Product Monograph

Including Patient Medication Information

PrVOXZOGO®

Vosoritide for injection

Modified recombinant human C-type natriuretic peptide 39 (CNP-39)

Lyophilized powder in single-use vial for reconstitution

For subcutaneous use

0.4 mg/vial, 0.56 mg/vial and 1.2 mg/vial

Drugs for Treatment of Bone Diseases

ATC Code: M05BX07

VOXZOGO® (vosoritide for injection), indicated to:

- increase linear growth in patients with achondroplasia who are 4 months of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for VOXZOGO please refer to Health Canada's Notice of Compliance with conditions - drug products web site.

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork, Ireland

Date of Authorization:
2026-01-21

Distributor:
BioMarin Pharmaceutical (Canada) Inc.
Toronto, ON
Canada M5H 0B4

Control Number: 290788

What is a Notice of Compliance with Conditions (NOC/c)?

A NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

Recent Major Label Changes

There are no recent major changes to this product monograph.

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

VOXZOGO® (vosoritide for injection) is indicated to increase linear growth in patients with achondroplasia who are 4 months of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

This indication is approved based on an improvement in annualized growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.1. Pediatrics

Pediatrics (4 months to < 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of VOXZOGO in pediatric patients with achondroplasia who are 4 months of age and older has been established. Considering current data, no recommendation on dosing can be provided for patients less than 4 months of age at this time (see 7.1.3. Pediatrics, 10.2. Pharmacodynamics, 10.3. Pharmacokinetics, and 14. Clinical Trials).

1.2. Geriatrics

Geriatrics (> 65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use. This product is not intended for use in geriatric patients.

2. Contraindications

VOXZOGO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6. Dosage Forms, Strengths, Composition and Packaging.

4. Dosage and Administration

4.1. Dosing Considerations

Confirm presence of *FGFR3* mutation using a validated test prior to initiation of VOXZOGO.

VOXZOGO treatment should be started and supervised by a physician experienced in managing growth disorders or skeletal dysplasias. To reduce the risk of low blood pressure and associated symptoms (dizziness, fatigue and/or nausea), patients should be adequately fed and hydrated before the time of injection. It is recommended patients eat a light snack and drink an adequate amount of fluid (e.g., water, milk, juice, baby formula, etc.) in the hour prior to VOXZOGO administration.

Caregivers should be trained by a healthcare professional on the preparation and subcutaneous injection of VOXZOGO prior to administering the drug (see Instructions for Use). Training should also include how to recognize and manage signs and symptoms of decreased blood pressure in the event of a symptomatic episode.

4.2. Recommended Dose and Dosage Adjustment

VOXZOGO is given as a daily subcutaneous injection. The recommended dose of VOXZOGO is based on the patient's actual body weight (see Table 1).

VOXZOGO must be reconstituted prior to use (see 4.3 Reconstitution). If possible, this medicine should be injected at approximately the same time each day.

The volume of VOXZOGO to be administered (injection volume) is based on the patient's weight and the concentration of reconstituted VOXZOGO (0.8 mg/mL or 2 mg/mL) (see Table 1).

Table 1 – Single Use Volumes by Body Weight

Body Weight (kg)[a]	**Dose (mg)**	**Vosoritide 0.4 mg** **Diluent (Water for Injection): 0.5 mL** **Concentration: 0.8 mg/mL**		**Vosoritide 0.56 mg** **Diluent (Water for Injection): 0.7 mL** **Concentration: 0.8 mg/mL**		**Vosoritide 1.2 mg** **Diluent (Water for Injection): 0.6 mL** **Concentration: 2 mg/mL**	
		Daily Injection Volume[b]					
		mL	Units	mL	Units	mL	Units
5	0.16 mg	0.20 mL	20 U				
6-7	0.20 mg	0.25 mL	25 U				
8-11	0.24 mg	0.30 mL	30 U				
12-16	0.28 mg			0.35 mL	35 U		
17-21	0.32 mg			0.40 mL	40 U		
22-32	0.40 mg			0.50 mL	50 U		
33-43	0.50 mg					0.25 mL	25 U
44-59	0.60 mg					0.30 mL	30 U
60-89	0.70 mg					0.35 mL	35 U
≥ 90	0.80 mg					0.40 mL	40 U

[a] Intermediate body weights that fall within these weight bands should be rounded to the nearest whole number

[b] The VOXZOGO kit includes syringes with mL graduations

Duration of Treatment

Treatment with VOXZOGO should be stopped upon confirmation of no further growth potential, indicated by a growth velocity of < 1.5 cm/year and closure of epiphyses.

Growth Monitoring

Patients should be monitored and assessed regularly every 3-6 months to check body weight, growth and physical development.

Renal Impairment

The safety and efficacy of vosoritide in patients with renal impairment has not been evaluated. No dosage adjustment is needed for patients with mild renal impairment (i.e., eGFR ≥ 60 mL/min/1.73 m^2). There is a lack of data in patients with moderate to severe renal impairment (i.e., eGFR < 60 mL/min/1.73 m^2), so clinical judgment should be used when considering treatment in this population (see 7.1.5. Renal Impairment and 10.3. Pharmacokinetics).

4.3. Reconstitution

Table 2 – Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Maximum Volume to be Withdrawn	Concentration per mL
0.4 mg	0.5 mL	0.3 mL	0.8 mg/mL
0.56 mg	0.7 mL	0.5 mL	0.8 mg/mL
1.2 mg	0.6 mL	0.4 mL	2 mg/mL

Reconstitution Instructions

- Select the correct VOXZOGO strength (co-packed with prefilled diluent syringe) based on the patient's actual body weight (see 4.2. Recommended Dose and Dosage Adjustment).
- Remove VOXZOGO vial and prefilled diluent syringe (sterile water for injection) from the refrigerator and allow them reach room temperature before reconstituting VOXZOGO.
- Attach the diluent needle provided with ancillary supplies to the diluent prefilled syringe (sterile water for injection).
- 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 discolouration prior to administration whenever solution and container permit. Once reconstituted VOXZOGO is a clear, colourless to yellow liquid. The solution should not be used if discoloured or cloudy, or if particles are present.
- After reconstitution, VOXZOGO can be held in the vial at a room temperature 20°C to 25°C for a maximum of 3 hours (see 11. Storage, Stability and Disposal).
- For administration, extract the required dose volume from the single use vial using the supplied administration syringe (see 4.2. Recommended Dose and Dosage Adjustment).

Discard any unused portion. Do not pool unused portions from the vials. Do not administer more than one dose from a vial.

VOXZOGO must not be mixed with other medicinal products.

4.4. Administration

See Instructions for Use document for detailed, illustrated instructions.

- Ensure patients have had adequate food and fluid intake prior to VOXZOGO administration (see 4.1 Dosing Considerations).
- Slowly withdraw the dosing volume of the reconstituted VOXZOGO solution from the single use 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 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.

4.5. Missed Dose

If a dose of VOXZOGO is missed, it can be administered within 12 hours of the scheduled time of administration. If more than 12 hours have passed since the original dosing schedule, skip the missed dose and administer the next daily dose according to the usual dosing schedule.

5. Overdose

In clinical trials, doses of vosoritide up to 30 µg/kg/day were explored. Two patients received up to 3 times the recommended daily dose of 15 µg/kg/day for up to 5-weeks. No signs, symptoms or adverse reactions associated with the higher than intended dose were observed.

If a higher than prescribed dose is injected, the patient should contact their healthcare professional and be carefully monitored.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of biologic products, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 3 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Subcutaneous	Powder and diluent for injection <u>Lyophilized Powder:</u> 0.4 mg/vial 0.56 mg/vial 1.2 mg/vial <u>Reconstituted Strengths:</u> 0.4 mg/0.5 mL per vial (0.8 mg/mL) 0.56 mg/0.7 mL per vial (0.8 mg/mL) 1.2 mg/0.6 mL per vial (2 mg/mL)	Powder: Citric acid monohydrate, mannitol, methionine, polysorbate 80, sodium citrate dihydrate, trehalose dihydrate Diluent: Water for injection

Description

VOXZOGO is provided as a single-use vial with a pre-filled syringe containing sterile water for injection for use as a diluent. Contains no preservative.

Each carton contains:

- 10 vials of VOXZOGO
- 10 pre-filled syringes of sterile water for injection
- 10 individual single use needles (23 gauge) for reconstitution
- 10 individual single use syringes (30 gauge) for administration

All dosage strengths of VOXZOGO are provided in a 2 mL vial (glass) with a rubber stopper (bromobutyl). The sterile water for injection diluent is provided in a pre-filled syringe (glass) with plunger (bromobutyl) and tip cap with a luer lock and tamper-evident seal.

VOXZOGO vials include a flip cap with a colour that correspond to the strength: 0.4 mg (white), 0.56 mg (magenta), or 1.2 mg (gray).

7. Warnings and Precautions

Cardiovascular

Blood Pressure Effects

Transient decreases in blood pressure were observed in clinical studies of VOXZOGO. 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 potential decrease in blood pressure and associated symptoms (dizziness, fatigue and/or nausea), patients should be well hydrated and have adequate food intake at the time of injection.

Driving and Operating Machinery

VOXZOGO has moderate influence on the ability to drive, cycle and use machines. Vosoritide may cause transient decreases in blood pressure that are usually mild but syncope, pre-syncope, and dizziness, as well as other signs and symptoms of hypotension have been reported as adverse reactions with VOXZOGO. The patient's response to treatment should be considered and if appropriate, advised not to drive, cycle or use machines for at least 60 minutes after injection.

Monitoring and Laboratory Tests

Ensure that patients do not have severe serum 25-hydroxyvitamin D deficiency (< 12 ng/mL or < 30 nmol/L) before initiating treatment with VOXZOGO and monitor periodically during therapy.

Reproductive Health

- **Fertility**

There is no data on the effect of VOXZOGO on fertility in humans.

7.1. Special Populations

7.1.1. Pregnancy

There are no available data on the use of VOXZOGO in pregnant women to inform the drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, there were no adverse developmental effects in offspring of pregnant rats and rabbits administered vosoritide subcutaneously during gestation. Vosoritide was detectable in pooled fetal plasma on gestational day (GD) 18 and 20 in an embryofetal developmental toxicity study in the rat, and rabbit, respectively, and in plasma of offspring in a pre- and post-natal developmental toxicity study in the rat on post-natal day (PND) 1. The fetal and neonatal plasma concentrations were less than 1% of the maternal plasma C_{max} on GD 17 in rats and GD 19 in rabbits (see 16. Non-Clinical Toxicology).

As a precautionary measure, it is preferable to avoid the use of VOXZOGO during pregnancy.

7.1.2. Breastfeeding

Available pharmacodynamic/toxicological data in animals have shown excretion of vosoritide in milk up to the last observation on lactation day (LD) 14 (see 16. Non-Clinical Toxicology).

A risk to nursing newborns/infants cannot be excluded. Vosoritide should not be used during breast-feeding.

7.1.3. Pediatrics

Pediatrics (4 months to < 18 years of age): The safety and efficacy of VOXZOGO for improving in linear growth in pediatric patient with achondroplasia with open epiphyses is supported by studies performed in patients 4 months to 15 years of age. The use of VOXZOGO for this indication is supported by evidence from a controlled study involving 121 pediatric patients 5 to 15 years of age with achondroplasia, supplemented by pharmacokinetic data in patients aged 4.5 months to 15 years of age and additional efficacy and safety data in those aged 4.4 months to 5 years of age. Limited efficacy and safety data are available for infants younger than 4 months of age.

7.1.4. Geriatrics

Geriatrics (> 65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use. This product is not intended for use in geriatric patients.

7.1.5. Renal Impairment

The safety and efficacy of vosoritide in patients with renal impairment has not been evaluated.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The safety profile of VOXZOGO was derived from 239 patients with achondroplasia, aged 1.2 months to 16 years, who received any dose of vosoritide across 7 Phase 2 and 3 interventional studies. The median duration of treatment was 32.69 months. In the pooled safety population, the most common (≥ 10%) adverse reactions reported in VOXZOGO clinical trials including laboratory abnormalities, were injection site reactions (50.6%), increased alkaline phosphatase (31.0%), vomiting (30.1%), rash (22.6%), viral infection (18.0%), arthralgia (17.2%), ear pain (17.2%), hypotension (14.6%), diarrhea (14.6%), dizziness (10.0%), and influenza (9.6%). The majority of events in the Phase 2 or 3 clinical studies were Grade 1 (mild) or Grade 2 (moderate) in severity. Only 12.1% of participants experienced Grade ≥ 3 events.

Serious adverse events were reported in 13.8% of patients treated with VOXZOGO. The serious adverse events reported in > 1 participant were sleep apnea syndrome (1.7%), cervical cord compression (1.3%), knee deformity (1.3%), spinal stenosis (0.8%), adenoidal hypertrophy (0.8%) and syringomyelia (0.8%). Of these serious adverse events, one event of knee deformity (genu valgum) was considered related to vosoritide by the investigator. A fatal adverse event was reported in one patient, and it was due to due to a fatal respiratory arrest, assessed as unrelated to the study treatment.

Three (1.3%) participants discontinued VOXZOGO due to non-serious events of transaminases increased, Wolff-Parkison-White Syndrome and procedural anxiety.

A total of 35.6% participants experienced adverse events leading to skipped doses. Most frequent adverse events (≥ 5%) causing treatment interruption were pyrexia (10.0%), vomiting (9.2%), gastroenteritis (5.4%), and viral infection (5.0%).

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The safety of VOXZOGO in pediatric patients 5 years of age and older with achondroplasia, was studied in a 52-week, randomized, double-blind, placebo-controlled trial of 121 patients (ACH Study 111-301). The patients' ages ranged from 5.1 to 14.9 years with a mean of 8.7 years. The patients received either VOXZOGO 15 µg/kg, or placebo administered subcutaneously once daily.

Table 4 shows adverse reactions that occurred in ≥ 5% of patients treated with VOXZOGO in ACH Study 111-301.

Table 4 – Adverse Drug Reactions Reported in ≥ 5% of Patients Treated with VOXZOGO in ACH Study 111-301

System Organ Class/ Preferred Term	Placebo N = 61 n (%)	Vosoritide (15 µg/kg/day) N = 60 n (%)
Ear and labyrinth disorder		
Ear pain	3 (5%)	6 (10%)
Gastrointestinal disorders		
Vomiting	12 (20%)	16 (27%)
Diarrhea	2 (3%)	6 (10%)
Nausea	4 (7%)	3 (5%)
General disorders and administration site conditions		
Injection site erythema	42 (69%)	45 (75%)
Injection site swelling[a]	19 (31%)	37 (62%)
Injection site urticaria[b]	6 (10%)	20 (33%)
Fatigue[c]	0 (0%)	4 (7%)
Immune system disorders		
Seasonal allergy	1 (2%)	4 (7%)
Infections and infestations		
Influenza	3 (5%)	6 (10%)
Gastroenteritis viral	1 (2%)	4 (7%)
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (7%)	9 (15%)
Nervous system disorders		
Dizziness[d]	2 (3%)	6 (10%)
Skin and subcutaneous tissue disorders		
Dry skin	0 (0%)	3 (5%)
Vascular disorders		
Hypotension[e]	3 (5%)	8 (13%)

[a] Includes the preferred terms: injection site swelling, injection site induration, injection site mass and injection site inflammation.
[b] Includes the preferred terms: injection site urticaria and injection site rash
[c] Includes the preferred terms: fatigue, lethargy, malaise
[d] Includes the preferred terms: dizziness, presyncope, procedural dizziness, vertigo
[e] Hypotension includes both asymptomatic and symptomatic adverse reactions.

Safety in Patients 4 Months to 5 Years of Age (ACH Study 111-206)

The safety of VOXZOGO in pediatric patients with achondroplasia younger than 5 years, was evaluated in a 52-week randomized, double blind, placebo-controlled trial (ACH Study 111-206). In this study, 64 patients from 4.4 months to 5 years of age were randomized to receive either a daily vosoritide dose with similar exposure to that characterized to be safe and effective in children with achondroplasia aged ≥ 5 years old, or placebo. An additional 11 patients received open-label treatment as part of this study. Patients received 30 µg/kg while they were < 2 years of age. The daily dose for patients was adjusted to 15 µg/kg when they turned 2 years old. The most common adverse reactions (> 15%) reported in pediatric patients < 5 years of age were injection site reactions (86%), rash (33%) and viral infections (19%).

Discussion of Selected Adverse Reactions

Hypotension

In ACH Study 111-301 conducted with patients aged ≥ 5 years, 13% of patients treated with vosoritide had events of decreases in blood pressure compared to 5% of patients treated with placebo. These events were transient and resolved without intervention. The median (range) time to onset from injection was 31 (18 to 120) minutes with resolution within 31 (5 to 90) minutes. The reported events were identified predominantly during periods of frequent vital signs monitoring at clinical visits after dosing over a 52-week treatment period. 2% of VOXZOGO-treated patients had a symptomatic episode of decreased blood pressure, with dizziness and vomiting, compared to 0% of patients in the placebo group.

In ACH Study 111-206, events of decrease in blood pressure occurred in 2 patients (5%) aged < 5 years treated with vosoritide compared to 2 patients (6%) on placebo. All events were transient, resolved without intervention and were not treatment limiting.

Injection Site Reactions

In ACH Study 111-301, in patients aged ≥ 5 years, injection site reactions were reported in 85% patients treated with vosoritide and 82% patients on placebo. Patients receiving vosoritide reported a median of 76 events over a 52-week period, compared to a median of 7.5 events in patients receiving. Most injection site reactions were Grade 1 (mild) in severity, with the exception of 5 events in two patients that were Grade 2 (moderate). The median time to onset from injection was 5 min (0-12 hours) with a media duration of 35 minutes.

In ACH Study 111-206, patients aged < 5 years, injections site reactions were reported in 86% of patients treated with vosoritide compared to 53% patients on placebo. Among the participants treated with vosoritide, injection site reactions were more commonly reported in patients < 6 months of age (92%), than in the 6 months to < 2 years (83%) or > 2 years to < 5 years (84%) age groups. Patients receiving vosoritide who experienced injection site reactions reported a median of 224 events, compared to patients receiving placebo who reported a median of 114 events over a 52-week period, all of which were Grade 1 (mild) in severity, transient and not treatment limiting. The median duration of the events was 52 min.

The most common injection site symptoms (frequency ≥ 15%) reported in patients treated with vosoritide were injection site erythema (46%), injection site swelling (38%), and injection site urticaria (18%).

8.3. Less Common Clinical Trial Adverse Reactions

Adverse reactions reported in less than 5% of patients treated with VOXZOGO across clinical studies included:

Vascular disorders: Syncope (1 patient; 0.4%).

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Parameter	ACH Study 111-206				ACH Study 111-301			
	Placebo		Vosoritide		Placebo		Vosoritide	
	All Grade	Grade 3 or 4	All Grade	Grade 3 or 4	All Grade	Grade 3 or 4	All Grade	Grade 3 or 4
Clinical Chemistry, n (%)								
ALP increased	5 (16)	1 (3)	9 (21)	1 (2)	4 (7)	0	10 (17)	0

Alkaline phosphatase (ALP) is an enzyme associated with bone formation, produced primarily by osteoblasts within growth plates and mineralized bones. Increases in ALP have been observed in patients treated with VOXZOGO and are consistent with its pharmacological effect on bone formation and growth.

8.5. Post-Market Adverse Reactions

The following adverse reactions have been identified during post approval use of VOXZOGO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Hypertrichosis (includes the preferred terms: hair growth abnormal and hypertrichosis).

9. Drug Interactions

9.4. Drug-Drug Interactions

In vitro cytochrome P450 (CYP) inhibition and induction studies indicated that vosoritide did not inhibit CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5, nor induce CYP 1A2, 2B6, or 3A4/5 at clinically relevant concentrations. *In vitro* interaction studies also indicated that the potential for interaction with the drug-transporters OAT1, OAT3, OCT 1, OCT 2, OATP1B1, OATP1B3, MATE 1, MATE2-K, BCRP, P-gp, and BSEP is low at clinically relevant concentrations.

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

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Vosoritide is a modified type C natriuretic peptide (CNP). In patients with achondroplasia, endochondral bone growth is negatively regulated due to a gain of function mutation in fibroblast growth factor receptor 3 (FGFR3). FGFR3 inhibits endochondral bone growth through the mitogen-activated protein kinase (MAPK) pathway. Binding of vosoritide to natriuretic peptide receptor-B (NPR-B) antagonizes FGFR3 downstream signaling of extracellular signal-regulated kinases 1 and 2 (ERK1/2) at the level of rapidly accelerating fibrosarcoma serine/threonine protein kinase (RAF-1) of the MAPK pathway and positively regulates endochondral bone growth through chondrocyte proliferation and differentiation.

10.2. Pharmacodynamics

An increase in the 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 treatment of pediatric patients with achondroplasia. Daily administration of this medicine also led to the increase in the serum endochondral ossification biomarker collagen type X marker (CXM) over baseline and remains elevated beyond 24 months.

In patients 4.5 months to 13 years of age at initial dosing, exposure-response analyses showed that vosoritide activity measured by urinary cGMP was near saturation at the dose of 15 mcg/kg (> 2 year of age) or 30 mcg/kg (< 2 year of age) once daily, while maximal increase in growth plate activity indicated by CXM was achieved at this dose.

10.3. Pharmacokinetics

The pharmacokinetics of vosoritide were evaluated in a total of 58 patients 5 to 13 years of age with achondroplasia who received subcutaneous injections of vosoritide 15 µg/kg once daily for 52 weeks. The pharmacokinetic exposure of vosoritide in 19 patients 2 to < 5 years of age were comparable with older children.

In 11 patients 6 months to < 2 years of age, receiving 30 µg/kg once daily the pharmacokinetic exposure of vosoritide was 10% to 400% higher than the older children (> 2 years of age) receiving 15 µg/kg once daily. In 12 patients < 6 months of age receiving 30 µg/kg once daily, the pharmacokinetic exposure of vosoritide was -13% to 265% higher than the older children (> 2 years of age) receiving 15 µg/kg once daily.

The subsections below present the pharmacokinetic data from the 5 to 13 year old population described above.

Absorption

Vosoritide was absorbed with a median T_{max} of 15 minutes. The mean (± SD) peak concentration (C_{max}) and area under the concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}) observed after 52 weeks of treatment was 5,800 (± 3,680) pg/mL, and 290,000 (± 235,000) pg-min/mL respectively. The bioavailability of vosoritide was not assessed in clinical studies.

Distribution

The mean (± SD) apparent volume of distribution after 52 weeks of treatment was 2,910 (± 1,660) mL/kg.

Metabolism

Vosoritide is expected to be metabolized via catabolic pathways and degraded into small peptide fragments and amino acids.

Elimination

The mean (± SD) apparent clearance across 52 weeks of treatment ranged from 79.4 (53.0) to 104 (98.8) mL/min/kg. The mean (± SD) half-life ranged from 21.0 (4.7) to 27.9 (9.9) minutes.

Special populations and conditions

- **Pediatrics**

  No clinically significant differences in the vosoritide pharmacokinetics were observed based on age (0.4 to 15 years).

- **Sex**

  No clinically significant differences in the vosoritide pharmacokinetics were observed based on sex.

- **Ethnic Origin**

  No clinically significant differences in the vosoritide pharmacokinetics were observed based on race or ethnicity.

- **Hepatic Insufficiency**

  The effect of hepatic impairment on the pharmacokinetics of VOXZOGO has not been established and is unknown.

- **Renal Insufficiency**

  The effect of renal impairment on the pharmacokinetics of VOXZOGO has not been established and is unknown. No dosage adjustment is needed for patients with mild renal impairment (i.e., eGFR ≥ 60 mL/min/1.73 m^2). There is a lack of data in patients with moderate to severe renal impairment (i.e., eGFR < 60 mL/min/1.73 m^2) (see 4.2. Recommended Dose and Dosage Adjustment).

- **Obesity**

  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 (5.2 to 74.5 kg) (see 4.2. Recommended Dose and Dosage Adjustment).

10.4. Immunogenicity

All therapeutic proteins have the 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

incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Of 131 patients aged 5 years and older with achondroplasia who were treated with vosoritide 15 µg/kg/day and evaluable for the presence of anti-drug antibodies (ADA) for up to 240 weeks, ADA were detected in 35% of patients (46/131). The earliest time to ADA development was day 85. All ADA-positive patients 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 titre. There was no association between ADA positivity or mean ADA titre 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.

In patients under 5 years of age, 19% (8/43) of vosoritide-treated patients tested positive for ADA responses and all placebo-treated patients tested negative for ADA. The earliest time to ADA development was week 26. All of the ADA-positive patients tested negative for neutralizing antibodies (NAb) at all time points. There was no impact of ADA development on safety, efficacy or PK of vosoritide up to month 12 of treatment.

11. Storage, Stability, and Disposal

Temperature

Store in a refrigerator 2°C – 8°C. Do not freeze.

VOXZOGO may be stored at room temperature below 30°C for a single period up to 90 days, but not beyond the expiry date. Do not return VOXZOGO to refrigerator after storage at room temperature.

Reconstituted Product: Chemical and physical stability has been demonstrated for 3 hours at 25°C. If not used immediately, VOXZOGO must be administered within 3 hours of reconstitution (see 4.3. Reconstitution).

Light

Store in the original package in order to protect from light.

Others

Keep in a safe place out of the reach and sight of children.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Part 2: Scientific Information

13. Pharmaceutical Information

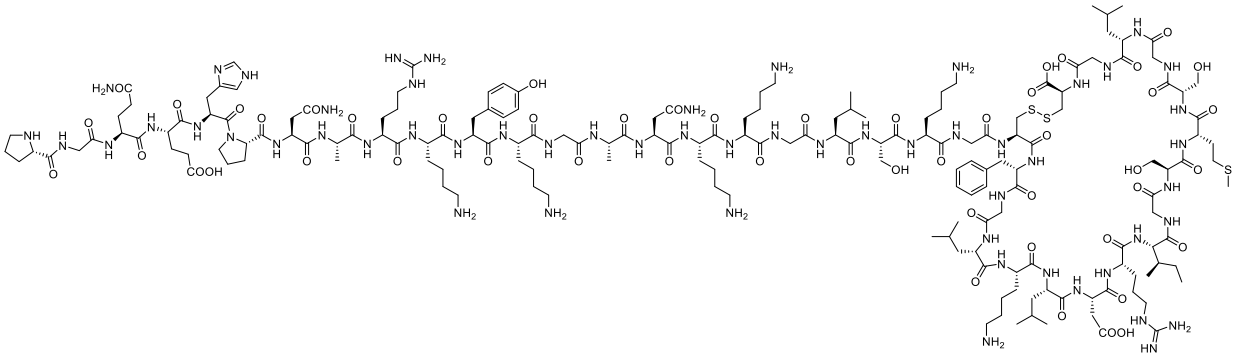
Drug Substance

Non-proprietary name of the drug substance: vosoritide

Chemical name: Modified recombinant human C-type natriuretic peptide 39 (CNP-39)

Molecular formula and molecular mass: $C_{176}H_{290}N_{56}O_{51}S_3$ (4100 Daltons)

Structural formula:



Physicochemical properties: Vosoritide is a 39 amino acid peptide analog that includes the 37 C terminal amino acids of the human CNP53 sequence plus the addition of 2 amino acids (Pro Gly) on the N terminus to convey resistance to neutral endopeptidase (NEP) degradation, resulting in prolonged half-life in comparison to endogenous CNP.

Product Characteristics

Vosoritide is manufactured by expression of TAF-vosoritide fusion protein in recombinant *Escherichia coli* cells. The manufacturing process consists of fermentation and inclusion body recovery, cleavage of TAF-vosoritide to yield the vosoritide peptide, purification, and formulation.

14. Clinical Trials

14.1. Clinical Trials by Indication

Achondroplasia

Trial Design and Study Demographics:

Table 5 – Summary of Clinical Trials in Achondroplasia

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
ACH Study 111-301	Phase 3 Randomized, double-blind, placebo-controlled, multi-center	15 µg/kg/day SC for 52 weeks	121	8.7 years (5.1 – 14.9)	64 M / 57 F
ACH Study 111-206	Phase 2 Randomized, double-blind, placebo-controlled, multi-center	Cohort 1 (24 to < 60 months): 15 µg/kg/day SC Cohort 2 (6 to < 24 months): 15 µg/kg/day and 30 µg/kg/day SC Cohort 3 (0 to < 6 months): 30 µg/kg/day SC 52-week treatment period	64	2.2 years (0.4 – 5.0)	30 M / 34 F

Table 6 – Demographics and Baseline Characteristics for Clinical Trials in Achondroplasia

	ACH Study 111-301		ACH Study 111-206	
Parameter	**Placebo (N=61)**	**VOXZOGO (N=60)**	**Placebo (N=32)**	**VOXZOGO (N=32)**
Age at Day 1 (years)				
Mean (SD)	9.1 (2.5)	8.4 (2.4)	2.3 (1.6)	2.0 (1.4)
Min, Max	5.1, 14.9	5.1, 13.1	0.4, 5.0	0.4, 4.6
Tanner Stage, n (%)[a]				
I	48 (78.7)	48 (80.0)	32 (100.0)	32 (100.0)
> I	13 (21.3)	12 (20.0)	0 (0)	0 (0)
Sex, n (%)[a]				
Male	33 (54.1)	31 (51.7)	13 (40.6)	17 (53.1)
Female	28 (45.9)	29 (48.3)	19 (59.4)	15 (46.9)
Height (cm)				
Mean (SD)	102.94 (10.98)	100.20 (11.90)	70.84 (10.88)	70.90 (10.42)
Min, Max	79.9, 129.3	80.1, 136.8	54.6, 94.5	54.7, 89.3
Weight (kg)				
Mean (SD)	24.62 (9.07)	22.88 (7.96)	10.55 (4.31)	10.20 (3.83)
Min, Max	11.6, 68.9	13.6, 53.0	5.2, 24.9	5.2, 19.1

Max = maximum; Min = minimum; SD = standard deviation.

[a] Percentages were calculated using the total number of patients in the full analysis set (N for each treatment group) as the denominator.

Pediatric Population > 5 Years of Age

The efficacy and safety of vosoritide in patients with achondroplasia with confirmed FGFR3 mutation were assessed in a phase III, randomized, double-blind, placebo-controlled 52-week study (ACH Study 111-301).

In ACH Study 111-301, patients were randomized to either vosoritide (n=60) or placebo (n=61). The dosage of vosoritide was 15 µg/kg administered subcutaneously once daily. Prior to randomization, all patients enrolled in an observational study (ACH Study 111-901) for pediatric patients with achondroplasia for at least a 6-month period during which baseline standing height, weight Z-score, body mass index (BMI) Z-score and upper to lower body ratio were collected. Patients 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 comprised a 52-week placebo-controlled treatment phase followed by an open-label treatment extension study in which all patients received vosoritide (ACH Study 111-302). The primary efficacy endpoint was the change from baseline in AGV at Week 52 compared with placebo. The key secondary endpoint was the change from baseline in height Z-score at Week 52. The efficacy findings are shown in Table 7.

Table 7 – Results from Placebo-Controlled Clinical Trial (ACH Study 111-301)

	Placebo (N=61)			**VOXZOGO 15 µg/kg Daily (N=60)**			**VOXZOGO vs. Placebo**
	Baseline[a]	**Week 52**	**Change**	**Baseline[a]**	**Week 52**	**Change**	**LS Mean Difference[b] (95% CI)**
Annualized Growth Velocity (cm/year)							
Mean ± SD	4.06 ± 1.20	3.94 ± 1.07	-0.12 ± 1.74	4.26 ± 1.53	5.61 ± 1.05	1.35 ± 1.71	**1.57 (1.22, 1.93) (p < 0.0001)[c]**
Height Z-score							
Mean ± SD	-5.14 ± 1.07	-5.14 ± 1.09	0.00 ± 0.28	-5.13 ± 1.11	-4.89 ± 1.09	0.24 ± 0.32	**0.28 (0.17, 0.39) (p < 0.0001)[c]**

AGV, annualized growth velocity; 95% CI, 95% confidence interval; LS, least-squares; Max, maximum; Min, minimum; SD, standard deviation.

[a] Baseline AGV was derived from height data collected from an observational run-in study in pediatric patients with achondroplasia (ACH Study 111-901). Patients had at least 6 months of height data prior to enrollment in ACH Study 111-301.

[b] LS means were estimated from an ANCOVA (analysis of covariance) model. The model was adjusted for covariates, including baseline age, baseline AGV, baseline height Z-score, and randomization stratum defined by sex and Tanner stage.

[c] Two-sided p-value. The overall family-wise Type I error rate was controlled at the 0.05 significance level using 3-step serial gatekeeping multiple comparisons procedure to test AGV, height Z-score, and upper to lower body segment ratio.

By week 52, the observed increase in growth was proportional in both the spine and the lower limbs.

Pediatric Population < 5 Years of Age

A total of 64 patients aged 4.4 months to 59.8 months were randomized in a phase 2, randomized, double-blind, placebo-controlled 52-week study (ACH Study 111-206). The study grouped patients into cohorts of 0 – < 6, 6 – < 24, and 24 – < 60 months. Baseline growth data were obtained for at least 6 months in patients aged ≥ 6 months and for at least 3 months in those aged < 6 months. The primary efficacy endpoint was the change from baseline to Week 52 in height Z-score

At 52 weeks, the estimated change from baseline in height Z-score was +0.25 SDS (95% CI: -0.02, 0.53).

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General toxicology

In a 26-week repeat-dose toxicity study in rats, 35 to 39 week old males and females were administered vosoritide at doses of 50, 150 or 500 mcg/kg by subcutaneous injection followed by a 4-week recovery period. No test article-related mortalities occurred in the study. Tail kinking and altered ambulation and valgus were reported in animals receiving 150 mcg/kg or greater. These findings were associated with increased bone growth plate thickness and/or minimal to moderate growth plate dysplasia that persisted until the end of the recovery period. Sperm count were significantly reduced in animals receiving 150 mcg/kg/day or greater and persisted until the end of the recovery period. The no observed adverse effect level (NOAEL) was 50 mcg/kg, equivalent to a systemic exposure 0.9-fold of that seen in humans at the maximum recommended human dose (MRHD) of 30 mcg/kg based on $AUC_{0\text{-}t}$.

In a 26-week repeat dose study in 7-day old neonatal rats, animals were administered 10, 30 or 90 mcg/kg/day until post-natal day (PND) 188, followed by a 6 week recovery period. Marked impairment of the hindlimbs/hindpaws and gait, which resulted in decreased functionality in the functional observational battery and swim and maze tests were observed in animals receiving 30 mcg/kg/day or greater. Bone changes were associated with increased radiolucency and clear changes at the distal physis and metaphysis of multiple long bones correlated with proliferative and degenerative lesions and other histological changes. The NOAEL was 10 mcg/kg/day, equivalent to systemic exposure 0.02-fold of humans at the MRHD (30 mcg/kg) based on $AUC_{0\text{-}t}$.

In repeat dose studies in cynomolgus monkeys, 2-3 year old (juvenile) animals were administered 20, 90 or 300 mcg/kg/day for up to 26 weeks and 4-5 year old (sexually mature) animals were administered 25, 75 or 250 mcg/kg/day for 44 weeks. Adverse clinical signs included reduced hip use leading to decreased mobility and range of motion of the hind limbs primarily in males receiving 300 mcg/kg/day in the 26-week study that were sustained through to the end of the recovery period. Changes correlated with partially reversible histopathology observations, including increased thickness of proliferative and hypertrophic/calcified zones of the physeal cartilage and primary spongiosa in the femur. In the 44-week study, limited use of hips and decreased range of motion in hind legs was observed in males at 75 mcg/kg/day or higher and slipped capital epiphyses and increased heart rate were seen in high dose males and females. Hypoactivity and transient recumbency was observed after dosing in high-dose animals. Severity of clinical findings in the hindlimbs increased from the date of onset in most animals. NOAELs for the 26- and 44-week studies were 90 mcg/kg/day and 25 mcg/kg/day, respectively, equivalent to systemic exposures 0.73-fold and 0.1-fold that of humans at the MRHD (30 mcg/kg/day) based on $AUC_{0\text{-}t}$.

Genotoxicity

No studies have been performed to evaluate the genotoxic potential of vosoritide.

Carcinogenicity

No long-term animal studies have been performed to evaluate the carcinogenic potential of vosoritide.

Reproductive and developmental toxicology

In a fertility study in rats, females were administered 90, 270 or 540 mcg/kg vosoritide by daily subcutaneous injection every day for 15 days prior to mating and continuing through gestation day 7 (GD 7). Males were administered 90, 270 or 540 mcg/kg by daily subcutaneous injection for 28 days prior to mating with dosed females and until study day 52. Reduced testicular sperm count and density and reduced seminal vesicle weights were observed in males of all dose levels, however, fertility indices were not affected in either males or females up to the highest dose, equivalent to 4.5-fold that of human exposure at the MRHD (30 mcg/kg) based on $AUC_{0\text{-}t}$.

No adverse developmental observations were reported in in an embryo fetal development study in pregnant New Zealand White rabbits, administered 45, 135 or 240 mcg/kg/day vosoritide by subcutaneous injection during gestation from GD 7 to GD 20 or in pregnant rats administered 90, 270 or 540 mcg/kg/day vosoritide from GD 6 to 18. Vosoritide was detected in fetuses from pregnant rats and rabbits at concentrations approximately < 1% of maternal plasma levels. The NOAEL for developmental toxicity in these studies was 540 mcg/kg/day, greater than 8-fold higher than the 15 mcg/kg clinical dose when adjusted for body surface area in a 23 kg patient.

In a pre- and post-natal development study in rats, pregnant animals were administered 90, 270 or 540 mcg/kg/day vosoritide by subcutaneous injection during gestation from GD 6 to lactation day (LD) 20. No adverse effects on natural delivery or litter viability was observed up to the weaning phase and F1 development and reproductive capacity was not adversely affected at the highest maternal dose. The NOAEL was 540 mcg/kg/day, greater than 8-fold higher than the 15 mcg/kg clinical dose when adjusted for body surface area in a 23 kg patient. Evaluation of maternal milk from LD 14 showed transfer of vosoritide into milk at up to 5% of mean time-matched plasma levels. Vosoritide was detected in neonatal pups of high-dose group dams on post-natal day 1.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]VOXZOGO®

Vosoritide for injection

This patient medication information is written for the person who will be taking **VOXZOGO**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **VOXZOGO**, talk to a healthcare professional.

What VOXZOGO is used for:

For the following indication(s) VOXZOGO has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- VOXZOGO (vosoritide for injection) is indicated to increase linear growth in patients with achondroplasia who are 4 months of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How VOXZOGO works:

Individuals with achondroplasia usually have a genetic change that makes a protein called FGFR3 overactive. This protein limits bone growth. VOXZOGO contains vosoritide, which blocks FGFR3's effect and helps bones grow more normally.

The ingredients in VOXZOGO are:

Medicinal ingredient: vosoritide

Non-medicinal ingredients: citric acid monohydrate, mannitol, methionine, polysorbate 80, sodium citrate dihydrate, trehalose dihydrate.

VOXZOGO comes in the following dosage form:

Powder and diluent for injection

- White flip cap: 0.4 milligrams (mg)/0.5 milliliter (mL) per vial
- Magenta flip cap: 0.56 mg/0.7 mL per vial
- Gray flip cap: 1.2 mg/0.6 mL per vial.

Do not use VOXZOGO if:

You or your child are allergic (hypersensitive) to vosoritide or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to a healthcare professional about any health conditions or problems, including if you or your child:

- have significant heart disease or blood pressure problems.
- are taking or have recently taken medicines that lower blood pressure.
- are pregnant or plan to become pregnant. It is not known if VOXZOGO will harm an unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if VOXZOGO passes into breast milk. A healthcare professional can advise on the best way to feed a baby if the breastfeeding parent is taking VOXZOGO.
- have severe vitamin D deficiency.

Other warnings you should know about:

VOXZOGO can lower blood pressure. As a result, you or your child may feel dizzy, tired, or nauseous. Blood pressure usually returns to normal within 90 minutes of VOXZOGO injection. If these effects occur and are severe, tell your doctor.

Drinking plenty of fluids at the time of injection may reduce the likelihood of these effects. It is recommended that patients eat a light snack and drink a glass of fluid (e.g., water, milk, juice, or baby formula) about 30 minutes before injection.

If the patient experiences side effects of low blood pressure, they should avoid driving, riding a bicycle, doing physical activities or using machines for about an hour after injection or until they feel better.

Your doctor will test if you or your child have low vitamin D levels prior to treatment with VOXZOGO and will continue to test for low vitamin D levels throughout treatment. Your doctor may require that vitamin D deficiency be managed prior to initiating treatment with VOXZOGO.

Tell your healthcare professional about all the medicines you or your child are taking, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take VOXZOGO:

- See the detailed **Instructions for Use**, that comes with this Patient Medical Information leaflet, for instructions about the right way to store, prepare, and give VOXZOGO injections at home.
- A caregiver should give the VOXZOGO injection to younger children. Do not inject yourself or your child with VOXZOGO until you have received proper training from a healthcare professional on how to prepare and inject VOXZOGO.

- VOXZOGO is given as an injection under the skin (subcutaneous injection). Inject VOXZOGO once a day, at about the same time each day.
- Patients should eat a light snack and drink an adequate amount of fluid (e.g., water, milk, juice, or baby formula) about 1 hour before the injection. This can reduce side effects such as dizziness, tiredness or nausea (feeling sick).
- It is recommended that you give the injection in a different place each day and do not use the same site 2 days in a row. Do not inject this medicine into moles, scars, birthmarks, or areas where the skin is tender, bruised, red, or hard.

Usual dose:

Your healthcare professional will choose the correct dose depending on your or your child's bodyweight. The doctor will tell you how much of the injection solution to inject. If you are not sure, ask your doctor or pharmacist.

Table 1 shows the dose of VOXZOGO (volume) to be injected daily, based on the actual body weight of the patient.

Table 1: Single dose volumes by body weight in mL

Body Weight (kg)[a]	Dose (mg)	VOXZOGO 0.4 mg Diluent (water for injection): 0.5 mL Concentration: 0.8 mg/mL	VOXZOGO 0.56 mg Diluent (water for injection): 0.7 mL Concentration: 0.8 mg/mL	VOXZOGO 1.2 mg Diluent (water for injection): 0.6 mL Concentration: 2 mg/mL
		Daily Injection Volume (mL)		
5	0.16 mg	0.20 mL		
6-7	0.20 mg	0.25 mL		
8-11	0.24 mg	0.30 mL		
12-16	0.28 mg		0.35 mL	
17-21	0.32 mg		0.40 mL	
22-32	0.40 mg		0.50 mL	
33-43	0.50 mg			0.25 mL
44-59	0.60 mg			0.30 mL
60-89	0.70 mg			0.35 mL
≥ 90	0.80 mg			0.40 mL

[a] Body weights that fall within these weight bands should be rounded to the nearest whole number

Overdose:

If you think you, or a person you are caring for, have taken too much VOXZOGO, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you or your child miss a dose, the injection should still be given if it is within 12 hours of the

scheduled time. If more than 12 hours have passed since the scheduled dose time, do not inject the missed dose. Wait until the next day and continue with the usual dose at the usual time.

Possible side effects from using VOXZOGO:

These are not all the possible side effects you may have when taking VOXZOGO. If you experience any side effects not listed here, tell your healthcare professional.

Very common: may affect more than 1 in 10 people

- Low blood pressure (dizziness, feeling tired or feeling sick shortly after an injection)
- Injection site reactions: redness, itching, inflammation, swelling, bruising, rash, hives, pain
- High levels of blood alkaline phosphatase (shown in blood tests)
- Vomiting
- Redness, swelling or pain of the skin (rash)
- Flu-like symptoms (fever, chills, cough, headache, muscle aches, and tiredness)
- Joint pain
- Ear pain
- Diarrhea
- Dizziness, felling faint or lightheaded

Common: may affect up to 1 in 10 people

- Stomach flu
- Seasonal allergy
- Nausea
- Tiredness
- Dry skin

Uncommon: may affect up to 1 in 100 people

- Passing out

Frequency not known:

- Abnormal hair growth

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep this medicine **out of reach and sight of children**.
- Do not use this medicine past the expiration date.
- Store the VOXZOGO vial and prefilled diluent syringe in the refrigerator (2°C – 8°C). **Do not freeze**. Store in the original package in order to protect from light.
- VOXZOGO may be stored (before mixing) at room temperature (below 30°C) for up to 90 days. **Do not** return VOXZOGO to refrigerator after storage at room temperature. Throw VOXZOGO away if unused within 90 days of storing at room temperature.
- Record on the carton the date you started storing VOXZOGO at room temperature.
- Use VOXZOGO as soon as it has been made up as a solution. If not used immediately, VOXZOGO must be administered within 3 hours of reconstitution. Do not use this medicine if the solution for injection is cloudy or contains any particles.

If you want more information about VOXZOGO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the manufacturer's website www.biomarin.ca, or by calling 1-800-983-4587.

This leaflet was prepared by BioMarin International Limited.

Date of Authorization: 2026-01-21

Instructions for Use
VOXZOGO (vosoritide for injection)
Single-Use

Instructions for Use of the syringe graduated in milliliters (mL)

Please read these Instructions for Use before using VOXZOGO and each time you get a refill. There may be new information. Before you use VOXZOGO for the first time, make sure your healthcare provider shows you the right way to use it. Contact a healthcare provider if you have any questions.

Important Information You Need to Know Before Injecting VOXZOGO

- **Wash your hands** with soap and water.
- **Do not** drop VOXZOGO or put opened items down on surfaces that are not clean.
- VOXZOGO is available in more than 1 strength. **Make sure the strength matches your prescription strength**. **Do not** open packaging until ready to use.
- Take the VOXZOGO vial and prefilled diluent syringe out of the refrigerator and allow them to reach room temperature before mixing.
- **Inspect the vial and supplies for any signs of damage or contamination**. **Do not** use if damaged or contaminated.
- **Check the expiration date**. The expiration date can be found on the carton, vial and prefilled diluent syringe. Do not use if expired.
- **Your child should eat a light meal and an adequate amount of fluid (such as water, milk, juice, or baby formula) within 1 hour before injection.**
- **VOXZOGO should be given at about the same time every day.**
- Do not mix VOXZOGO with other medicines.
- **After mixing the VOXZOGO, use it right away**. **Do not** use the mixed VOXZOGO if it has been sitting at room temperature for more than 3 hours. Throw it away (dispose of) in a sharps container. **See step 19 and "How to Throw Away (Dispose of) VOXZOGO"** for more information.
- **Do not reuse any of the supplies. After the injection, throw away (dispose of) the used vial even if there is VOXZOGO remaining**. **See** step 19 and **"How to Throw Away (Dispose of) VOXZOGO"** for more information.

How to Store VOXZOGO

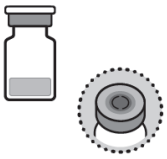
- Store the VOXZOGO vial and prefilled diluent syringe in the refrigerator between 2°C to 8°C.
- You may store VOXZOGO (before mixing) at room temperature (below 30°C) for up to 90 days. Record the date you started storing VOXZOGO at room temperature on the carton to keep track of the 90 days. **Do not 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** freeze VOXZOGO.
- Store VOXZOGO out of direct sunlight.
- Keep VOXZOGO and all other medicines out of the reach of children.

Supplies needed to inject VOXZOGO

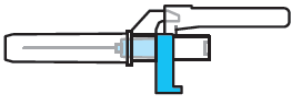
Gather all of these supplies on a clean, flat surface before injecting.

Items provided

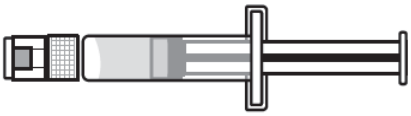
VOXZOGO Vial



Diluent Needle
(blue tab retracts needle)



Prefilled Diluent Syringe
(Contains water for injection for reconstitution of VOXZOGO)



Injection Syringe

Please speak to your doctor or healthcare professional if you are unsure of your recommended dose or how to use the diluent needle and injection syringe.

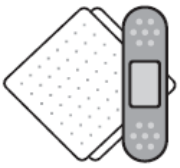
Items needed but not provided in the pack

If you don't have these items, ask your pharmacist.

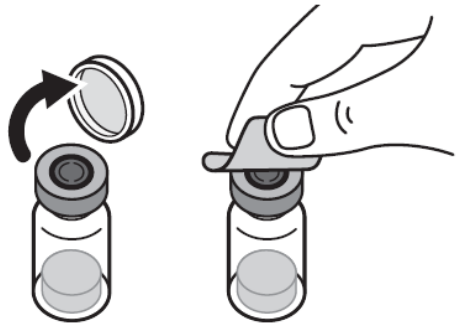
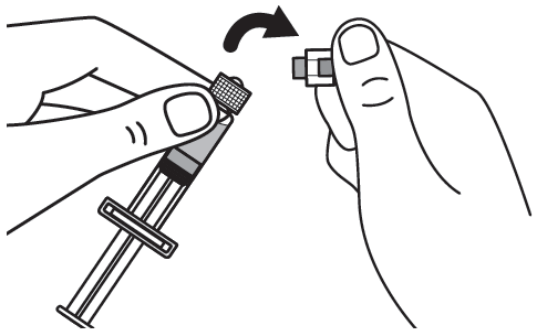
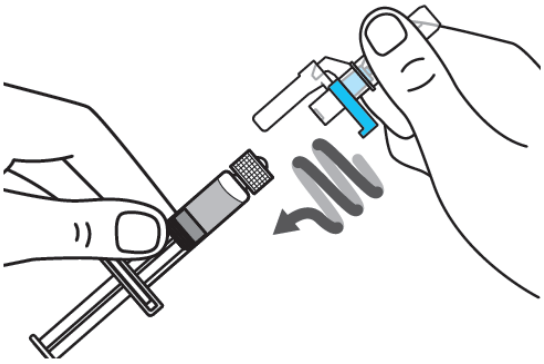
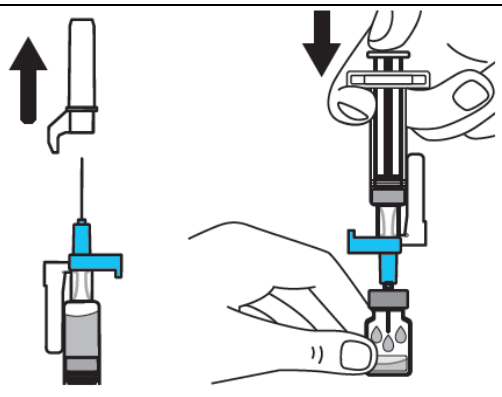
Alcohol Pads

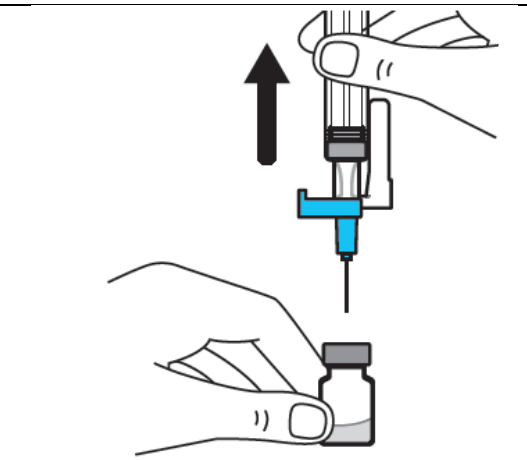
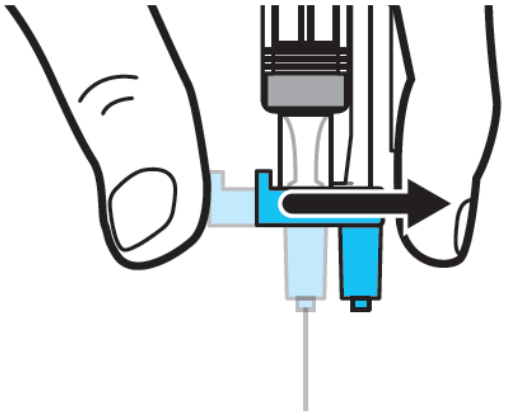
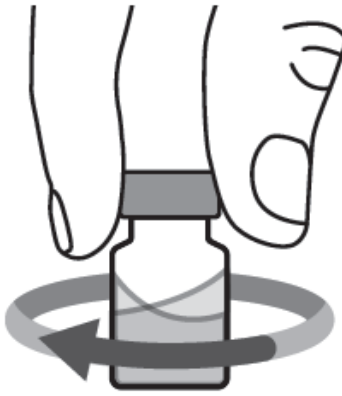
Sharps Container

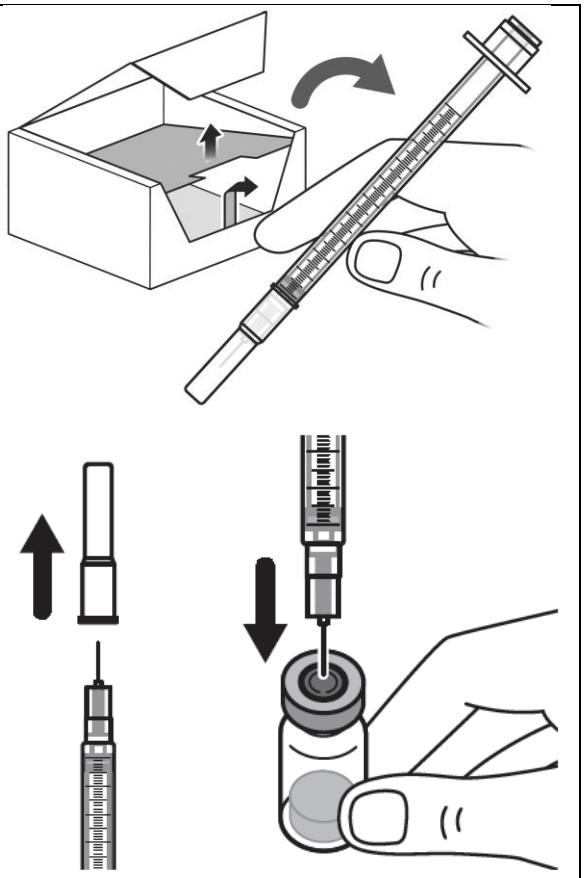
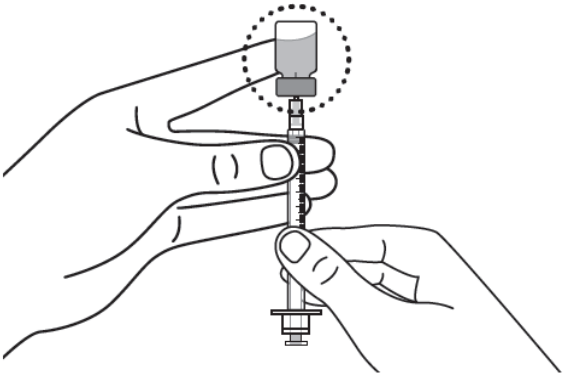
Gauze or Bandage

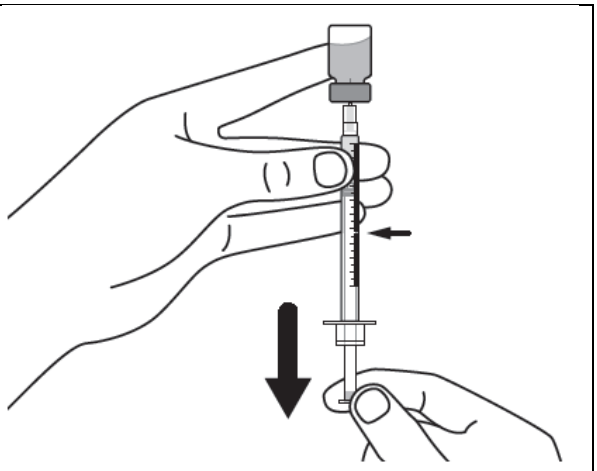
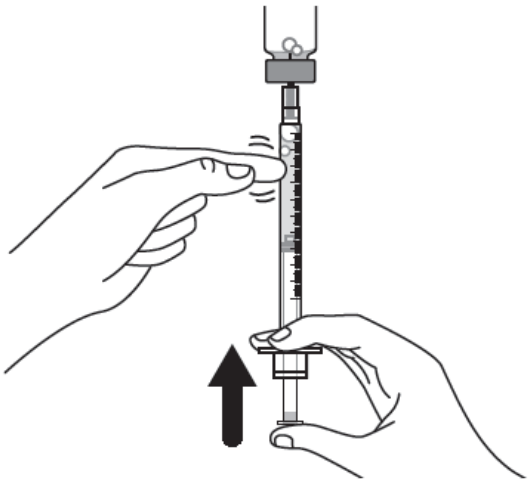
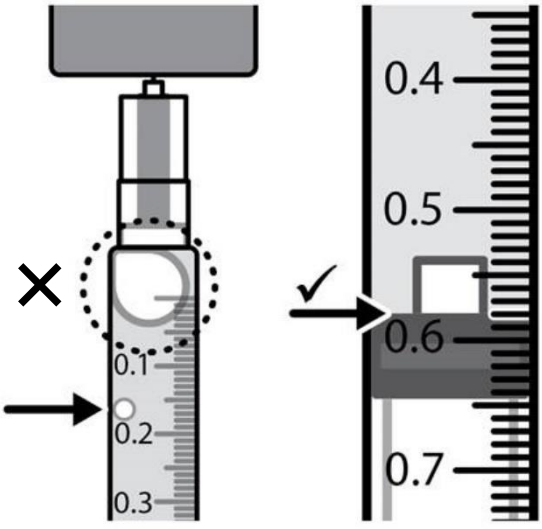


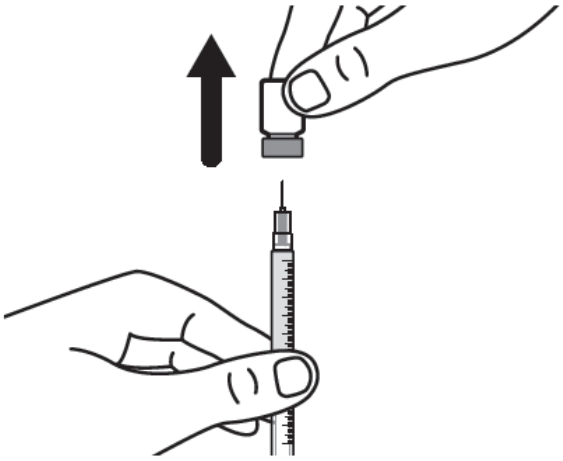
PREPARING FOR INJECTION

Step 1: On a clean flat surface, flip off the vial cap and wipe the top with an alcohol pad. ⚠ **ATTENTION: Do not touch the vial stopper with your fingers after wiping it with an alcohol pad.**	
Step 2: Gently bend to snap off the cap from the diluent syringe.	
Step 3: Twist the diluent needle onto the prefilled diluent syringe until you can no longer twist it.	
Step 4: Pull off the needle cap and insert the needle into the vial through the middle of the vial stopper. Slowly push the plunger rod down to inject **all of the liquid**. ⚠ **ATTENTION: Be careful not to push the blue tab until Step 5.**	

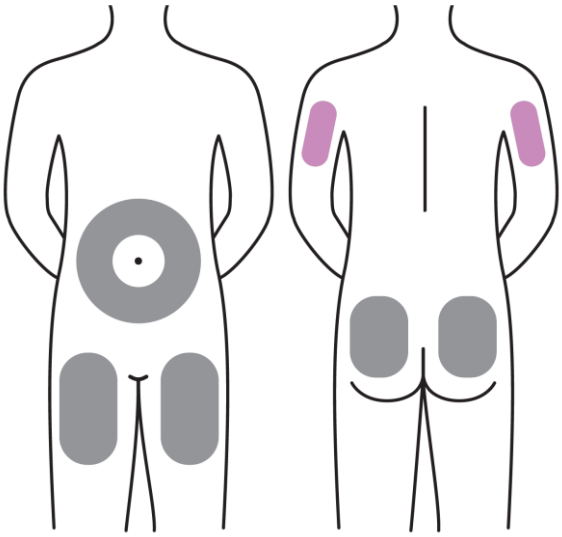
Step 5: Remove the needle from the vial, then press the blue tab for the needle to pull back (retract). Throw away the needle and syringe into a sharps container. See step 19 and "How to throw away (dispose of) VOXZOGO." **Do not use the prefilled diluent syringe to give the injection.** ⚠ **ATTENTION: Be careful not to touch the needle tip.**	 
Step 6: Gently swirl the vial until the powder has completely dissolved and the solution is clear. **Do not shake.** Make sure medicine is clear to yellow, not cloudy and does not have particles.	

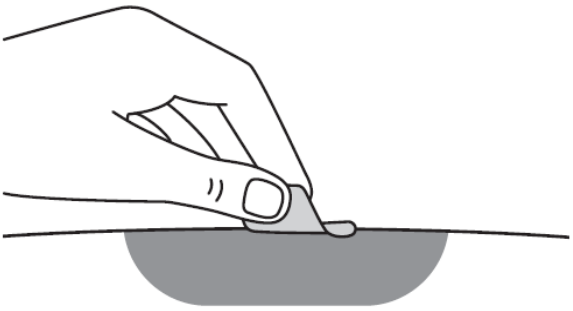
Step 7: Take the injection syringe out of the carton. Pull off the needle cap from the injection syringe and insert the needle into the vial straight through the middle of the vial stopper. **Be careful not to bend the needle.** ⚠ **ATTENTION: Do not place the cap back on the needle.**	
Step 8: Carefully hold the vial and syringe and turn the vial upside down with the needle still inserted. The vial should be on top. ⚠ **ATTENTION: Be careful not to bend the needle.**	

Step 9: Keep the needle tip in the medicine and slowly pull the plunger rod back to draw up the prescribed dose in the syringe. **Check the prescription label for how much to draw up.** ⚠ **ATTENTION: Draw up the prescribed dose.**	
Step 10: Remove large air bubbles in the syringe by gently tapping the syringe. Then **slowly** push the bubbles back into the vial.	
Step 11: Repeat steps 9 and 10 until you have the correct prescribed dose in the syringe and no large bubbles. **Make sure the dose in the syringe matches the prescribed dose. Measure from the base of the plunger as shown.** ⚠ **ATTENTION: Remove any large bubbles.** 1 or 2 small bubbles are acceptable.	

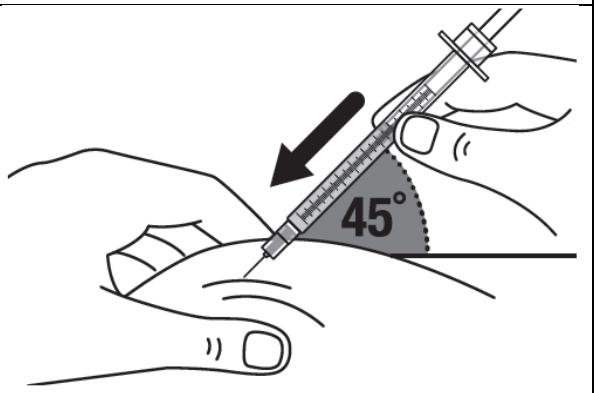
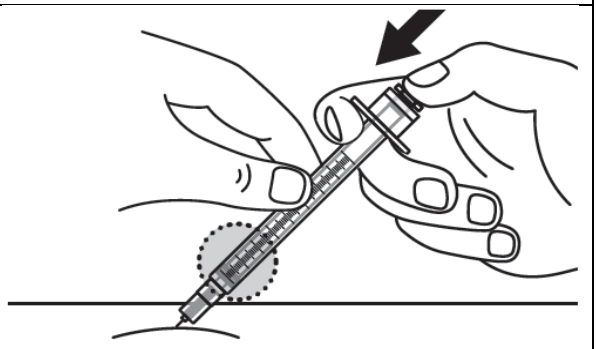
Step 12: Make sure you have the prescribed dose in the syringe, then remove the vial and prepare to give the dose. ⚠ **ATTENTION:** Confirm that the dose in the syringe matches the prescribed dose before removing vial.	

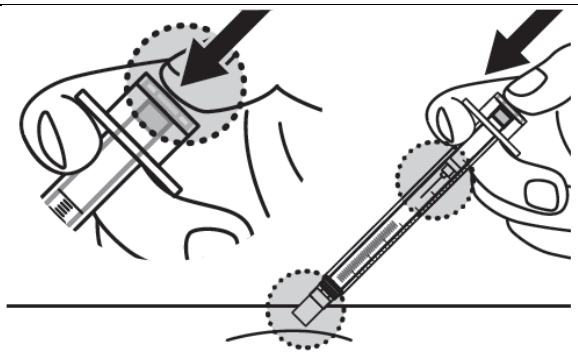
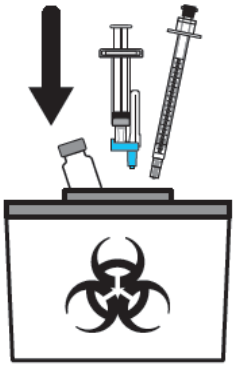
SELECTING AND PREPARING INJECTION SITE

Step 13: VOXZOGO should be injected into the fatty layer under the skin (subcutaneous) only. • Do not inject through clothes. • Do not inject in the same site 2 times in a row. • Do not inject into skin that is swollen, sore, bruised, red, hard, or scarred.	The following sites are recommended for injection: • **Thighs** or • **Abdomen** (5 centimeters from belly button) or • **Buttocks** • **Healthcare providers and caregivers may also inject VOXZOGO into the back of upper arms** 

Step 14: Wipe the injection site with an alcohol pad and let the skin air dry. ⚠ **ATTENTION: Do not touch the area again before injecting.**	

GIVING VOXZOGO INJECTION

Step 15: After wiping the site with an alcohol pad, **pinch** the skin up around the selected injection site.	
Step 16: Quickly insert the needle all the way into the skin **at a 45-degree angle**.	
Step 17: Release the pinch and slowly push the plunger rod all the way down.	

Step 18: Continue pressing the plunger rod until the needle retracts into the syringe.	
Step 19: Throw away the used vial, syringes and needles in a sharps container. **See "How to Throw Away (Dispose of) VOXZOGO"** for more information.	

After injecting VOXZOGO

- Check the injection site. If there is a small amount of blood at the injection site, gently press a gauze pad on it for a few seconds or apply a bandage.
- **Do not** rub the injection site.
- Monitor for signs of low blood pressure, such as dizziness, tiredness, or nausea (feeling sick). If the patient has these symptoms call your doctor or healthcare provider, then lie the patient down on their back and place cushions under their legs to raise them.

How to throw away (dispose of) VOXZOGO

Put your used or expired vials, needles and syringes in a sharps disposal container right away after use. **Do not throw away (dispose of) vials, loose needles and syringes in your household trash.**

If you do not have a sharps disposal container, you may use a household container that:

- is made of a heavy-duty plastic,
- can be closed with a tight fitting, puncture-resistant lid without sharps being able to come out,
- is upright and stable during use
- is leak-resistant, and
- is properly labelled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your local guidelines for the right way to dispose of your sharps disposal container.

Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

For Help or More Information

- Call your healthcare provider
- Call BioMarin at 1-800-983-4587
- Visit www.biomarin.ca

Instructions for Use
VOXZOGO (vosoritide for injection)
Single-Use

Instructions for Use of the syringe graduated in Units (U)

Please read these Instructions for Use before using VOXZOGO and each time you get a refill. There may be new information. Before you use VOXZOGO for the first time, make sure your healthcare provider shows you the right way to use it. Contact a healthcare provider if you have any questions.

Important Information You Need to Know Before Injecting VOXZOGO

- **Wash your hands** with soap and water.
- **Do not** drop VOXZOGO or put opened items down on surfaces that are not clean.
- VOXZOGO is available in more than 1 strength. **Make sure the strength matches your prescription strength**. **Do not** open packaging until ready to use.
- Take the VOXZOGO vial and prefilled diluent syringe out of the refrigerator and allow them to reach room temperature before mixing.
- **Inspect the vial and supplies for any signs of damage or contamination**. **Do not** use if damaged or contaminated.
- **Check the expiration date**. The expiration date can be found on the carton, vial and prefilled diluent syringe. Do not use if expired.
- **Your child should eat a light meal and an adequate amount of fluid (such as water, milk, juice, or baby formula) within 1 hour before injection.**
- **VOXZOGO should be given at about the same time every day.**
- Do not mix VOXZOGO with other medicines.
- **After mixing the VOXZOGO, use it right away**. **Do not** use the mixed VOXZOGO if it has been sitting at room temperature for more than 3 hours. Throw it away (dispose of) in a sharps container. **See step 18 and "How to Throw Away (Dispose of) VOXZOGO"** for more information.
- **Do not reuse any of the supplies. After the injection, throw away (dispose of) the used vial even if there is VOXZOGO remaining**. **See** step 18 and **"How to Throw Away (Dispose of) VOXZOGO"** for more information.

How to Store VOXZOGO

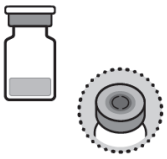
- Store the VOXZOGO vial and prefilled diluent syringe in the refrigerator between 2°C to 8°C.
- You may store VOXZOGO (before mixing) at room temperature (below 30°C) for up to 90 days. Record the date you started storing VOXZOGO at room temperature on the carton to keep track of the 90 days. **Do not 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** freeze VOXZOGO.
- Store VOXZOGO out of direct sunlight.
- Keep VOXZOGO and all other medicines out of the reach of children.

Supplies needed to inject VOXZOGO

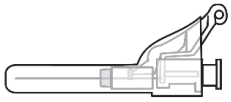
Gather all of these supplies on a clean, flat surface before injecting.

Items provided

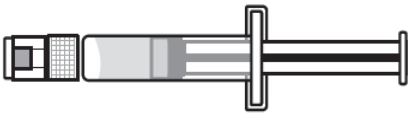
VOXZOGO Vial



Diluent Needle



Prefilled Diluent Syringe
(Contains water for injection for reconstitution of VOXZOGO)



Injection Syringe

The measurements for the syringe provided is equivalent to mL as follows: 0.1 mL = 10 Units.

Please speak to your doctor or healthcare professional if you are unsure of your recommended dose or how to use the diluent needle and injection syringe.

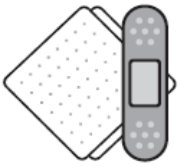
Items needed but not provided in the pack

If you don't have these items, ask your pharmacist.

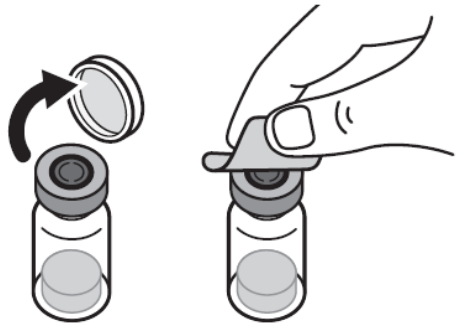
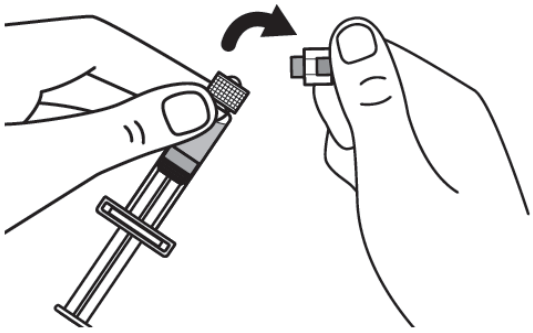
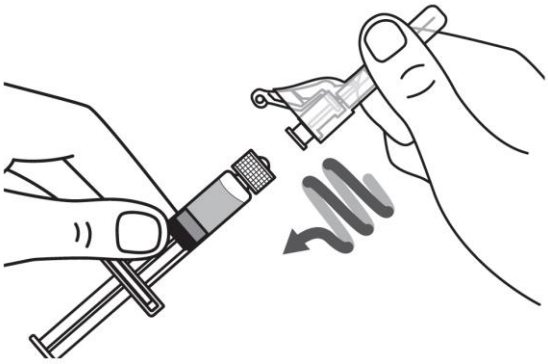
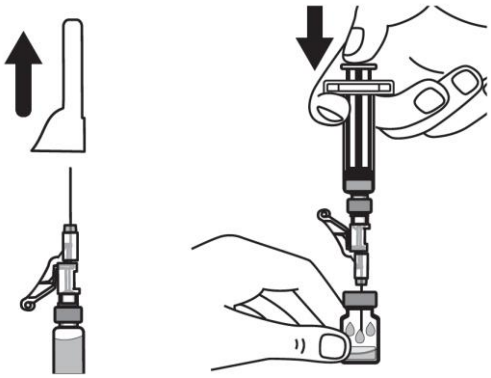
Alcohol Pads

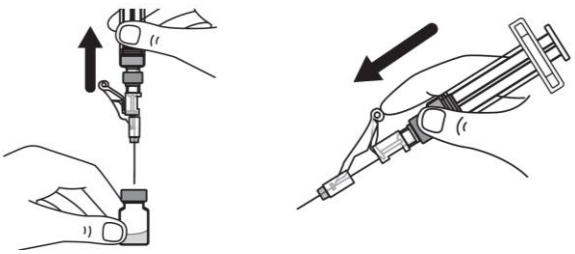
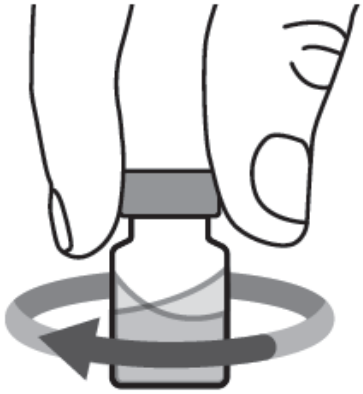
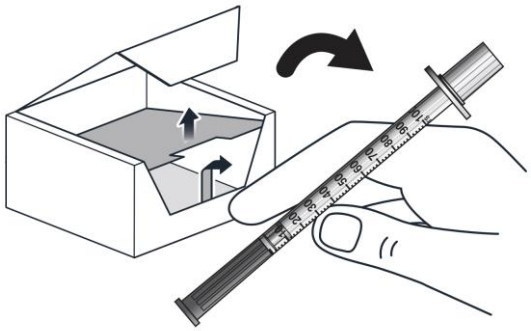
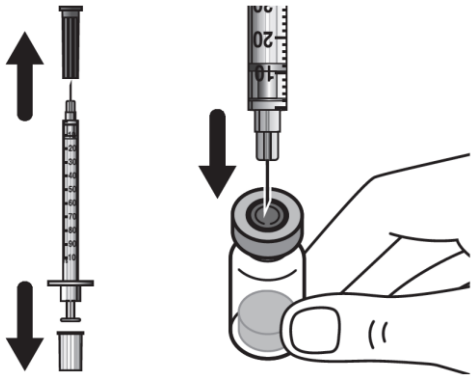
Sharps Container

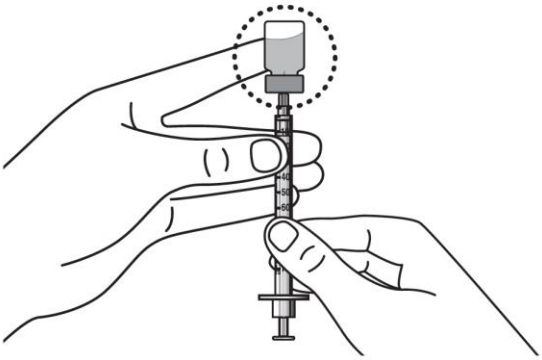
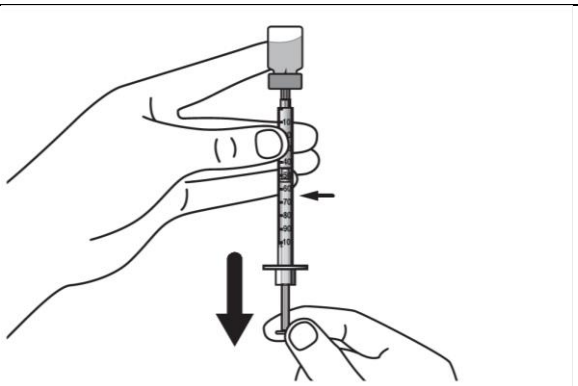
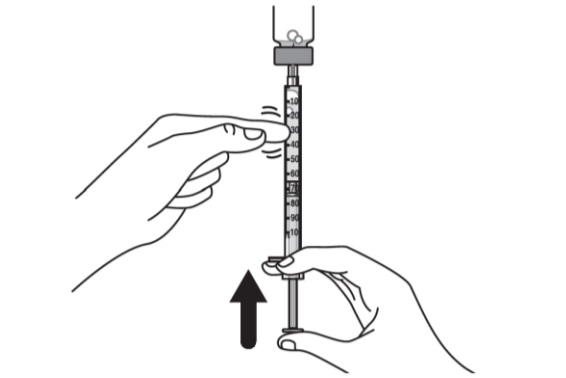
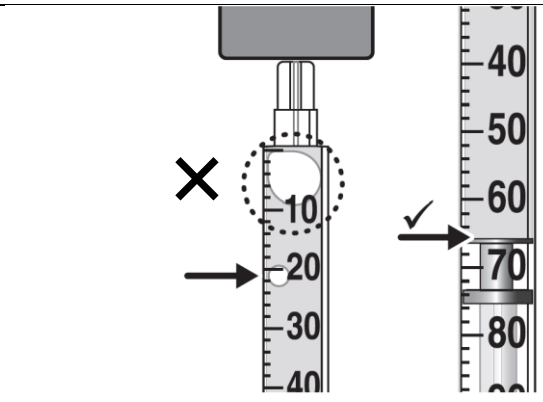
Gauze or Bandage

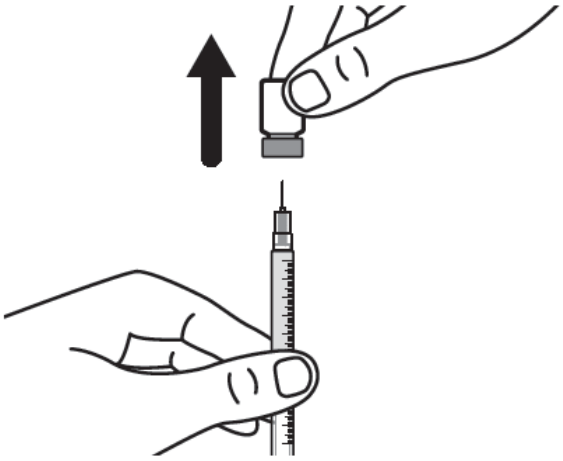


PREPARING FOR INJECTION

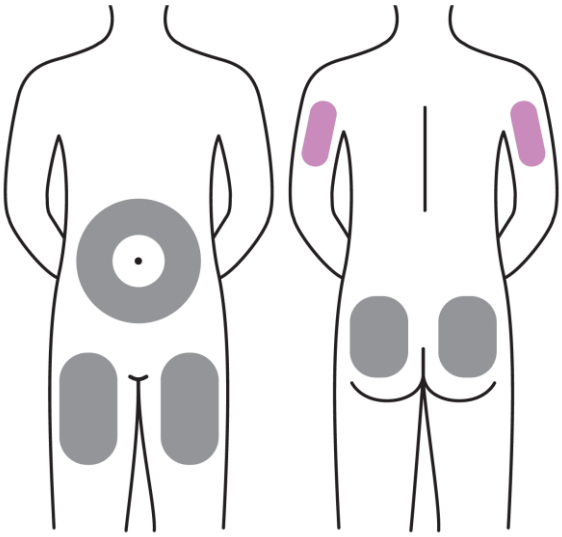
Step 1: On a clean flat surface, flip off the vial cap and wipe the top with an alcohol pad. ⚠ **ATTENTION: Do not touch the vial stopper with your fingers after wiping it with an alcohol pad.**	
Step 2: Gently bend to snap off the cap from the diluent syringe.	
Step 3: Twist the diluent needle onto the prefilled diluent syringe until you can no longer twist it.	
Step 4: Pull off the needle cap and insert the needle into the vial through the middle of the vial stopper. Slowly push the plunger rod down to inject **all of the liquid**.	

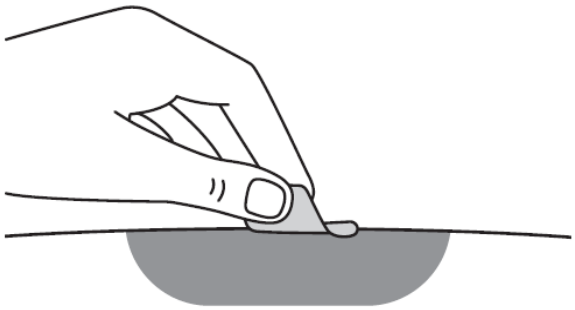
Step 5: Remove the needle from the vial. Throw away the needle and syringe into a sharps container. See step 18 and "How to throw away (dispose of) VOXZOGO." **Do not use the prefilled diluent syringe to give the injection.** ⚠ **ATTENTION: Be careful not to touch the needle tip.**	
Step 6: Gently swirl the vial until the powder has completely dissolved and the solution is clear. **Do not shake.** Make sure medicine is clear to yellow, not cloudy and does not have particles.	
Step 7: Take the injection syringe out of the carton. Pull off the needle cap from the injection syringe and insert the needle into the vial straight through the middle of the vial stopper. **Be careful not to bend the needle.** ⚠ **ATTENTION: Do not place the cap back on the needle.**	 

Step 8: Carefully hold the vial and syringe and turn the vial upside down with the needle still inserted. The vial should be on top. ⚠ **ATTENTION: Be careful not to bend the needle.**	
Step 9: Keep the needle tip in the medicine and slowly pull the plunger rod back to draw up the prescribed dose in the syringe. **Check the prescription label for how much to draw up.** ⚠ **ATTENTION: Draw up the prescribed dose.**	
Step 10: Remove large air bubbles in the syringe by gently tapping the syringe. Then **slowly** push the bubbles back into the vial.	
Step 11: Repeat steps 9 and 10 until you have the correct prescribed dose in the syringe and no large bubbles. **Make sure the dose in the syringe matches the prescribed dose. Measure from the base of the plunger as shown.** ⚠ **ATTENTION: Remove any large bubbles.** 1 or 2 small bubbles are acceptable.	

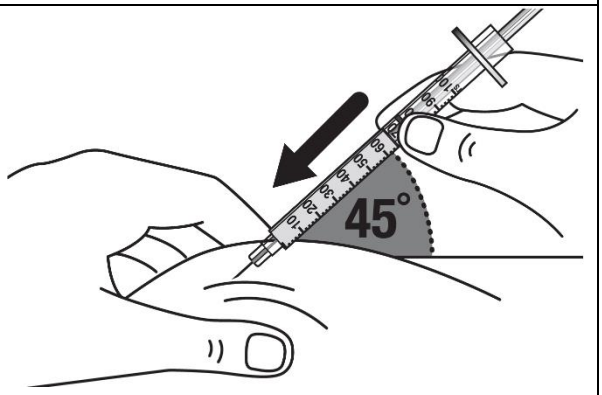
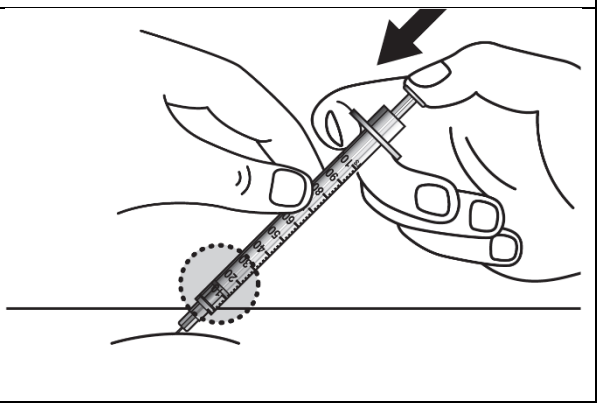
Step 12: Make sure you have the prescribed dose in the syringe, then remove the vial and prepare to give the dose. ⚠ **ATTENTION:** Confirm that the dose in the syringe matches the prescribed dose before removing vial.	

SELECTING AND PREPARING INJECTION SITE

Step 13: VOXZOGO should be injected into the fatty layer under the skin (subcutaneous) only. • Do not inject through clothes. • Do not inject in the same site 2 times in a row. • Do not inject into skin that is swollen, sore, bruised, red, hard, or scarred.	The following sites are recommended for injection: • **Thighs** or • **Abdomen** (5 centimeters from belly button) or • **Buttocks** • **Healthcare providers and caregivers may also inject VOXZOGO into the back of upper arms** 

Step 14: Wipe the injection site with an alcohol pad and let the skin air dry. ⚠ **ATTENTION: Do not touch the area again before injecting.**	

GIVING VOXZOGO INJECTION

Step 15: After wiping the site with an alcohol pad, **pinch** the skin up around the selected injection site.	
Step 16: Quickly insert the needle all the way into the skin **at a 45-degree angle**.	
Step 17: Release the pinch and slowly push the plunger rod all the way down.	

Step 18: Throw away the used vial, syringes and needles in a sharps container. **See "How to Throw Away (Dispose of) VOXZOGO"** for more information.	

After injecting VOXZOGO

- Check the injection site. If there is a small amount of blood at the injection site, gently press a gauze pad on it for a few seconds or apply a bandage.
- **Do not** rub the injection site.
- Monitor for signs of low blood pressure, such as dizziness, tiredness, or nausea (feeling sick). If the patient has these symptoms call your doctor or healthcare provider, then lie the patient down on their back and place cushions under their legs to raise them.

How to throw away (dispose of) VOXZOGO

Put your used or expired vials, needles and syringes in a sharps disposal container right away after use. **Do not throw away (dispose of) vials, loose needles and syringes in your household trash.**

If you do not have a sharps disposal container, you may use a household container that:

- is made of a heavy-duty plastic,
- can be closed with a tight fitting, puncture-resistant lid without sharps being able to come out,
- is upright and stable during use
- is leak-resistant, and
- is properly labelled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your local guidelines for the right way to dispose of your sharps disposal container.

Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

For Help or More Information

- Call your healthcare provider
- Call BioMarin at 1-800-983-4587
- Visit www.biomarin.ca