PHYSICIAN'S PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Voxzogo 0.4 mg
Voxzogo 0.56 mg
Voxzogo 1.2 mg

powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Voxzogo 0.4 mg powder and solvent for solution for injection

Each vial of powder contains 0.4 mg of vosoritide*.
After reconstitution, each vial contains 0.4 mg vosoritide in 0.5 mL of solution, corresponding to a concentration of 0.8 mg/mL.

Voxzogo 0.56 mg powder and solvent for solution for injection

Each vial of powder contains 0.56 mg of vosoritide*.
After reconstitution, each vial contains 0.56 mg vosoritide in 0.7 mL of solution, corresponding to a concentration of 0.8 mg/mL.

Voxzogo 1.2 mg powder and solvent for solution for injection

Each vial of powder contains 1.2 mg of vosoritide*.
After reconstitution, each vial contains 1.2 mg vosoritide in 0.6 mL of solution, corresponding to a concentration of 2 mg/mL.

*produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white to yellow and the solvent is clear and colourless, see section 6.6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Voxzogo is indicated for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

4.2 Posology and method of administration

Treatment with vosoritide should be initiated and directed by a physician appropriately qualified in the management of growth disorders or skeletal dysplasias.

Posology

It is important to initiate treatment in children as young as possible.

The volume of vosoritide to be administered at the recommended dose is based on the patient's weight and the vosoritide concentration (see Table 1). The usual dose is 15 µg/kg body weight. For practicality reasons and to account for weight-related PK changes (see section 5.2), the following dosing is recommended.

Table 1: Single dose volumes by body weight

Body weight (kg)	**Vosoritide 0.4 mg** **solvent (water for injections): 0.5 mL** **concentration: 0.8 mg/mL**	**Vosoritide 0.56 mg** **solvent (water for injections): 0.7 mL** **concentration: 0.8 mg/mL**	**Vosoritide 1.2 mg** **solvent (water for injections): 0.6 mL** **concentration: 2 mg/mL**
	Daily injection volume (mL)		
10-11	0.30 mL		
12-16		0.35 mL	
17-21		0.40 mL	
22-32		0.50 mL	
33-43			0.25 mL
44-59			0.30 mL
60-89			0.35 mL
≥ 90			0.40 mL

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

Missed dose
If a dose of vosoritide is missed, it can be administered within 12 hours. If more than 12 hours have passed since the original dosing schedule, the missed dose should NOT be administered. Patients/caregivers should be advised to continue with the next scheduled dose the following day.

Growth monitoring
Patients should be monitored and assessed regularly every 3-6 months to check body weight, growth and physical development. Dose should be adjusted according to the patient's body weight (see Table 1).

Special populations

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

Paediatric population
Voxzogo is not indicated in children aged less than 2 years. Currently available data are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

Voxzogo is for subcutaneous single use only. This medicinal product must be administered within 3 hours of reconstitution, see section 6.3.

Prior to injecting, a healthcare professional should:
- train caregivers on the preparation and subcutaneous injection of this medicinal product.
- train caregivers and patients to recognise signs and symptoms of decreased blood pressure.
- inform caregivers and patients what to do in the event of symptomatic decreases in blood pressure.

Patients and caregivers should be instructed to rotate sites for subcutaneous injections. Recommended injection sites on the body include the front middle of the thighs, the lower part of the abdomen except for 5 cm directly around 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. Voxzogo should not be injected into sites that are red, swollen, or tender.

Patients should be well hydrated at the time of injection. It is recommended patients eat a light snack and drink a glass of fluid (e.g., water, milk, juice, etc.) about 30 minutes before injecting. This is to reduce the signs and symptoms of potential decreases in blood pressure (dizziness, fatigue and/or nausea) occurring (see section 4.4, Blood pressure effects).

If possible, this medicinal product should be injected at approximately the same time each day.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal product should be clearly recorded.

Blood pressure effects

Patients with significant cardiac or vascular disease and patients on anti-hypertensive medicinal products were excluded from participation in premarketing clinical trials, see section 4.8.

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 (see sections 4.2 and 4.8).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per unit volume, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro cytochrome P450 (CYP) inhibition and induction studies and *in vitro* transporter inhibition studies have been performed. Results suggested that vosoritide is unlikely to cause CYP- or transporter-mediated drug-drug interactions in humans when the medicinal product is administered concomitantly with other medicinal products.

No other interaction studies have been performed. Because it is a recombinant human protein, vosoritide is an unlikely candidate for drug-drug interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of vosoritide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of vosoritide during pregnancy.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of vosoritide in milk (see section 5.3). A risk to newborns/infants cannot be excluded. Vosoritide should not be used during breast-feeding.

Fertility

No impairment of male or female fertility has been observed in nonclinical studies (see section 5.3).

4.7 Effects on ability to drive and use machines

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 decreased blood pressure 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.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions to vosoritide were injection site reactions (85%), vomiting (27%), and decreased blood pressure (13%).

Tabulated list of adverse reactions

Adverse reactions in patients treated with vosoritide are tabulated below.

Adverse reactions are listed below by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions in patients treated with Voxzogo

System organ class	Very common	Common
Nervous system disorders		Syncope
		Pre-syncope
		Dizziness
Vascular disorders	Hypotension[a]	
Gastrointestinal disorders	Vomiting	Nausea
General disorders and administration site conditions	Injection site reaction[b]	Fatigue
Investigations		Increased alkaline phosphatase

a. Hypotension includes both asymptomatic and symptomatic adverse reactions.
b. Injection site reactions include 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 haemorrhage, injection site discolouration, and injection site induration.

Description of selected adverse reactions

Hypotension
In ACH study 111-301, 13% of patients treated with vosoritide reported events of decreases in blood pressure which were transient and resolved without intervention. The median 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 patients had a symptomatic episode with dizziness and vomiting.

Injection site reactions
Injection site reactions were reported in 85% patients treated with vosoritide compared to 82% patients on placebo. Patients receiving this medicinal product who experienced injection site reactions reported a median of 76 events, compared to patients receiving placebo who reported a median of 7.5 events over a 52-week period. The most common injection site reactions (occurring in at least 10% of patients treated with vosoritide) were injection site reaction (73%), injection site erythema (68%), injection site swelling (38%), and injection site urticaria (13%). All injection site reactions were Grade 1 (mild) in severity, with the exception of 5 events in two patients that were Grade 2 (moderate). Reported Grade 2 events included; two patients who reported two events of injection site urticaria, and one event of injection site vesicles.

Immunogenicity

Of 131 patients 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. The earliest time to ADA development was day 85. All ADA-positive patients tested negative for anti-vosoritide neutralising 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.

Paediatric population

The safety profile of vosoritide in clinical studies involving children aged 2 to < 5 years was similar to that observed in older children (see section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.

4.9 Overdose

In clinical trials, doses of vosoritide were explored up to 30 µg/kg/day. 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.

In the event a patient takes more than they should, the patient should contact their healthcare professional.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of bone diseases, Other drugs affecting bone structure and mineralisation, ATC code: M05BX07

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)*. Binding of vosoritide to natriuretic peptide receptor-B (NPR-B) antagonises *FGFR3* downstream signalling 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.

Pharmacodynamic effects

Exposure-dependent (AUC and C_{max}) increases from baseline in urinary cyclic guanosine monophosphate (cGMP, a biomarker for NPR-B activity) concentrations and serum collagen type X marker (CXM, a biomarker for endochondral ossification) were observed on treatment with vosoritide. Increase in the urinary cGMP concentrations from pre-dose baseline took place within the first four hours post-dose. Median serum CXM concentration increased over baseline by day 29 of daily administration of this medicinal product. This effect was maintained beyond 24 months of treatment. Vosoritide activity as measured by urine cGMP was near saturation while maximal increase in growth plate activity indicated by CXM was achieved at the dose of 15 µg/kg administered subcutaneously once daily.

Clinical efficacy and safety

The efficacy and safety of vosoritide in patients with achondroplasia with confirmed FGFR3 mutation were assessed in a randomised, double-blind, placebo-controlled 52-week study (ACH study 111-301). In ACH study 111-301, patients were randomised to either vosoritide (n=60) or placebo (n=61) and the dose of vosoritide was 15 µg/kg administered subcutaneously once daily. Prior to randomisation, all patients enrolled in an observational study (ACH study 111-901) for paediatric patients with achondroplasia for at least a 6-month period during which baseline standing height and other pre-treatment growth assessments 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. The primary efficacy endpoint was the change from baseline in AGV at Week 52 compared with placebo.

Patients with achondroplasia were also treated with vosoritide 15 µg/kg/day in an open label, dose-escalation study and in its long-term extension study (ACH study 111-205). Data was collected from observational studies in patients to characterise the natural history of achondroplasia. Height data from untreated patients with achondroplasia in the same age range as the clinical studies was used as an historical control to assess the effect on height after up to 5 years of vosoritide treatment.

Patient demographics and baseline characteristics are shown in Table 3.

Table 3: Patient demographics and characteristics in ACH study 111-301 and ACH study 111-205

	ACH study 111-301		ACH study 111-205[b]
Parameter	Placebo (N=61)	15 µg/kg/day Voxzogo (N=60)	15 µg/kg/day Voxzogo (N=10)
Age at day 1 (years)			
Mean (SD)	9.06 (2.47)	8.35 (2.43)	8.54 (1.54)
Min, max	5.1, 14.9	5.1, 13.1	6.3, 11.1
Age at day 1, n (%)[a]			
≥ 5 to < 8 years	24 (39.3)	31 (51.7)	4 (40.0)
≥ 8 to < 11 years	24 (39.3)	17 (28.3)	5 (50.0)
≥ 11 to < 15 years	13 (21.3)	12 (20.0)	1 (10.0)
Tanner stage b, n (%)[a]			
I	48 (78.7)	48 (80.0)	10 (100.0)
> I	13 (21.3)	12 (20.0)	
Sex, n (%)[a]			
Male	33 (54.1)	31 (51.7)	4 (40.0)
Female	28 (45.9)	29 (48.3)	6 (60.0)
Weight (kg)			
Mean (SD)	24.62 (9.07)	22.88 (7.96)	25.13 (5.74)
Min, max	11.6, 68.9	13.6, 53.0	18.2, 36.4

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

[b] Analysis from 10 out of 35 patients who only received 15 mcg/kg/day in an open label, dose-escalation study and continued into the long-term extension ACH study 111-205

In ACH study 111-301, improvements in AGV and height Z-score from baseline were observed in patients treated with Voxzogo 15 µg/kg/day compared with placebo. Efficacy results are shown in Table 4.

Table 4: Results from placebo-controlled clinical trial

	Placebo (N=61)			**Voxzogo 15 µg/kg daily (N=60[c])**			**Voxzogo vs. placebo**
	Baseline	**Week 52**	**Change**	**Baseline**	**Week 52**	**Change**	**LS Mean difference in changes (95% CI)**
Annualised 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[a] (1.22, 1.93)** **(p = < 0.0001)[b]**
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[a] (0.17, 0.39)** **(p = < 0.0001)[b]**

AGV, annualised growth velocity; 95% CI, 95% confidence interval; LS, least-square; SD, standard deviation.

[a] Difference is 15 µg/kg Voxzogo minus placebo.

[b] Two-sided p-value.

[c] Two patients in the Voxzogo group discontinued from the study before Week 52. The values for these 2 patients were imputed for this analysis.

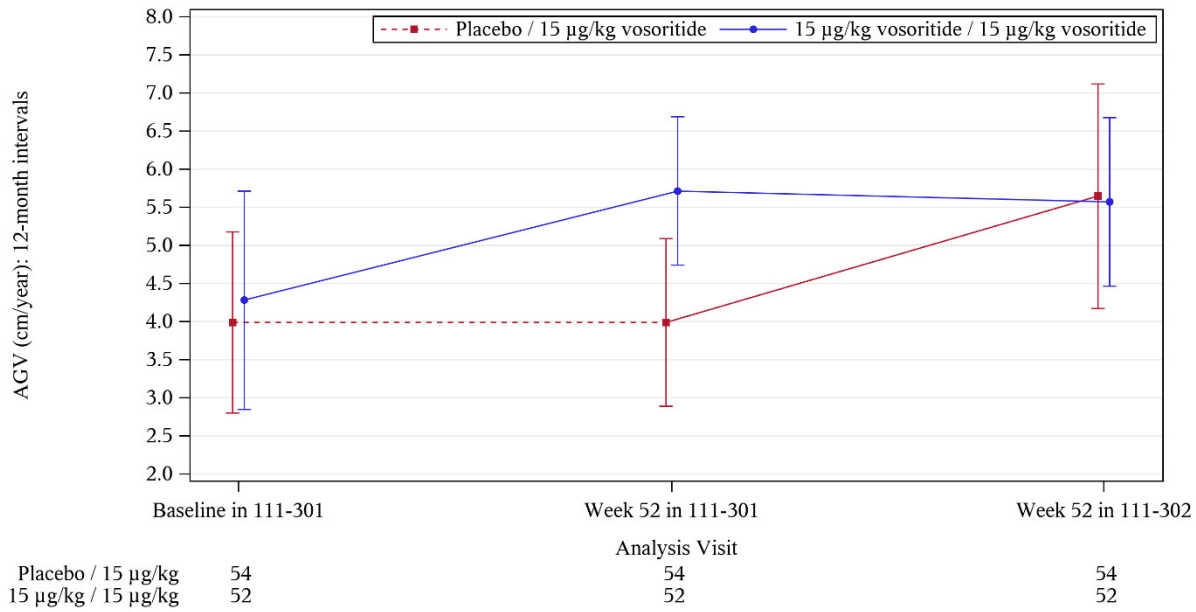
LS mean estimated from the ANCOVA (analysis of covariance) model adjusted for baseline differences between the two arms, analysis of covariance.

The benefit of improvement in AGV in favour of Voxzogo was consistent across all predefined subgroups analysed including sex, age group, Tanner stage, baseline height Z-score, and baseline AGV. In the subgroup of males Tanner stage > I, the point estimate of treatment effect was in favour of vosoritide however there were only 8 subjects in this subgroup (3 and 5 subjects in vosoritide and placebo arms, respectively).

The observed increase in growth occurred proportionally in both the spine and the lower limbs. There was no difference in bone mineral density after treatment with Voxzogo compared to placebo. During treatment with this medicinal product, the mean increase in bone age was comparable to the mean increase in chronological age, indicating no acceleration of bone maturation.

Figure 1 shows the effect of Voxzogo over the two-year period in the Voxzogo treatment group, as well as the effect in the placebo control group after receiving daily subcutaneous injections of Voxzogo for 52 weeks in the open label extension study. Improvements in AGV were maintained during continued Voxzogo therapy, with no evidence of tachyphylaxis.

Figure 1: Mean (±SD) 12-Month Interval AGV Over Time



The figure includes all subjects enrolled in the pivotal trial who had a height assessment at week 52 in the extension study. Solid lines represent treatment with vosoritide 15 ug/kg; dashed lines represent placebo. Baseline is defined as the last assessment before the first dose of active study drug (i.e. vosoritide) or Placebo in 111-301.
12-Month AGV at post-baseline visits is derived over the previous 12 months. For example, 12-Month Interval AGV at Week 52 111-302 = [(Height at Week 52 111-302 Visit- Height at Week 52 111-301 Visit)/(Date of Week 52 111-302 Visit - Date of Week 52 111-301 Visit)] x 365.25.

Open-label extension study
In the long-term extension study (ACH study 111-205), 10 patients were treated with Voxzogo 15 µg/kg/day dose continuously for up to 5 years. The mean (SD) improvement in AGV compared to baseline at 60 months was 1.34 (1.31) cm/year.

The gain in height after 5 years of treatment with 15 µg/kg/day of Voxzogo was compared with an age and sex matched historical control. The 5-year cross-sectional comparative analysis adjusted for baseline height differences, demonstrated, there was a statistically significant mean (95% CI) difference in height in favour of Voxzogo (9.08 [5.77, 12.38] cm; p=0.0002) compared with untreated patients with achondroplasia.

Paediatric population < 5 years

Paediatric patients aged ≥ 2 to < 5 years
Use in the age group 2 to < 5 is supported by evidence from studies in children aged 5 to 18 and children aged less than 5 years of age. The safety and efficacy profiles were similar between children aged 5 years and above and children aged 2 to < 5 years. An ongoing study (ACH study 111-206) is assessing the safety and efficacy of vosoritide in patients aged between 0 to < 5 years and has enrolled 62 patients by a 30 June 2020 data cut-off. Interim data from ACH study 111-206 showed a positive effect on growth in 4 patients aged ≥ 2 to < 5 years treated with vosoritide 15 µg/kg/day for 2 years. Voxzogo is not indicated in children aged less than 2 years. Currently available data are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

5.2 Pharmacokinetic properties

Vosoritide is a modified recombinant human CNP. The 39 amino acid peptide analogue includes the 37 C terminal amino acids of the human CNP53 sequence plus the addition of 2 amino acids (Pro Gly) to convey resistant to neutral endopeptidase (NEP) degradation, resulting in prolonged half-life in comparison to endogenous CNP.

The pharmacokinetics of vosoritide were evaluated in a total of 58 patients aged 5 to 18 years with achondroplasia who received subcutaneous injections of vosoritide 15 µg/kg once daily for 52 weeks. The pharmacokinetics of vosoritide in 18 patients aged 2 to < 5 years old were comparable with older children.

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), 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.

Biotransformation

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

Elimination

The mean (± SD) apparent clearance after 52 weeks of treatment was 79.4 (53.0) mL/min/kg. The mean (± SD) half-life was 27.9 (9.9) minutes.

The inter-subject variability (coefficient of variation) in apparent clearance was 33.6 %.

Linearity/non-linearity

The increase in plasma exposure (AUC and C_{max}) with dose was greater than dose proportional across the dose range of 2.5 (0.17 times the recommended dose) to 30.0 µg/kg/day (twice the approved dose).

Special populations

No clinically significant differences in the vosoritide pharmacokinetics was observed based on age (0.9 to 16 years), sex, race or ethnicity.

Body weight
Body weight is the only significant covariate for vosoritide clearance or 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). The proposed posology (see section 4.2) takes account of this deviation and recommends the use of doses above (in patients between 10 and 16 kg body weight), or below (in those above a body weight of 44 kg) the 15 µg/kg "standard dose" in order to enable a similar level of exposure across all weight-ranges.

Patients with renal and hepatic impairment
The safety and efficacy of vosoritide in patients with renal or hepatic impairment has not been evaluated. Based on the elimination mechanism, renal or hepatic impairment is not expected to alter the pharmacokinetics of vosoritide.

Drug interaction studies

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, KATE2-K, BCRP, P-gp, and BSEP is low at clinically relevant concentrations.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies but seen in animals at exposure levels similar to clinical exposure levels, and with possible relevance to clinical use.

Transient decreases in blood pressure and increases in heart rate were observed in healthy monkeys across multiple studies in doses of 28 to 300 µg/kg in a dose-related manner. Peak effects were typically observed within the first hour post dose and were generally asymptomatic. In some monkeys receiving higher doses of vosoritide, brief bouts of sternal/lateral recumbency or hypoactivity, were observed. These effects could be related to decreased blood pressure.

Adverse effects on body posture, bone shape, mobility, and bone strength were observed in normal animals in repeat-dose toxicity studies in rats and monkeys. In monkeys, the NOAEL for vosoritide is

25 µg/kg (mean C_{max} value of 1 170 pg/mL; approximately equivalent to the recommended human dose in a 20 kg human) when administered daily via subcutaneous injection for 44 weeks.

Carcinogenicity / mutagenicity

Carcinogenicity and genotoxicity studies have not been performed with vosoritide. Based on the mechanism of action, vosoritide is not expected to be tumorigenic.

Impairment of fertility

In a fertility and reproductive study in male and female rats at dose levels up to 540 µg/kg/day, vosoritide had no effect on mating performance, fertility, or litter characteristics.

Reproductive and developmental toxicity

Vosoritide was not associated with effects on reproductive performance, in utero or developmental parameters measured in rats and rabbits to investigate fertility, or embryo-foetal development in pre- and post-natal development studies.

Vosoritide was detected in the breast milk in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Trehalose dihydrate
D-Mannitol
Sodium citrate Dihdrate
L-Methionine
Citric acid Monohydrate
Polysorbate 80

Solvent

Sterile water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

The expiry date of the product is indicated on the packaging materials.

Reconstituted solution

Chemical and physical stability has been demonstrated for 3 hours at 25°C.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the solution should be used immediately.

If not used immediately, Voxzogo must be administered within 3 hours of reconstitution (see section 4.2).

6.4 Special precautions for storage

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

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

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.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vosoritide 0.4 mg powder and solvent for solution for injection

Powder
2 mL vial (glass) with rubber stopper (bromobutyl) and white flip cap.

Solvent
Pre-filled syringe (glass) with plunger (bromobutyl) and tip cap with a luer lock and tamper evident seal containing 0.5 mL of water for injections.

Vosoritide 0.56 mg powder and solvent for solution for injection

Powder
2 mL vial (glass) with rubber stopper (bromobutyl) and magenta flip cap.

Solvent
Pre-filled syringe (glass) with plungers (bromobutyl) and tip cap with a luer lock and tamper evident seal containing 0.7 mL of water for injections.

Vosoritide 1.2 mg powder and solvent for solution for injection

Powder
2 mL vial (glass) with rubber stopper (bromobutyl) and grey flip cap.

Solvent
Pre-filled syringe (glass) with plungers (bromobutyl) and tip cap with a luer lock and tamper evident seal containing 0.6 mL of water for injections

Each carton contains:
- 10 vials of Voxzogo
- 10 pre-filled syringes of water for injections
- 10 individual single use needles (23 gauge, for reconstitution)
- 10 individual single use syringes (30 gauge, for administration)

6.6 Special precautions for disposal and other handling

Preparation of Voxzogo for subcutaneous injection

- The correct Voxzogo strength and correct pre-filled syringe of solvent (reconstitution volume) should be confirmed based on the patient's body weight (see Table 1).
- All necessary ancillary supplies must be in place before starting.
  - Alcohol pads
  - Gauze or bandages
  - Sharps container
- The Voxzogo vial and solvent in a pre-filled syringe (water for injections) should be removed from the refrigerator and allowed to reach room temperature before reconstituting Voxzogo.
- The solvent needle must be attached to the solvent in the pre-filled syringe (water for injections).
- The entire solvent volume must be injected into the vial.
- The solvent in the vial should be gently swirled until the white powder is completely dissolved. The vial should not be shaken.
- The dosing volume of the reconstituted solution should be slowly withdrawn from the single use vial into a syringe.
- Once reconstituted this medicinal product 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 up to 25 °C for a maximum of 3 hours. The medicinal product contains no preservative.
- For administration, the required dose volume must be extracted from the vial using the supplied administration syringe (see Table 1).
- Each vial and pre-filled syringe are for single use only.
- Only the administration syringe provided should be used .

Disposal

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

All needles and syringes should be disposed of in a sharps disposal container.

7. MANUFACTURER

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork, P43 R298
Ireland

8. LICENCE HOLDER:

Medison Pharma Ltd. POB 7090 Petach Tikva

9. REGISTRATION NUMBER

Voxzogo 0.4 mg -175-72-37698
Voxzogo 0.56 mg -175-73-37699
Voxzogo 1.2 mg-175-74-37700

Voxzogo-SPC-03/24-V1

Approved in 02/2024

תאריך עדכון עלון	פרקים שהתעדכנו	אסמכתא לעדכון	הערות
11/2023	**NA**	עלון EMA SPC 26/08/2021	תכשיר חדש. עלון מוגש לבדיקה במשרד הבריאות