Drug Monograph

Drug Name: **Voxzogo™ (vosoritide) vial**
Drug Class: **Endocrine and Metabolic Agents: C Type Natriuretic Peptide (CNP) Analog for Growth**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Voxzogo is available in 0.4 mg, 0.56 mg, or 1.2 mg single-dose vials.
Manufacturer:	Distributed by: BioMarin Pharmaceutical Inc., Novato, CA 94949.
Summary of Findings:	The approval of Voxzogo was based on one 52-week, multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of 121 participants and the open-label extension of the Phase 3 study. Patients treated with Voxzogo experienced an increase in annualized growth velocity (AGV) of 1.57 centimeters/year greater than placebo and published results show that the AGV benefit was observed by Week 26. The prescribing information states that the improvement in AGV in favor of Voxzogo was consistent across sex, age group, Tanner Stage, baseline height Z-score, and baseline AGV. The secondary endpoint of height standard deviation score (SDS) found a least squares (LS) mean change from baseline to Week 52 in height SDS was –0.02 in the placebo group and 0.26 in the Voxzogo group. The difference in LS mean change from baseline was 0.28 in favor of Voxzogo (95% CI: 0.17, 0.39; *P<0.0001*).
Status Recommendation:	☒ Clinical Edit ☐ Open Access ☐ PA Required ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ No PA Required ☐ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Achondroplasia (ACH) is a genetic disorder caused by a pathogenic variant in the *FGFR3* gene which results in the FGFR3 protein becoming overly active. When FGFR3 is overly active, it causes abnormal bone growth by inhibition of chondrocyte proliferation resulting in decreased endochondral bone growth. The *FGFR3* pathogenic variant is frequently spontaneously acquired (80% of patients) rather than inherited (20% of patients via autosomal dominant pattern). ACH occurs in 1 in 15,000 to 40,000 newborns worldwide making it the most common type of short-limbed dwarfism. ACH commonly presents as shortened limbs, macrocephaly (large head circumference), and short stature. It is not commonly associated with mental impairment or deficiencies, but it can cause several health complications such as apnea, obesity, lordosis, and recurrent ear infections. In more serious cases, spinal stenosis and hydrocephalus have been noted. The average height of an adult male with ACH is 131 centimeters (4 feet, 4 inches); for females the average height is 124 centimeters (4 feet, 1 inch). There are currently no published guidelines available for the treatment of ACH.

Dosage Form [3]

Voxzogo is available in 0.4 mg, 0.56 mg, or 1.2 mg single-dose vials.

Manufacturer [3]

Distributed by: BioMarin Pharmaceutical Inc., Novato, CA 94949.

Indication(s) [3]

Voxzogo is indicated to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses. This indication is approved under accelerated approval and continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Binding of Voxzogo to natriuretic peptide receptor-B (NPR-B) antagonizes fibroblast growth factor receptor 3 (*FGFR3)* downstream signaling by inhibiting the extracellular signal-regulated kinases 1 and 2 (ERK1/2) in the mitogen-activated protein kinase (MAPK) pathway at the level of rapidly accelerating fibrosarcoma serine/threonine protein kinase (RAF-1). Voxzogo, like C-type natriuretic peptide (CNP), acts as a positive regulator of endochondral bone growth as it promotes chondrocyte proliferation and differentiation.

Pharmacokinetics:

Absorption	T_{max}: 15 minutes
Metabolism	Catabolic pathways with degradation into small peptide fragments and amino acids
Excretion	N/A
Half-life	21.0-27.9 minutes

Clinical Trials Experience

STUDY DESIGN (NCT03197766 and NCT03424018)	Multi-center, randomized, double-blind, placebo-controlled, phase III, 52-week efficacy and safety study (N=121)
INCLUSION CRITERIA	• Diagnosis of ACH confirmed by genetic testing • Patient is ambulatory and able to stand without assistance
EXCLUSION CRITERIA	• Participants with limb-lengthening surgery in the prior 18 months or participants who planned to have limb-lengthening surgery during the study period • Treatment with growth hormone, insulin-like growth factor 1 or anabolic steroids within the past 6 months or ≥ 6 months of treatment at any time • Evidence of growth plate closure in proximal tibia or distal femur • Decreased growth velocity (AGV < 1.5 cm/year) over a 6-month period • Greater than 1 month treatment with oral corticosteroids in the previous 12 months • Fracture in long bone or spine within prior 6 months • Participants taking antihypertensive medications • Participants with any of the following diagnoses: hypothyroidism/ hyperthyroidism, insulin-dependent diabetes mellitus, inflammatory bowel disease, autonomic neuropathy, autoimmune inflammatory disease, chronic anemia, baseline systolic blood pressure < 70 mmHg or recurrent symptomatic hypotension, cardiac or vascular disease, severe untreated sleep apnea
TREATMENT REGIMEN	After a genetically confirmed diagnosis of ACH, 121 participants were randomized to either Voxzogo 15 mcg/kg SC once daily (N=60) or placebo (N=61).
RESULTS	Primary endpoint was the change from baseline in AGV at week 52. The secondary endpoint was the height standard deviation score (SDS).

	Placebo (N=61)	**Voxzogo (N=60)**
Primary Outcome		
AGV baseline mean (SD)	4.06 (1.20)	4.26 (1.53)
Change from baseline	-0.17	1.40
Difference in change of Voxzogo – Placebo (95% CI)	1.57 (1.22, 1.93) P <0.0001 for superiority	
Secondary Outcome		
LS mean change from baseline in height	-0.02	0.26
Difference in change of Voxzogo – Placebo (95% CI)	0.28 (0.17, 0.39) P <0.0001 for superiority	

- When treated with Voxzogo versus placebo, there was a change from baseline in AGV of 1.57 cm/year after 52 weeks of

	treatment. Improvement of AGV because of Voxzogo treatment was consistent across all subgroups including sex, age, Tanner stage*, baseline height Z-score±, and baseline AGV. • After 52 weeks of treatment, there were no significant improvements in the secondary outcomes of upper to lower body segment proportionality, quality of life, activities of daily living, and frequency and type of medical and surgical intervention. It is important to note that a duration longer than 52 weeks is typically required to detect changes in these types of outcomes. • Open label extension: after the 52 treatment weeks, 58 subjects in the Voxzogo arm enrolled into an open-label extension. In patients in the Voxzogo arm, AGV increased from 4.26 cm per year at baseline to 5.39 cm per year at 52 weeks and 5.52 cm per year at week 104. Although AGV did not continue to significantly increase after the 52-week period, the extension trial showed that the initial improvement in AGV from Voxzogo was maintained over time. ○ The open-label extension also switched patients from placebo group to Voxzogo and found an increase in AGV like that of the Voxzogo group in the initial 52-week trial.
SAFETY	Discussed in the Adverse Effects section below.

Abbreviations: AGV=annualized growth velocity; CI=confidence interval; LS=least square; SD=standard deviation; SC=subcutaneously

* Tanner Staging, also known as Sexual Maturity Rating (SMR), is an objective classification system that providers use to document and track the development and sequence of secondary sex characteristics of children during puberty.

± A z-score is the deviation of the value for an individual from the mean value of the reference population divided by the standard deviation for the reference population.

Contraindications (3,4)

- None

Warnings and Precautions (3,4)

- Risk of Low Blood Pressure: Transient decreases in blood pressure were observed in clinical studies of Voxzogo. To reduce the risk of a decrease in blood pressure and associated symptoms (dizziness, fatigue, and/or nausea), instruct patients to be well hydrated and have adequate food intake prior to administration of Voxzogo.

Adverse Effects (3,4)

Most common, ≥5%	Voxzogo (N=60) n (%)	Placebo (N=61) n (%)
Injection site erythema	45 (75)	42 (69)
Injection site swelling	37 (62)	22 (36)
Vomiting	16 (27)	12 (20)
Injection site urticaria	15 (25)	6 (10)
Arthralgia	9 (15)	4 (7)
Decreased blood pressure	8 (13)	3 (5)
Gastroenteritis[a]	8 (13)	5 (8)
Diarrhea	6 (10)	2 (3)
Dizziness[b]	6 (10)	2 (3)
Ear pain	6 (10)	3 (5)
Influenza	6 (10)	3 (5)

Fatigue[c]	5 (8)	2 (3)
Seasonal allergy	4 (7)	1 (2)
Dry skin	3 (5)	0

Abbreviations: N=total number of subjects in the treatment arm; n=number of subjects with the adverse reaction; %=percent of subjects with the adverse reaction.
* Includes adverse reactions occurring more frequently in the vosoritide arm and with a risk difference of ≥5% (i.e., difference of >2 subjects) between treatment arms
[a] Includes the preferred terms: gastroenteritis and gastroenteritis, viral
[b] Includes the preferred terms: dizziness, presyncope, procedural dizziness, vertigo
[c] Includes the preferred terms: fatigue, lethargy, malaise

Drug Interactions (3,4)

- None

Dosage and Administration (3,4)

- Ensure adequate food and fluid intake prior to administration.
- Recommended dosage based on patient's weight. Administer subcutaneously once daily.

Actual Body Weight	Vial Strength for Reconstitution*	Daily Dose	Injection Volume
10-11 kg	0.4 mg	0.24 mg	0.3 mL
12-16 kg	0.56 mg	0.28 mg	0.35 mL
17-21 kg	0.56 mg	0.32 mg	0.4 mL
22-32 kg	0.56 mg	0.4 mg	0.5 mL
33-43 kg	1.2 mg	0.5 mg	0.25 mL
44-59 kg	1.2 mg	0.6 mg	0.3 mL
60-89 kg	1.2 mg	0.7 mg	0.35 mL
≥ 90 kg	1.2 mg	0.8 mg	0.4 mL

- Reconstitute prior to use. The injection volume is based on both patient's weight and concentration of reconstituted Voxzogo.
- Monitor growth and adjust dosage according to body weight. Permanently discontinue upon closure of epiphyses.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
Vosoritide	Voxzogo™	BioMarin	Based on body weight and administered SC once daily	$899 per vial

** Wholesale Acquisition Cost

Conclusion

Voxzogo, a C type natriuretic peptide (CNP) analog, is the first FDA approved medication indicated to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses. The approval of Voxzogo was based on one 52-week, multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of 121 participants and the open-label extension of the Phase 3 study. Patients treated with Voxzogo experienced an increase in AGV greater than placebo and published results show that benefit was observed by Week 26. The secondary endpoint of height standard deviation score (SDS) found the difference in LS mean change from baseline was statistically significant in favor of Voxzogo. There is a warning in the Voxzogo label for transient decreases in blood pressure. The most

common adverse reactions are injection site erythema, swelling, and urticaria; vomiting; arthralgia; decreased blood pressure; gastroenteritis; diarrhea; dizziness; ear pain; and influenza.

Recommendation

The MO Healthnet Division recommends adding this drug to a Voxzogo clinical edit.

References

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Prepared by: Blake Shrout, PharmD and April Ash, PharmD

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