) are injection site erythema, injection site swelling, vomiting, injection site urticaria, arthralgia, decreased blood pressure, and gastroenteritis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Renal Impairment: Not recommended in patients with eGFR < 60 mL/min/1.73 m². (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

1	INDICATIONS AND USAGE	8.1	Pregnancy
2	DOSAGE AND ADMINISTRATION	8.2	Lactation
2.1	Important Instructions Prior to Administration of VOXZOGO	8.4	Pediatric Use
2.2	Recommended Dosage and Administration	8.6	Renal Impairment
2.3	Growth Monitoring	11	DESCRIPTION
2.4	Preparation and Administration	12	CLINICAL PHARMACOLOGY
3	DOSAGE FORMS AND STRENGTHS	12.1	Mechanism of Action
4	CONTRAINDICATIONS	12.2	Pharmacodynamics
5	WARNINGS AND PRECAUTIONS	12.3	Pharmacokinetics
5.1	Risk of Low Blood Pressure	13	NONCLINICAL TOXICOLOGY
6	ADVERSE REACTIONS	13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
6.1	Clinical Trials Experience	14	CLINICAL STUDIES
6.2	Immunogenicity	16	HOW SUPPLIED/STORAGE AND HANDLING
8	USE IN SPECIFIC POPULATIONS	17	PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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 [see *Clinical Studies (14)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Important Instructions Prior to Administration of VOXZOGO

To reduce the risk of low blood pressure and its associated signs and symptoms, instruct the caregiver and patient that the patient should [see *Warnings and Precautions (5.1)*]:

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

2.2 Recommended Dosage and Administration

The recommended dosage of VOXZOGO is based on the patient's actual body weight (see Table 1). VOXZOGO is administered by subcutaneous injection once daily [see *Dosage and Administration (2.4)*].

Inject VOXZOGO at approximately the same time each day, if possible. The volume of VOXZOGO to be administered (injection volume) is based on the patient's actual body weight and the concentration of reconstituted VOXZOGO (0.8 mg/mL or 2 mg/mL) (Table 1). VOXZOGO must be reconstituted prior to use [see *Dosage and Administration (2.4)*].

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.

Missed dose

If a dose of VOXZOGO 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 according to the usual dosing schedule.

2.3 Growth Monitoring

Monitor and assess patient body weight, growth, and physical development regularly every 3-6 months. Adjust the dosage according to the patient's actual body weight [see *Dosage and Administration (2.2)*].

Permanently discontinue VOXZOGO upon confirmation of no further growth potential, indicated by closure of epiphyses.

2.4 Preparation and Administration

Reconstitute VOXZOGO before administration using the provided diluent syringe containing Sterile Water for Injection, USP (see Reconstitution Instructions below).

Caregivers may inject VOXZOGO subcutaneously after proper training by a healthcare professional on the preparation and administration of VOXZOGO [see *Instructions for Use*].

Reconstitution Instructions

- Select the correct VOXZOGO strength and prefilled diluent syringe co-pack based on the patient's actual body weight [see *Dosage and Administration (2.2)*].
- Remove VOXZOGO vial and prefilled diluent syringe (Sterile Water for Injection, USP) from the refrigerator and allow the vial and prefilled diluent syringe to reach room temperature before reconstituting VOXZOGO.
- Attach the diluent needle provided with ancillary supplies to the diluent prefilled syringe.
- Inject the entire diluent prefilled syringe volume into the vial.
- Gently swirl the diluent in the vial until the white powder is completely dissolved. Do not shake.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Once reconstituted VOXZOGO is a clear, colorless to yellow liquid. The solution should not be used if discolored or cloudy, or if particles are present. The concentration of reconstituted solution is 0.8 mg/mL or 2.0 mg/mL.
- After reconstitution, VOXZOGO can be held in the vial at a room temperature 20°C to 25°C (68°F to 77°F) for a maximum of 3 hours.
- For administration, extract the required dose volume from the vial using the supplied administration syringe [see *Dosage and Administration (2.2)*].

Discard any unused portion. Do not pool unused portions from the vials. Do not administer more than 1 dose from a vial. Do not mix with other medications.

Instructions for Subcutaneous Administration

See the Instructions for Use document for detailed, illustrated instructions.

- Ensure patients have had adequate food and fluid intake prior to VOXZOGO administration [see *Dosage and Administration (2.1)*]. Slowly withdraw the dosing volume of the reconstituted VOXZOGO solution from the single-dose vial into a syringe.

- Rotate sites for subcutaneous injections.
- The recommended injection sites for VOXZOGO are: the front middle of the thighs, the lower part of the abdomen at least 2 inches (5 centimeters) 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. Do not inject VOXZOGO into sites that are red, swollen, or tender.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 0.4 mg, 0.56 mg, or 1.2 mg as a white to yellow lyophilized powder for reconstitution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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 [see *Dosage and Administration (2.1) and Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risk of Low Blood Pressure [see *Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

VOXZOGO was studied in a 52-week, randomized, double-blind, placebo-controlled trial in 121 subjects with achondroplasia (Study 1) [see *Clinical Studies (14)*].

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" race. 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 2 shows adverse reactions that occurred in $\geq 5\%$ of patients treated with VOXZOGO and at a percentage greater than placebo.

Table 2: Adverse Reactions that Occurred in $\geq 5\%$ 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%)

Abbreviations: 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 $\geq 5\%$ (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

Discussion of Selected Adverse Reactions

Decreased blood pressure

Eight (13%) of 60 subjects treated with VOXZOGO had a total of 11 events of transient decrease in blood pressure compared to 3 (5%) of 61 subjects on placebo, identified predominantly during periods of frequent monitoring at clinical visits after dosing 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 subjects each had one symptomatic episode of decreased blood pressure with vomiting and/or dizziness compared to 0 of 61 (0%) subjects on placebo.

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. Injection site reactions included the preferred terms injection site erythema, injection site reaction, injection site swelling, injection site urticaria, injection site pain, injection site bruising, injection site pruritus, injection site hemorrhage, injection site discoloration, and injection site induration. Over a 52 week period, 51 (85%) of 60 subjects receiving VOXZOGO

experienced a total of 6983 events of injection site reactions, while 50 (82%) of 61 subjects receiving placebo experienced a total of 1776 events of injections site reactions, representing 120.4 events per person/year exposure and 29.2 per person/year exposure, respectively. One injection site reaction event could have been associated with one or more injection site reaction symptoms (e.g., injection site swelling, injection site erythema, injection site urticaria, etc.). Two subjects in the VOXZOGO arm discontinued treatment due to adverse reactions of pain and anxiety with injections.

6.2 Immunogenicity

As with all peptides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Of 131 subjects who were treated with VOXZOGO 15 mcg/kg/day and evaluable for the presence of anti-drug antibodies (ADA) for up to 240 weeks, ADA were detected in 35% (46/131). The earliest time to ADA development was day 85. All ADA-positive subjects tested negative for anti-vosoritide neutralizing antibodies. There was no correlation between the number, duration, or severity of hypersensitivity adverse reactions or injection site reactions and ADA positivity or mean ADA titer. There was no association between ADA positivity or mean ADA titer and change from baseline in annual growth velocity (AGV) or height Z-score at month 12. There was no impact of serum ADA detected on the plasma PK measurements of vosoritide.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on vosoritide use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, there was no evidence of embryo-fetal toxicity or congenital malformations when pregnant rats and rabbits were administered vosoritide subcutaneously at doses equivalent to 14-times and 200-times, respectively, the exposure at the maximum recommended human dose (MRHD) (*see Data*).

The estimated background risk of major birth defects for the indicated population is higher than the general population. The estimated background risk of miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryofetal developmental toxicity study in rats, vosoritide was administered at 90, 270, 540 mcg/kg once daily by subcutaneous injection during the period of major organogenesis from gestation day (GD) 6 – 17. There were no effects on maternal animals or on embryofetal development at the highest dose administered (14-times the exposure at the MRHD).

In an embryofetal developmental toxicity study in rabbits, vosoritide was administered at 45, 135, 240 mcg/kg once daily by subcutaneous injection during the period of major organogenesis (GD 7 – 19). No effects were observed in maternal animals or on embryofetal development at the highest dose administered (200-times the exposure at the MRHD).

In a pre- and postnatal toxicity study in rats, vosoritide was administered at 90, 270, and 540 mcg/kg once daily by subcutaneous injection during the period of major organogenesis and continuing to weaning (GD 6 through postpartum day 20). There were no effects on maternal animals, including maintenance of pregnancy, parturition, or care of offspring, and no effects were noted on offspring growth and development or ability to reproduce at the highest dose (14-times the exposure at the MRHD).

8.2 Lactation

Risk Summary

There is no information regarding the presence of vosoritide in human milk, the effects on the breastfed infant, or the effects on milk production. Vosoritide is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VOXZOGO and any potential adverse effects on the breastfed child from VOXZOGO or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of VOXZOGO have been established in pediatric patients aged 5 years and older for the improvement in linear growth in patients with achondroplasia. Use of VOXZOGO for this indication is supported by evidence from adequate and well-controlled studies in pediatric patients aged 5 years and older [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14)*].

Safety and effectiveness of VOXZOGO in pediatric patients with achondroplasia below the age of 5 years have not been established.

8.6 Renal Impairment

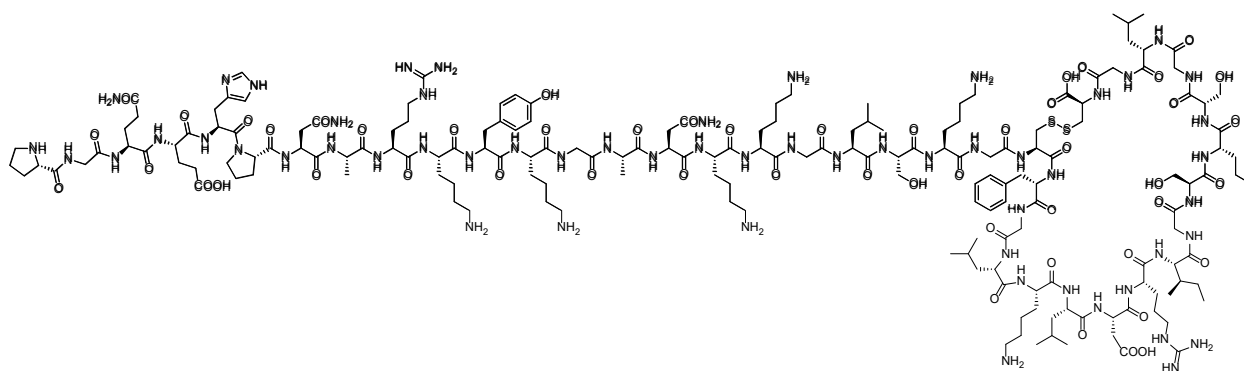
The influence of renal impairment on the pharmacokinetics of VOXZOGO has not been evaluated. No dosage adjustment is needed for patients with eGFR ≥ 60 mL/min/1.73 m². VOXZOGO is not recommended for patients with eGFR < 60 mL/min/1.73 m².

11 DESCRIPTION

VOXZOGO contains vosoritide, a human C type natriuretic peptide (CNP) analog. Vosoritide is a 39 amino acid peptide. Its amino acid sequence includes the 37 C terminal amino acids of the human CNP53 sequence plus Pro Gly on the N terminus to convey resistance to neutral endopeptidase (NEP) degradation. Vosoritide is manufactured from *Escherichia coli* using recombinant DNA technology. Vosoritide has a chemical formula of C₁₇₆H₂₉₀N₅₆O₅₁S₃ with a molecular weight of 4.1 kDa.

Vosoritide has the structural formula shown in Figure 1.

Figure 1



VOXZOGO (vosoritide) for injection, is a sterile, preservative-free white-to-yellow lyophilized powder, for subcutaneous administration after reconstitution with Sterile Water for Injection, USP.

VOXZOGO is provided as a single-dose vial containing 0.4 mg, 0.56 mg, or 1.2 mg of vosoritide per vial. A pre-filled syringe containing Sterile Water for Injection, USP for use as a diluent is also provided. The contents of each single dose vial are summarized by strength in Table 3. The product contains no preservative.

Table 3: Contents of VOXZOGO

Strength	Inactive Ingredients per Vial
VOXZOGO 0.4 mg	Trehalose dihydrate (29.01 mg), mannitol (7.5 mg), sodium citrate dihydrate (0.54 mg), methionine (0.36 mg), citric acid monohydrate (0.14 mg), and polysorbate 80 (0.025 mg). After reconstitution with 0.5 mL Sterile Water for Injection USP, the resulting concentration is 0.4 mg/0.5 mL of vosoritide and the nominal deliverable volume is 0.4 mL.
VOXZOGO 0.56 mg	Trehalose dihydrate (40.61 mg), mannitol (10.50 mg), sodium citrate dihydrate (0.76 mg), methionine (0.51 mg), citric acid monohydrate (0.20 mg), and polysorbate 80 (0.035 mg). After reconstitution with 0.7 mL Sterile Water for Injection USP, the resulting concentration is 0.56 mg/0.7 mL of vosoritide and the nominal deliverable volume is 0.6 mL.
VOXZOGO 1.2 mg	Trehalose dihydrate (34.81 mg), mannitol (9 mg), sodium citrate dihydrate (0.65 mg), methionine (0.44 mg), citric acid monohydrate (0.17 mg), and polysorbate 80 (0.030 mg). After reconstitution with 0.6 mL Sterile Water for Injection USP, the resulting concentration is 1.2 mg/0.6 mL of vosoritide and the nominal deliverable volume is 0.5 mL.

Trehalose dihydrate and D-Mannitol are used as isotonic agent. Citric acid monohydrate and sodium citrate dihydrate are used as buffering agent.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism 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.

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. In the mouse models of *FGFR3*-related chondrodysplasia, a partial or complete normalization of the dwarfism phenotype was observed.

12.2 Pharmacodynamics

NPR-B Binding Activity Biomarker and Bone Metabolism Biomarker

An increase in urinary cyclic guanosine monophosphate (cGMP) concentrations from pre-dose baseline were observed within the first four hours post-dose, with a maximum level at 2 hours post-dose, after VOXZOGO administration to pediatric patients with achondroplasia.

Daily administration of VOXZOGO also led to the increase from baseline in serum collagen type X marker (CXM), an endochondral ossification biomarker and remains elevated beyond 24 months. In subjects aged 5 - 14 years old at screening, exposure-response analyses showed that vosoritide activity measured by urinary cGMP was near saturation at the dose of 15 mcg/kg once daily, while maximal increase in growth plate activity indicated by CXM was achieved at this dose.

Cardiac Electrophysiology

At the maximum approved recommended dose, Voxzogo does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

The area under the concentration-time curve (AUC) and peak concentration (C_{max}) of vosoritide increased greater than proportionally following subcutaneous administration to pediatric subjects with achondroplasia in the dose range of 7.5 to 30.0 mcg/kg. The pharmacokinetics of vosoritide were evaluated in 58 subjects aged 5 to 13 years with achondroplasia who received subcutaneous injections of vosoritide 15 mcg/kg once daily for 52 weeks. The mean (\pm SD) C_{max} and area under the concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}) observed across 52 weeks of treatment ranged from 4.71 (\pm 2.32) to 7.18 (\pm 9.65) ng/mL, and 161 (\pm 98.1) to 290 (\pm 235) ng-min/mL, respectively. No drug accumulation was observed following 15 mcg/kg once daily dosing. The exposure of vosoritide increased with the duration of treatment. The mean AUC_{0-t} at week 52 increased approximately 20% compared to that at day 1.

Absorption

Absolute bioavailability for vosoritide following subcutaneous injection was not determined. Vosoritide was absorbed with a median T_{\max} of 15 minutes after dosing.

Distribution

The mean (\pm SD) apparent volume of distribution of vosoritide across 52 weeks of subcutaneous administration of VOXZOGO 15 mcg/kg once daily ranged from 2880 (\pm 2450) to 3020 (\pm 1980) mL/kg.

Elimination

The mean (\pm SD) apparent clearance of vosoritide across 52 weeks of subcutaneous administration of VOXZOGO 15 mcg/kg once daily ranged from 79.4 (\pm 53.0) to 104 (\pm 98.8) mL/min/kg. The mean (\pm SD) half-life ranged from 21.0 (\pm 4.7) to 27.9 (\pm 9.9) minutes.

Metabolism

The metabolism of vosoritide is expected to occur via catabolic pathways with degradation into small peptide fragments and amino acids.

Special Populations

No clinically significant differences in the vosoritide pharmacokinetics were observed based on age (0.9 to 16 years), sex or race. The effect of hepatic or renal impairment on the pharmacokinetics of vosoritide is unknown.

Body weight

Population pharmacokinetic analyses indicated that body weight is a significant covariate for vosoritide clearance and volume of distribution. The apparent clearance and volume of distribution of vosoritide increased with increasing body weight in patients with achondroplasia (9 to 74.5 kg).

Drug Interaction Studies

In vitro assessment of drug-drug interactions

In vitro studies showed that vosoritide, at therapeutic concentrations, does not inhibit or induce Cytochrome P450 enzymes.

In vivo assessment of drug-drug interactions

No clinical studies evaluating the drug-drug interaction potential of vosoritide have been conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term carcinogenicity studies and genotoxicity studies with vosoritide have not been performed.

In a fertility and reproductive study in male and female rats at doses up to 540 mcg/kg/day (15-times the exposure at the MRHD), vosoritide had no effect on mating performance, fertility, or litter characteristics.

14 CLINICAL STUDIES

The safety and effectiveness of VOXZOGO in patients with achondroplasia were assessed in one 52-week, multi-center, randomized, double-blind, placebo-controlled, phase 3 study - Study 1 (NCT03197766).

Study 1 was conducted in 121 subjects with genetically-confirmed achondroplasia, who were randomized to either VOXZOGO (N=60) or placebo (N=61). The dosage of VOXZOGO was 15 mcg/kg administered subcutaneously once daily. 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. Subjects with limb-lengthening surgery in the prior 18 months or who planned to have limb-lengthening surgery during the study period were excluded. The study included a 52-week placebo-controlled treatment phase followed by an open-label treatment extension study period in which all subjects received VOXZOGO. The primary efficacy endpoint was the change from baseline in annualized growth velocity (AGV) at Week 52 compared with placebo.

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" race. The subjects had a mean baseline height standard deviation score (SDS) of -5.13.

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 (Table 4).

Table 4: Annualized Growth Velocity (cm/year) at Week 52 in Subjects 5 Years of Age and Older with Achondroplasia - Study 1

	Placebo (N=61 ^a)	VOXZOGO 15 mcg/kg Daily (N=60 ^a)
Baseline mean (SD)^b	4.06 (1.20)	4.26 (1.53)
Change from baseline^c	-0.17	1.40
Difference in change of VOXZOGO – Placebo^c (95% CI)	1.57 (1.22, 1.93) ^d	

Abbreviations: AGV, annualized growth velocity; 95% CI, 95% confidence interval; LS, least-square; SD, standard deviation
^a 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.

^b Baseline AGV was based on standing height at least 6 months prior to enrollment into the study.

^c 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.

^d 2-sided p-value <0.0001 for superiority.

The improvement in AGV in favor of VOXZOGO was consistent across all predefined subgroups analyzed including sex, age group, Tanner stage, baseline height Z-score, and baseline AGV.

Height Standard Deviation Score (SDS)

The 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 (95% CI 0.17, 0.39; 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 (95% CI -0.05, 0.02; p=0.5).

Open-label extension

After the 52 week double blind, placebo-controlled, phase 3 study, Study 1, 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

VOXZOGO for injection is a white to yellow lyophilized powder for reconstitution and is provided as a co-pack which includes ten:

- Sterile, single-dose 2 mL glass vials containing VOXZOGO
- Diluent (Sterile Water for Injection, USP) in a single-dose prefilled syringe
- Diluent transfer needles (23 gauge)
- Single-dose administration syringes (30 gauge) both with needle retraction safety devices

Strength (mg)	Diluent (mL)	Co-pack NDC Number	Flip Cap Color
0.4	0.5	NDC 68135-082-36	White
0.56	0.7	NDC 68135-119-66	Magenta
1.2	0.6	NDC 68135-181-93	Grey

The following items to be obtained separately; alcohol aseptic wipes, gauze, bandages and sharps container.

Storage

Refrigerate VOXZOGO vials and prefilled diluent syringes at 2°C to 8°C (36°F to 46°F). Do not freeze.

VOXZOGO can be stored at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) for 90 days. Do not return VOXZOGO to the refrigerator once stored at room temperature.

After reconstitution, VOXZOGO can be held in the vial at room temperature 20°C to 25°C (68°F to 77°F) for a maximum of 3 hours [see *Dosage and Administration (2.4)*].

Record the starting date of room-temperature storage clearly on the unopened product carton.

Do not use beyond expiration date on the label.

Store in the original package to protect from light.

Handling

Reconstituted VOXZOGO must be administered within 3 hours of reconstitution [see *Dosage and Administration (2.4)*].

17 PATIENT COUNSELING INFORMATION

Advise the patient and caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Preparation and Administration

Instruct caregivers on proper preparation and administration of VOXZOGO. Ensure caregivers have demonstrated the ability to perform a subcutaneous injection [see *Dosage and Administration (2.4)*].

Instruct caregivers in the technique of proper syringe and needle disposal, and advise them not to reuse these items. Instruct caregivers to dispose needles and syringes in a puncture-resistant container.

Risk of Low Blood Pressure

Inform caregivers and patients that VOXZOGO may lower blood pressure after administration. Instruct caregivers and patients that prior to VOXZOGO administration, the patient should have adequate food intake and within the hour prior to administration, the patient should drink approximately 8-10 ounces (240-300 mL) of fluid [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.1)*].

Manufactured for:
BioMarin Pharmaceutical Inc.
105 Digital Drive, Novato, CA 94949

PATIENT INFORMATION
VOXZOGO (vox zoe' goe)
(vosoritide)
for injection, for subcutaneous use

What is VOXZOGO?

VOXZOGO is a prescription medicine used to increase linear growth in children with achondroplasia who are 5 years of age and older with open bone growth plates (epiphyses).

It is not known if VOXZOGO is safe and effective in children with achondroplasia under 5 years of age.

Before you give your child VOXZOGO, tell your child's healthcare provider about all your child's medical conditions, including if they:

- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if VOXZOGO will harm your child's unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if VOXZOGO passes into your child's breast milk. Talk to your child's healthcare provider about the best way to feed your child's baby if your child takes VOXZOGO.

Tell your child's healthcare provider about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines your child takes. Keep a list of them to show your child's healthcare provider and pharmacist when your child gets a new medicine.

How should I give VOXZOGO?

- See the detailed **Instructions for Use** that comes with this Patient Information leaflet for instructions about the right way to store, prepare, and give VOXZOGO injections at home.
- VOXZOGO is given as an injection under the skin (subcutaneous or SC). Inject VOXZOGO 1 time every day, at about the same time each day.
- If your child's healthcare provider decides a caregiver can give the injections of VOXZOGO at home, your child's caregiver should receive training on the right way to prepare and inject VOXZOGO. Do not try to inject VOXZOGO until you have been shown the right way by your child's healthcare provider or nurse.
- Your child's healthcare provider will tell you how often you should give VOXZOGO. If your child misses a dose of VOXZOGO, it can be given within 12 hours of the scheduled time of injection. If more than 12 hours have passed, do not give the missed dose. Give the next daily dose according to your child's usual schedule.
- Your child should eat a meal and drink about 8 to 10 ounces of fluid within 1 hour before injection.
- In case you are not sure when to inject VOXZOGO, call your child's healthcare provider or pharmacist. Do not give VOXZOGO more often than as directed by your child's healthcare provider.
- Your child's dose of VOXZOGO depends on his or her body weight. Your child's healthcare provider will tell you which strength of VOXZOGO to use and how much to give your child.
- Your child's healthcare provider will monitor your child's growth and instruct you on when your child should stop VOXZOGO if they determine that your child is no longer able to grow. Stop giving VOXZOGO to your child if instructed by your child's healthcare provider.

What are the possible side effects of VOXZOGO?

VOXZOGO may cause serious side effects, including:

- **risk of low blood pressure.** VOXZOGO may temporarily lower blood pressure in some people. To help reduce the risk of low blood pressure and its symptoms (dizziness, feeling tired, or nausea), your child should eat a meal and drink about 8 to 10 ounces of fluid within 1 hour before receiving VOXZOGO.

The most common side effects of VOXZOGO include:

- injection site reactions (redness, itching, swelling, bruising, rash, hives, pain)
- vomiting
- joint pain
- decreased blood pressure

- stomach ache

These are not all the possible side effects of VOXZOGO. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VOXZOGO?

- Store the VOXZOGO vial and prefilled diluent syringe in the refrigerator between 36°F to 46°F (2°C to 8°C).
- You may store VOXZOGO (before mixing) at room temperature between 68°F to 77°F (20°C to 25°C) for 90 days.
- Record the date you started storing VOXZOGO at room temperature on the carton to keep track of the 90 days.
- **Do not** return VOXZOGO to the refrigerator after it has been stored at room temperature. Throw VOXZOGO away if unused within 90 days of storing at room temperature.
- Do not use VOXZOGO past the expiration date.
- Do not freeze VOXZOGO.
- Store VOXZOGO out of direct sunlight.

Keep VOXZOGO and all medicines out of the reach of children.

General information about the safe and effective use of VOXZOGO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VOXZOGO for a condition for which it was not prescribed.

Do not give VOXZOGO to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about VOXZOGO that is written for health professionals.

What are the ingredients in VOXZOGO?

Active ingredient: vosoritide

Inactive ingredients: trehalose dihydrate, mannitol, sodium citrate dihydrate, methionine, citric acid monohydrate, and polysorbate 80

The logo for BioMarin, featuring the word "BOMARIN" in a blue, sans-serif font. The letter "O" is stylized with three vertical bars of increasing height to its left, resembling a bar chart or a molecular structure.

BioMarin Pharmaceutical Inc.
Novato, CA 94949

© BioMarin Pharmaceutical Inc. All rights reserved.

VOXZOGO is a registered trademark of BioMarin Pharmaceutical Inc.

For more information, go to www.VOXZOGO.com or call 1-877-695-8826.

This Patient Information has been approved by the U.S. Food and Drug Administration

Issued: 11/2021