swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Voxzogo

International non-proprietary name:	vosoritide
Pharmaceutical form:	powder and solvent for solution for injection
Dosage strength(s):	0.4 mg / 0.56 mg / 1.2 mg
Route(s) of administration:	subcutaneous use
Marketing authorisation holder:	DRAC AG
Marketing authorisation no.:	69569
Decision and decision date:	approved on 30 January 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations 3
2 Background information on the procedure 5
2.1 Applicant's request(s) 5
2.2 Indication and dosage 5
2.2.1 Requested indication 5
2.2.2 Approved indication 5
2.2.3 Requested dosage 5
2.2.4 Approved dosage 6
2.3 Regulatory history (milestones) 6
3 Medical context 7
4 Quality aspects 7
4.1 Drug substance 7
4.2 Drug product 8
4.3 Quality conclusions 9
5 Nonclinical aspects 10
5.1 Nonclinical conclusions 10
6 Clinical aspects 11
7 Risk management plan summary 12
8 Appendix 13

1 Terms, Definitions, Abbreviations

ACH	Achondroplasia
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BMN 111	Vosoritide
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DP	Drug product
EMA	European Medicines Agency
ERA	Environmental risk assessment
ERK	Extracellular signal-regulated kinase)
FDA	Food and Drug Administration (USA)
FGFR3	Fibroblast growth-factor receptor 3
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
MAPK-ERK	Mitogen-activated protein kinase - extracellular signal-regulated kinase
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
NPR B	Natriuretic peptide receptor-B
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
sWFI	Sterile water for injections
SwissPAR	Swiss Public Assessment Report
TAF	Transcription factor 12 (fragment)
TEAE	Treatment-emergent adverse event

TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for vosoritide in the above-mentioned medicinal product.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 30 November 2023.

2.2 Indication and dosage

2.2.1 Requested indication

Voxzogo is indicated for the treatment of achondroplasia in patients 4 months of age and older whose epiphyses are not closed.
The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

2.2.2 Approved indication

Voxzogo is indicated for the treatment of achondroplasia in patients 4 months of age and older whose epiphyses are not closed.
The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Voxzogo is administered as a daily subcutaneous injection. The recommended dose depends on the patient's body weight and is approximately between 15 and 30 µg/kg, with the smallest children receiving the higher dose. See Table 1:

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 (U)		
4	15 U		
5	20 U		
6-7	25 U		
8 - 11	30 U		
12 - 16		35 U	
17 - 21		40 U	

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
22 - 32		50 U	
33 - 43			25 U
44 - 59			30 U
60 - 89			35 U
≥ 90			40 U

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	29 April 2024
Formal control completed	2 May 2024
List of Questions (LoQ)	3 July 2024
Response to LoQ	5 September 2024
Preliminary decision	25 October 2024
Response to preliminary decision	23 December 2024
Labelling corrections and/or other aspects	20 January 2025
Response to labelling corrections and/or other aspects	24 January 2025
Final decision	30 January 2025
Decision	approval

3 Medical context

Achondroplasia (ACH) is an inherited disease caused by a mutation (change) in a gene called fibroblast growth-factor receptor 3 (*FGFR3*). The mutation affects growth of almost all bones in the body including the skull, spine, arms and legs, resulting in very short stature with a characteristic appearance.

Achondroplasia is a rare disease, but still the most common form of bone dysplasia.

The extremely short stature impacts daily life in multiple ways. Medical complications can include recurrent otitis media (narrow ear canal), sleep apnoea, obesity, hypertension. Severe complications are spinal stenosis and cervicomedullary compression (foramen magnum narrowing). The disease is also associated with an increased mortality rate, particularly in children younger than 5 years, due to the latter two comorbidities´ neurological complications. In that age group the risk of sudden death is increased 50-fold, and overall life expectancy is reduced by about 10 years compared to the general population, according to the Applicant and the literature.

No specific/causative treatment for ACH has been authorised so far in Switzerland. Treatment is limited to supportive measures for the lack of height. Limb-lengthening interventions are controversial and not widely considered anymore.

4 Quality aspects

4.1 Drug substance

Vosoritide is a 39-amino acid peptide. The peptide is an analogue of C-type natriuretic peptide (NCBI reference: NP_077720.1) containing two additional amino acids (proline (P) and glycine (G)) on the amino terminus. Vosoritide has a molecular weight of 4100 daltons. Two cysteine residues (Cys23 and Cys39) form a disulfide bond, creating a cyclic peptide. The peptide is not glycosylated.

Highly conserved residues in the ring of vosoritide formed by the disulfide bond (amino acids 23-39) bind to the extracellular domain of natriuretic peptide receptor-B (NPR B), which down-regulates aberrant fibroblast growth factor receptor 3 (FGFR3) signalling in chondrocytes and inhibits the MAPK-ERK pathway to promote bone growth.

Vosoritide (BMN 111) is manufactured by expression of TAF-BMN 111 (transcription factor 12 (fragment)) fusion protein in recombinant *E. coli* cells. The vosoritide drug substance manufacturing process consists of fermentation and inclusion body recovery, chemical cleavage of TAF-BMN 111 to yield the BMN 111 peptide, and purification and formulation, resulting in vosoritide formulated bulk drug substance.

The cell culture and purification processes for vosoritide drug substance are both validated with several consecutive batches, and the data demonstrated a consistent production and an efficient removal of impurities.

Several minor changes were implemented during development of the manufacturing process for the drug substance, including changes to manufacturing site, production scale and formulation composition. However, comparability studies, including batch release data, extended characterisation data, and stress stability data, demonstrated comparability between the different processes.

The characterisation of the physicochemical and biological properties of the vosoritide drug substance and its impurities were performed using state-of-the-art methods.

The specifications for release and stability of the drug substance include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on published limits, stability data, clinical experience, batch analysis data, stability data, and are in conformance with current compendial or regulatory guidelines.

Batch analysis data for development, clinical, and process validation batches of vosoritide drug substance were provided. All specific analytical methods are described and are validated.

No significant changes were observed during storage of vosoritide drug substance under the proposed storage conditions.

4.2 Drug product

Vosoritide drug product (DP) is a single-use, sterile, lyophilised powder for reconstitution with sterile water for injection (sWFI) and is intended for daily administration by subcutaneous injection. The vosoritide lyophilised powder is white to light yellow in colour and is preservative-free and not intended for multi-use. Vosoritide DP is supplied in three strengths: 0.4 mg/vial, 0.56 mg/vial, and 1.2 mg/vial. Each vosoritide DP strength is differentiated by the cap colour of the vial. The reconstituted solution contains 0.8 mg/mL or 2 mg/mL vosoritide. The diluent for vosoritide is sWFI provided in a ready-to-use prefilled syringe containing the appropriate volume required to reconstitute each vosoritide DP strength. A diluent needle and an administration syringe are co-packaged for daily administration.

All excipients selected (citric acid and citrate salt for buffering capacity, trehalose and mannitol for isotonicity and as bulking agent, methionine as a stabiliser and polysorbate 80 to minimise adsorptive losses) are typical for biopharmaceutical parenteral dosage forms for the stabilisation of proteins. Compatibility of vosoritide with the formulation excipients has been demonstrated on the basis of stability data of both the lyophilisate and compatibility data showing quality of product upon reconstitution. All excipients are of compendial grade, and none are of animal or human origin.

Several drug product dosage strengths, formulations, presentations, and filling facilities were used during clinical development. However, comparability studies, which included batch release data and stability data, demonstrated comparability of the relevant quality attributes between the different processes.

Compatibility studies were conducted to establish the in-use stability of diluted drug product with the intended materials and conditions of use.

Vosoritide drug product (DP) manufacturing consists of conventional steps commonly used for this type of dosage form: Compounding, sterile filtration, aseptic filling, and lyophilisation. The drug product manufacturing process is validated with several consecutive batches. The data demonstrated a consistent production.

The specifications for release and stability of the drug product include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, particles, bacterial endotoxins, and sterility. The drug product specifications comply with current compendial or regulatory guidelines.

Batch analysis data for several batches of the drug product, including development batches, clinical batches, and process validation batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release. All specific analytical methods are validated.

Vosoritide DP is supplied in a container closure system consisting of a 2 mL (2R) Type I untreated borosilicate, clear glass vial closed with fluorocarbon-coated bromobutyl rubber stopper and crimp sealed with flip-off aluminium cap. Lyophilised vosoritide drug product vial is co-packaged with a pre-filled diluent syringe containing sterile Water for Injections (sWFI) and two ancillary (device) administration components, namely a diluent transfer needle for drug product reconstitution and an administration syringe.

The vials are stored at 2°C to 8°C. The stability data support a shelf life of 36 months.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Regarding the marketing authorisation application for Voxzogo, the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the European Medicines Agency (EMA) assessment reports provided by the applicant: EMEA/H/C/005475/0000 dated 24 June 2021 and EMEA/H/C/005475/II/0006) dated 14 September 2023.

5.1 Nonclinical conclusions

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of vosoritide in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. The main adverse effect of vosoritide in mice, rats, and monkeys was exaggerated endochondral bone growth, causing joint issues, arthritis, and motor dysfunction. However, these effects were not evident in clinical studies. Consequently, despite the low safety margins their relevance to humans remains questionable.

All nonclinical data that are relevant for safety are adequately mentioned in the Information for healthcare professionals and in the RMP.

There is no safety concern regarding impurities and excipients.

Based on the ERA, the risk to the environment is low.

6 Clinical aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by EMA and FDA. The available assessment reports from these authorities were used as a basis for the clinical and clinical pharmacology evaluation.

For further details, see the Information for healthcare professional in the appendix of this report.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Voxzogo was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Voxzogo®, powder and solvent for solution for injection

Composition

Active substances

Vosoritide (produced from genetically modified E. coli cells)

Excipients

Powder: Citric acid monohydrate (E 330), Sodium citrate dihydrate (E 331), Trehalose dihydrate, Mannitol (E 421), Methionine, Polysorbate 80 (E 433).

Solvent: Water for injections

Voxzogo 0.4 mg contains max. 0.02 mg sodium per vial

Voxzogo 0.56 mg contains max. 0.04 mg sodium per vial

Voxzogo 1.2 mg contains max. 0.03 mg sodium per vial

Pharmaceutical form and active substance quantity per unit

Powder and solvent for solution for injection.

The powder is white to yellow and the solvent is clear and colourless.

Voxzogo 0.4 mg: Each vial of powder contains 0.4 mg of vosoritide.

Concentration after reconstitution: 0.8 mg/mL.

Voxzogo 0.56 mg: Each vial of powder contains 0.56 mg of vosoritide.

Concentration after reconstitution: 0.8 mg/mL.

Voxzogo 1.2 mg: Each vial of powder contains 1.2 mg of vosoritide.

Concentration after reconstitution: 2 mg/mL.

Indications/Uses

Voxzogo is indicated for the treatment of achondroplasia in patients 4 months of age and older whose epiphyseal joints are not closed.

The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

Dosage/Administration

Treatment with vosoritide should be initiated and directed by a physician appropriately qualified in the diagnostic and therapy of achondroplasia.

Mode of administration

Voxzogo is for subcutaneous use only. This medicinal product must be administered within 3 hours of reconstitution (for reconstitution see “Other information”, “Instructions for handling”).

Patients should have had enough to drink at the time of injection. It is recommended that the patient consumes a sufficient amount of fluid (e.g. water, milk, juice, etc.) and a small snack approximately 30 minutes before the injection. This reduces the likelihood of a symptomatic decrease in blood pressure (see “Warnings and precautions”, “Effects on blood pressure”).

Voxzogo should be injected centrally on the front of the thighs, in the lower part of the abdomen (with the exception of an area of 5 cm directly around the navel), in the upper part of the buttocks or in the back of the upper arms. Voxzogo must not be injected into areas that are reddened, swollen or hardened.

The injection site should be changed daily.

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

Before the patients or their caregiver carry out the Voxzogo injections themselves, a health care professional must have:

- instructed them in the correct preparation of the injection solution and the subcutaneous injection technique,
- trained them to recognise possible signs of a decrease in blood pressure (e.g. dizziness, tiredness and/or nausea),
- informed them what to do in the event of symptomatic hypotension.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Dosage

Voxzogo is given as a daily subcutaneous (s.c.) injection. The dosage is based on a population kinetic analysis (see “Pharmacokinetics”). The recommended dose depends on the patient's body weight (BW) and is approximately between 15 – 30 µg/kg once daily, whereby the children with the lowest BW receive a higher dose per kg of BW (see Table 1).

The syringes for subcutaneous injection contained in the pack are scaled in units (U). 10 units correspond to 0.10 ml of the reconstituted solution.

Table 1: Single dose volume by body weight in Units (U) volumes

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 (U)		
4	15 U		
5	20 U		
6 – 7	25 U		
8 – 11	30 U		
12 – 16		35 U	
17 – 21		40 U	
22 – 32		50 U	
33 – 43			25 U
44 – 59			30 U
60 – 89			35 U
≥ 90			40 U

Control assessments

Patients should be assessed regularly every 3 – 6 months to monitor body weight, growth and physical development. Dosage should be adjusted to the patient's current body weight according to Table 1.

Duration of treatment

Treatment should be stopped as soon as there is no further growth potential, indicated by a growth velocity of < 1.5 cm/year and closure of epiphyseal grooves.

Missed application

If an injection was missed, it can be made up within 12 hours. If more than 12 hours have passed since the originally planned time of administration, the missed dose should NOT be administered again. In this case, the dose should be skipped and the next scheduled dose should be continued on the following day.

Special dosage instructions

Children < 4 months

Voxzogo is not authorised for children aged <4 months. Only limited data are available for this age group, meaning that no benefit-risk assessment and in particular no dosage recommendations are possible.

Patients with hepatic or renal disorders

Safety and efficacy of vosoritide in patients with renal or hepatic impairment have not been evaluated.

Contraindications

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

Warnings and precautions

Blood pressure effects

Transient decreases in blood pressure were observed with vosoritide in clinical trials. The majority of the events were asymptomatic and self-limiting (see undesirable effects).

To reduce the risk of a potential decrease in blood pressure and associated symptoms (such as dizziness, fatigue and/or nausea), the patient should be well hydrated at the time of injection (see “Dosage/Administration”).

Patients with clinically relevant cardiovascular disease and patients undergoing antihypertensive therapy were excluded from participation in the studies.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say, essentially “sodium-free”.

Interactions

In vitro cytochrome P450 (CYP450) induction and inhibition studies show that vosoritide does not inhibit CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 and does not induce CYP 1A2, 2B6 and 3A4/5 at clinically relevant concentrations. Further *in vitro* studies also indicate that the potential for interactions 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. Overall, the results lead to the conclusion that interactions of vosoritide with CYP450 enzymes or transporters are unlikely. Other interaction studies have not been performed. Because vosoritide is a recombinant human protein, however, interactions are unlikely.

Pregnancy, lactation

Pregnancy

To date, there are no or limited amount of data from the use of vosoritide in pregnant women. Animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity (see "Preclinical Data"). As a precautionary measure, it is preferable to avoid the use of vosoritide during pregnancy.

Lactation

In animal studies, vosoritide passed into the milk (see "Preclinical data"). Corresponding human data are not available. A risk to newborns/infants cannot be excluded. Vosoritide should not be used during breast-feeding.

Fertility

A possible influence of vosoritide on fertility in humans has not been studied. Animal studies have not shown any impairment of male or female fertility (see "Preclinical data").

Effects on ability to drive and use machines

Vosoritide has moderate influence on driving of vehicles and the ability to operate machines. Vosoritide may cause transient decreases in blood pressure that are usually mild. However, dizziness, presyncope and syncope, as well as other symptoms of decreased blood pressure have been reported as undesirable effect with the use of vosoritide. The patient's individual reaction to treatment should be considered. If appropriate, advised the patient not to drive a vehicle or use machines for at least 60 minutes after injection.

Undesirable effects

Summary of the safety profile

The most common undesirable effects associated with the use of vosoritide were injection site reactions (85%), vomiting (27%), and decreased blood pressure (13%). Reactions at the injection site were erythema, swelling, pruritus, urticaria, discolouration, induration, bleeding/haematoma and/or pain.

The following table lists the undesirable effects by MedDRA system organ class and frequency that have been observed in patients treated with vosoritide.

Frequencies are defined as very common (≥ 1/10) common (≥ 1/100 to < 1/10) uncommon (≥ 1/1000 to < 1/100) rare (≥ 1/10 000 to < 1/1000) and very rare (< 1/10 000). Within each frequency category, undesirable effects are presented in order of decreasing seriousness.

Table 2: Undesirable effects during treatment with vosoritide

System organ class	Very common	Common	Uncommon
Nervous system disorders		Syncope, Presyncope, Dizziness	
Vascular disorders	Hypotension (13%) (see "Description of specific undesirable effects" and "Warnings and precautions")		
Gastrointestinal disorders	Vomiting (27%)	Nausea	
Skin and subcutaneous tissue disorders			Hypertrichosis
Musculoskeletal system disorders	Increased alkaline phosphatase (17%)		
General disorders and administration site conditions	Injection site reactions (85%) (see "Description of specific undesirable effects")	Fatigue	

Description of specific undesirable effects

Hypotension (symptomatic and asymptomatic cases)

In the phase III study (111–301) in patients aged 5 years and older, 13% of patients treated with vosoritide compared to 5% under placebo over a 52-week treatment period reported events of decreases in blood pressure which were transient and resolved without intervention. The median time to onset from injection was 31 (18 – 120) minutes with resolution within 31 (5 – 90) minutes. The reported events were identified predominantly during periods of frequent vital signs monitoring at clinical visits after dosing. In 2% of patients a symptomatic episode with dizziness and vomiting was documented.

In study 111-206 in patients initiating treatment aged < 5 years, events of decrease in blood pressure were reported at a similar frequency (5% versus 6%) and severity in patients receiving vosoritide and placebo respectively. All events were transient, resolved without intervention and were not treatment limiting.

Injection site reactions

In patients aged ≥ 5 years (study 111-301), injection site reactions were reported in 85% patients receiving vosoritide compared to 82% patients on placebo over a 52-week period; the median number of injection site reactions events was 76 versus 7.5, respectively. The most common injection site reactions (occurring in at least 10% of patients treated with vosoritide) were injection site reaction (73%), erythema (68%), swelling (38%), and urticaria (13%). All injection site reactions were mild in severity, with the exception of 2 patients in whom moderate injection site urticaria and injection site vesicles were reported.

In children aged < 5 years (Study 111-206), injections site reactions were reported in 86% of patients treated with vosoritide compared to 53% under placebo over a 52-week period. A median of 271 events were reported in the vosoritide group compared to 44 events in placebo group in this age group (< 5 years). All injections site reactions were mild in severity, transient, and not treatment-limiting.

Immunogenicity

Of 131 patients ≥5 years who were treated with vosoritide 15 µg/kg/day, findings of anti-drug antibodies (ADA) are available over a period of up to 240 weeks. ADAs were identified in 35% of these patients at day 85 at the earliest.

In the 43 analysable patients <5 years of age treated with vosoritide, the incidence of ADAs was 19%; all patients treated with placebo were ADA-negative. ADAs were detected in this age group at week 26 at the earliest.

Neutralising antibodies (NAb) were not detected. The presence of ADAs had no effect on the pharmacokinetics, efficacy or safety (including Injection site reactions) of vosoritide.

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any new or serious suspected adverse effects online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Vosoritide doses of up to 30 µg/kg/day were investigated in clinical studies. Two patients received up to 45 µg/kg/day for up to 5 weeks.

No undesirable effects beyond those described in the “Undesirable effects” section were observed.

A specific antidote does not exist. If a patient has used a higher dose than intended, he/she should consult his/her doctor.

Properties/Effects

ATC code

M05BX07

Mechanism of action

Vosoritide is a modified recombinant human natriuretic peptide of type C (CNP).
The 39 amino acid peptide analogue contains the 37 C-terminal amino acids of the human CNP53 sequence plus the addition of 2 amino acids (Pro-Gly) for resistance to degradation by neutral endopeptidase (NEP), resulting in a prolonged half-life compared to endogenous 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, similar to CNP, acts as a positive regulator of endochondral bone growth by promoting chondrocyte proliferation and differentiation.

Pharmacodynamics

An exposure-dependent (AUC and C_{max}) increase 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. Increase in the urinary cGMP concentrations occurred from pre-dose baseline within the first four hours post-dose. Mean serum CXM concentration increased with daily dosing over baseline by day 29. 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

Children and adolescents aged 5 years and older

The efficacy of vosoritide in achondroplasia was investigated in a 1:1 randomised, double-blind, placebo-controlled study with a duration of 52 weeks in n=121 paediatric patients with confirmed FGFR3 mutation (study 111-301). Children and adolescents aged 5 – < 18 years were included. Patients with relevant cardiac or vascular diseases and those undergoing antihypertensive drug therapy were excluded from participation in the study. Patients who had undergone leg lengthening surgery in the previous 18 months or were scheduled to undergo such surgery during the study were also excluded.

Prior to randomisation, morphometric and growth-related data were collected on all patients in an observational study over a period of at least 6 months.
Patients received either vosoritide 15 µg/kg once daily s.c. or placebo.
The primary endpoint was the change in annualised growth velocity (AGV) at week 52 compared to baseline. The main secondary endpoint was the change in the Z-score for height.
The included patients had an average age of approximately 9 years (range 5.1 – 14.9 years). 45% of the patients were 5 – < 8 years old, 34% – < 11 years old and 21% 11 – < 15 years old. 53% of the patients were boys, 47% girls. 71% of the patients were white, a further 19% Asian. Almost 80% of the patients had Tanner stage I, the remaining patients stage II. The average body weight was approx. 24 kg, the average BMI 22.4 kg/m^2.
The findings for the primary endpoint showed a significant superiority of vosoritide over placebo. Under vosoritide, the least square (LS) mean change from baseline for AGV was 1.71 cm/year, under placebo it was practically unchanged at 0.13 cm/year which represented an LS mean difference of 1.57 cm/year ($p < 0.0001$). The findings for the height Z-score were consistent with this, with a LS mean change of 0.27 with vosoritide versus -0.01 with placebo (LS mean difference of 0.28 ($p < 0.0001$)). The increase in growth was proportional in both the spine and lower extremities. The increase in bone age corresponded to the increase in chronological age, i.e., there was no evidence of accelerated bone maturation.
The efficacy of vosoritide was independent of age, gender, Tanner stage and baseline values for AGV and Z-score.
There was no difference in bone mineral density between the patients treated with vosoritide and the placebo group.
Following the 12-month double-blind study, patients were able to participate in an open-label extension until they reached near final adult height. So far, data from this study is available for a treatment duration of up to two years. During this period, the efficacy of vosoritide was maintained.
In addition, data from the extension of a phase II study are available for 10 patients (mean standard deviation) age at day 1 was 8.54 (1.54) years) over a treatment period of up to 5 years. After this period, the average increase in AGV (standard deviation) compared to baseline was 1.34 (1.31) cm/year.
The absolute gain in height after 5 years was compared with that of a historical control with a comparable age and sex distribution, corrected in each case for baseline size. This analysis showed a difference in size of 9.08 cm (95% CI 5.77; 12.38 cm) in favour of the patients treated with vosoritide ($p=0.0002$).

Children aged 4 months to <5 years

The efficacy of vosoritide in achondroplasia was also investigated in a randomised, double-blind, placebo-controlled study in patients aged 4.4 months to <5 years (study 111-206). Of the total n=75

patients in this age group, 64 were randomised 1:1 to vosoritide or placebo; the remaining 11 patients were treated openly with vosoritide.
Patients ≥2 years of age received a dose of 15 µg/kg/day. Patients <2 years of age, were treated with 30 µg/kg/day until the age of two, after which the dose was reduced to 15 µg/kg/day.
The treatment duration in this study was 52 weeks. The primary endpoint was defined as the change in the Z-score for height compared to baseline. The treatment difference between vosoritide and placebo after 52 weeks was 0.25 SDS (95% CI -0.02; 0.53) in favour of vosoritide.
Following the 12-month double-blind study, patients were able to participate in an open-label extension until they reached near final adult height. The changes in height Z-score were compared with those of a historical control group of untreated patients with achondroplasia with a comparable age and gender distribution. In the age group ≥ 24 to < 60 months, after 3 years of vosoritide, the Z-score was 1.22 SDS (95% CI 0.78; 1.66) higher in the treated patients than in the untreated controls. After 2 years of vosoritide in the age group from > 6 to < 24 months, the advantage in the Z-score in the treated patients was 0.79 SDS (95% CI 0.29; 1.28).

Pharmacokinetics
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 exposure of vosoritide in 15 patients aged 2 to < 5 years old were comparable with older children. In 8 patients aged 6 months to < 2 years old, receiving 30 µg/kg once daily the exposure of vosoritide was 65% to 70% higher than the children >2 years old receiving 15 µg/kg once daily. In 9 patients < 6 months of age receiving 30 µg/kg once daily, the exposure of vosoritide was 57% to 105% higher than the children >2 years old receiving 15 µg/kg once daily.

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 5800 (± 3680) 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 2910 (± 1660) mL/kg.

Metabolism

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 C_{max} and AUC with dose was greater than dose proportional in the dose range of 2.5 to 30.0 µg/kg/day.

Kinetics in specific patient groups

Body weight

Body weight (BW) was the only significant covariate for vosoritide clearance and volume of distribution. Clearance and volume of distribution increased with increasing body weight in the investigated range (9 to 74.5 kg). (for the corresponding effects on the required dose, see “Dosage/Administration”).

Age, sex, race and ethnicity

No clinically relevant differences in the vosoritide pharmacokinetics was observed based on age (0.4 –15 years), sex, race or ethnicity.

Impaired renal or hepatic function

The pharmacokinetics 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.

Preclinical data

Safety pharmacology and repeat dose toxicity

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 ≥ 200 µg/kg vosoritide (corresponding to 8.8 times of the C_{max} in human plasma at the recommended human dose), 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 (approximately 1.7 times the human AUC at the recommended human dose)

Genotoxicity/Carcinogenicity
Genotoxicity and carcinogenicity studies have not been performed with vosoritide.

Reproductive toxicity
In a fertility study in male and female rats at dose levels up to 540 µg/kg/day (about 4.5 times the human AUC at the recommended dose), vosoritide had no effect on mating performance, fertility, or litter characteristics. Treatment of rats and rabbits with vosoritide during gestation had no effect on the pre-natal development of the offspring. Similarly, in rats, after vosoritide exposure of the dams during the embryofetal and lactation period, post-natal development of offspring was not affected.

Lactation
Vosoritide was detected in the breast milk in rats.

Toxicity tests with juvenile animals
The nonclinical safety of vosoritide was evaluated in single and repeat dose toxicity studies in juvenile Sprague-Dawley rats and cynomolgus monkeys, up to 26 weeks.
The NOAEL in juvenile monkeys treated for up to 26 weeks, which is considered the most relevant species due to similarities in anatomy, growth plate physiology, and developmental chronology, was 90 µg/kg, based on adverse skeletal effects seen at higher doses.
This represented a 2 – 3.4 x safety factor based on dose and a 1.5 x safety factor in exposure ($AUC_{0\text{-}t}$) compared to paediatric ACH patients. There were no vosoritide-related effects on other organ systems/soft tissue noted in any toxicity studies.

Other information
Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section “Instructions for handling”.

Shelf life
Do not use this medicine after the expiry date (“EXP”) stated on the pack.

Shelf-life of the 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 "Posology/Administration").

Special precautions for storage
Store in a refrigerator (2 – 8 °C).
Do not freeze.
Store in the original package in order to protect from light.
Keep out of the reach of children.
Voxzogo may be stored at a temperature of maximal 30 °C outside the refrigerator for a single period up to 90 days, but not beyond the expiry date. It must not be returned to refrigerator afterwards.
For storage conditions after reconstitution of the medicinal product, see above "Reconstituted solution".

Instructions for handling
Preparation of Voxzogo for subcutaneous injection

- The appropriate strength of Voxzogo must be determined based on the patient's body weight (see "Dosage/administration", 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 needle for the solvent 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 required 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 volume of the reconstituted solution must be extracted from the vial using the supplied administration syringe (see “Dosage/Administration” Table 1).
- Only the administration syringe provided should be used.
- Each vial and pre-filled syringe are for single use only. Unused solution must be disposed of.

Disposal

Any unused medicinal product, syringes and needles must be disposed of in accordance with local requirements.

Authorisation number

69569 (Swissmedic)

Packs

Vosoritide 0.4 mg: packs of 10 vials with powder (white flip-off cap), 10 prefilled syringes with 0.5 mL solvent, 10 needles (23 G, for reconstitution), 10 disposable syringes with needle (30 G, for administration). [A].
Vosoritide 0.56 mg: packs of 10 vials with powder (pink flip-off cap), 10 prefilled syringes with 0.7 mL solvent, 10 needles (23 G, for reconstitution), 10 disposable syringes with needle (30 G, for administration). [A].
Vosoritide 1.2 mg: packs of 10 vials with powder (grey flip-off cap), 10 prefilled syringes with 0.7 mL solvent, 10 needles (23 G, for reconstitution), 10 disposable syringes with needle (30 G, for administration). [A].

Marketing authorisation holder

DRAC AG, Murten

Manufacturer

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

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