New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Voxzogo™ (vosoritide) [BioMarin Pharmaceutical Inc.]**
Dosage Formulations:	Subcutaneous injection: 0.4 mg, 0.56 mg, and 1.2 mg lyophilized powder in a single-dose vial for reconstitution
FDA Approval Date: **FDB File Date:**	FDA: November 19, 2021 FDB: November 28, 2021
Indication:	Voxzogo is indicated to increase linear growth in pediatric patients with achondroplasia (ACH) who are ≥ 5 years of age with open epiphyses.
Mechanism of Action:	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.
Dose/ Administration:	• Voxzogo is a subcutaneous once-daily injection. Recommended dosing is based on the patient's actual body weight. The following dosing guideline is provided by the manufacturer:

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

*The concentration of vosoritide in a reconstituted 0.4 mg vial or 0.56 mg vial is 0.8 mg/mL. The concentration of vosoritide in a reconstituted 1.2 mg vial is 2 mg/mL.

- To reduce the risk of hypotension associated with Voxzogo, ensure adequate food and hydration (approximately 240 – 300 mL of fluids within the hour) prior to Voxzogo administration.
- Administration should occur at approximately the same time each day, if possible.
- Missed doses can be administered within 12 hours of the scheduled administration time. If a dose is missed by more than 12 hours, the missed dose should be skipped, and the regular dosing schedule should be resumed at the next scheduled dose.
- Recommended injection sites are the front middle of the thighs, lower part of the abdomen at least 2 inches away from the navel, top of the buttocks or back of upper arms. Rotate injection sites: the same area should not be used on 2 consecutive days.
- Voxzogo is supplied as a co-pack which includes: 10 sterile Voxzogo vials, single-dose prefilled diluent syringes containing Sterile Water for Injection, USP which is to be used for reconstitution, diluent transfer needles (23-gauge) and single-dose administration syringes (30-gauge).
- Voxzogo vials and the prefilled diluent syringes should be stored in the refrigerator (2°C to 8°C) in the original package to protect from light. Before reconstitution, Voxzogo vials and the prefilled diluent syringes can be stored at room temperature (20°C to 25°C) for up to 90 days. Once stored at room temperature, Voxzogo vials cannot be returned to

	the refrigerator. After reconstitution, Voxzogo can be kept at room temperature for no more than 3 hours. • Caregivers may administer Voxzogo after proper training on the preparation and administration by a healthcare professional.
Disease State Clinical Highlights:	• 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.
Drug Clinical Highlights:	• Voxzogo is the first FDA-approved treatment indicated to increase linear growth in patients with ACH. • Voxzogo was approved under an accelerated approval pathway based on an improvement in annualized growth velocity (AGV). Continued approval for this indication may be dependent upon clinical benefit in confirmatory trials. Contraindications: None Warnings and Precautions: transient decreases in blood pressure were reported in 13% of patients. Drug Interactions: Voxzogo may enhance the hypotensive effect of blood pressure lowering agents. No clinical studies evaluating in-vivo drug-drug interactions have been conducted. Renal Impairment: Voxzogo has not been evaluated in patients with renal impairment and therefore, is not recommended for patients with eGFR < 60 mL/min/1.73m^2. Monitoring: Monitor patient body weight, growth, and physical development every 3 to 6 months and adjust dosage according to patient's actual body weight. Duration of Therapy: Discontinue Voxzogo upon confirmation of closure of epiphyses. Clinical Studies • Voxzogo Study 1 (NCT03197766): multi-center, randomized, double-blind, placebo-controlled, phase III, 52-week efficacy and safety study. After a genetically confirmed diagnosis of ACH, 121 participants were randomized to either Voxzogo 15mcg/kg SubQ once daily (N=60) or placebo (N=61). ○ Key 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 ▪ > 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

- Key Inclusion Criteria: diagnosis of ACH confirmed by genetic testing and patient is ambulatory and able to stand without assistance
- Primary endpoint: change from baseline in AGV at week 52
- Secondary endpoint: height standard deviation score (SDS)
- Key Baseline Characteristics:
  - Mean age: 8.7 years (range 5.1 years to 14.9 years)
  - 53% male; 47% female
  - 71% white, 19% Asian, 4% black or African American, 6% classified as "multiple" race
- Adverse reactions: (reported in ≥ 5% and at a rate greater than placebo)

Adverse Reaction	Placebo (N=61); n (%)	Voxzogo (N=60); n (%)
Injection site erythema	42 (69%)	45 (75%)
Injection site swelling	22 (36%)	37 (62%)
Vomiting	12 (20%)	16 (27%)
Injection site urticaria	6 (10%)	15 (25%)
Arthralgia	4 (7%)	9 (15%)
Decreased blood pressure	3 (5%)	8 (13%)
Gastroenteritis	5 (8%)	8 (13%)
Diarrhea	2 (3%)	6 (10%)
Dizziness	2 (3%)	6 (10%)
Ear pain	3 (5%)	6 (10%)
Influenza	3 (5%)	6 (10%)
Fatigue	2 (3%)	5 (8%)
Seasonal allergy	1 (2%)	4 (7%)
Dry skin	0	3 (5%)

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

	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	

LS= least-square

- Improvement of AGV as a result 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 similar to that of the Voxzogo group in the initial 52-week trial.
Price Per Unit (WAC):	$899 per vial across all 3 strengths $26,970 per month $328,135 per year for any given weight
Therapeutic Alternatives:	• Voxzogo is first in its class and currently the only FDA-approved treatment option for ACH. Management of ACH is tailored to the patient based on their individual symptoms. • Non-pharmacological options for ACH include limb lengthening surgery. • The use of growth hormone is not recommended in ACH because it may worsen the disproportionate stature.
Prior Authorization Approval Criteria:	**Must meet the following criteria:** <u>Initial Therapy:</u> • Prescribed by a geneticist, skeletal dysplasia specialist, pediatric endocrinologist or other specialist in the treated disease state **AND** • Participant is aged 5 years or older **AND** • Documented diagnosis of ACH (ICD10 Q77.4) by genetic testing (Gly380Arg) **AND** • Participant has eGFR ≥ 60 mL/min/1.73m^2 **AND** • Documented baseline AGV within last 90 days **AND** • Male participants aged 15 years or older have recent confirmatory X-ray showing epiphyses are open **OR** • Female participants aged 13 years or older have recent confirmatory X-ray showing epiphyses are open **AND** • Claim does not exceed 1 vial per day • Authorization Period: 12 months <u>Continuation of Therapy:</u> • Documentation of increase in AGV ≥ 1.0 cm/year from baseline **AND** • Male participants aged 15 years or older have recent confirmatory X-ray showing epiphyses are open **OR** • Female participants aged 13 years or older have recent confirmatory X-ray showing epiphyses are open • Continued approval for 12 months **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Participant lacks history of prescribed antihypertensive medications • Participant does not have planned or expected limb-lengthening surgery, or the surgery must have occurred at least 18 months ago • Documentation of baseline clinical criteria (body weight, blood pressure)

Implication to State Medicaid Program:	

- **LOE: 2035 - 2036**
- From 11/1/2019 to 10/31/2021, Missouri had 82 participants with the diagnosis of ACH. During that timeframe, none of the participants had a claim for a growth hormone product.
  - ≤ 10 years-old: 28 participants
  - 11-18 years-old: 22 participants
  - ≥ 19 years-old: 32 participants
- Ongoing Clinical Trials

Trial Description	Estimated Primary Completion	NCT
Phase 2 study of Voxzogo for genetic causes of short stature	January 2023	NCT04219007
Phase 2 extension study to evaluate efficacy and safety of Voxzogo until subjects reach near-adult final height*	September 2026	NCT03989947
Phase 2 study in infants and young children with ACH at a heightened risk of requiring cervicomedullary decompression surgery	December 2026	NCT04554940

*= awaiting results of this trial before full FDA approval can be achieved

- Pipeline Drugs:
  - Ascendis Pharma is developing an investigational prodrug of CNP – TransCon CNP – for treatment of ACH in children. It currently has orphan designation and is in phase 2 clinical trials. Estimated primary completion date of this study is June 2023.
  - Pfizer is conducting phase 2 trials to evaluate safety, tolerability, and efficacy of their new biologic drug, recifercept, in children with ACH. This medication currently has orphan status in the US. Estimated primary completion date of this study is April 2023.
  - QED Therapeutics, Inc. is conducting a phase 2 trial (PROPEL2) using its currently FDA-approved drug infigratinib, an FGFR 1-3 selective tyrosine kinase inhibitor, to gain a new indication for ACH treatment. Estimated study completion date of PROPEL2 is February 2023. Infigratinib (Truseltiq) is currently FDA-approved for FGFR2-positive bile duct cancer.

References:

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