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New Drug Evaluation: vosoritide injection, for subcutaneous use

Date of Review: April 2022
Generic Name: vosoritide

End Date of Literature Search: 1/31/2022
Brand Name (Manufacturer): VOXZOGO™ (Biomarin Pharmaceutical Inc.)
Dossier Received: yes

Research Questions:

1. What is the efficacy and effectiveness of vosoritide in reducing symptoms, avoiding complications, or improving functional outcomes in patients with achondroplasia?
2. What are the harms of vosoritide in the treatment of patients with achondroplasia?
3. Are there subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would benefit or be harmed from vosoritide therapy?

Conclusions:

- There was low quality evidence from one published study that reported treatment with vosoritide was associated with a statistically significant least-squares (LS) mean change in annualized growth velocity (AGV) compared with placebo (LS mean treatment difference 1.57 cm/year [95% CI, 1.22 to 1.93; p<0.0001]) at 52 weeks.[1,2] It is unclear if a change of 1.57 cm in AGV is clinically significant and whether treatment with vosoritide for achondroplasia leads to sustained AGV improvements throughout a child's natural growth period. The effects of vosoritide on final height, proportional growth, or other areas of clinical significance such as reduced symptoms, avoidance of medical complications, or improvements in functionality of achondroplasia patients are unknown.
- There is low quality evidence of no significant difference in discontinuations due to adverse events between vosoritide versus placebo, but a higher rate of injection site reactions (70% vs 43%, respectively). The most common adverse events in vosoritide treatment compared to placebo, respectively, were vomiting (27% vs. 20%), urticaria (25% vs. 10%), arthralgia (15% vs. 7%), hypotension (13% vs. 5%), gastroenteritis (13% vs. 8%), diarrhea (10% vs. 3%), dizziness (10% vs. 3%), ear pain (10% vs. 5%), and influenza (10% vs. 5%).[3] The long-term safety of vosoritide unknown as the required follow-up open-label study to evaluate the effects of vosoritide on final adult height, disproportionality, bone age, and safety endpoints in children with achondroplasia has yet to be completed.
- Outcome conclusions specific to race and ethnicity are insufficient due to variations of results, lack of statistical significance with many comparisons, and small subgroup sizes. The results are most applicable to white patients with achondroplasia ages 5 to 15 years which may not adequately represent diversity within the Oregon Medicaid population. There is insufficient evidence to evaluate the use of vosoritide in the treatment of other subpopulations with regard to gender, comorbidities, disease duration or severity.

Recommendations:

- Create prior authorization criteria for vosoritide to ensure appropriate use.

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Background:

Achondroplasia is an inherited, autosomal dominant skeletal dysplasia characterized by disproportionate growth and severe short stature. [4] The disorder is caused by a gain of function mutation in the fibroblast growth factor receptor 3 (FGFR3) gene region located on chromosome 4.[4] In most cases, the mutation is spontaneous and increases in frequency when the father is 35 years of age or older.[5,6] In addition to small stature, achondroplasia often leads to other serious neurological, musculoskeletal, cardiopulmonary, and metabolic complications such as subdural hematomas, cervicomedullary compression, restrictive pulmonary disease, spinal stenosis, obesity, sleep apnea, and other impairments of body structure and function.[7-11] Achondroplasia affects approximately 1 in 25,000 births or roughly 250,000 individuals worldwide.[12]

Bone formation and long bone elongation is a complex process that begins in embryonic development and involves numerous regulatory pathways.[13] In a process known as endochondral ossification, mesenchymal cells differentiate into the chondrocytes of cartilage which are used as a blueprint for future bone formation.[13] Regulation of endochondral bone growth involves the multifaceted interaction of many signaling molecules and receptors such as fibroblast growth factors (FGFs) and fibroblast growth factor receptor (FGFR) kinases.[14] FGFs and FGFRs also help regulate many cellular functions such as proliferation, differentiation, angiogenesis, and tissue repair.[14] FGFR3 has been shown to be a negative regulator of endochondral bone development by shortening the cell proliferation stage and accelerating terminal differentiation of chondrocytes.[14] In patients with achondroplasia, mutations on FGFR3 gene result in over-activation of FGFR3 which disrupts normal regulation of chondrocyte cell signaling and leads to impaired bone growth. [15,16]

Although diagnosis of achondroplasia typically takes place in early infancy, the availability of prenatal ultrasound has made a clinical diagnosis possible as early as the third trimester of pregnancy.[17,18] Patients with achondroplasia generally present with macrocephaly and an upper to lower body segment ratio higher than in children without achondroplasia.[19] Patients also show signs of disproportionately short extremities along with a nearly normal trunk, short fingers, hypermobile hips and knees, hypotonia, and the later development of lumbar lordosis and bow legs.[7,13] There are usually no significant effects on intramembranous ossification in areas such as the skull, face, clavicles, and other flat bones.[18] In the neonatal stage, patients with achondroplasia display an abnormally small pelvis, shortened long bones, and a relatively large and prominent cranium[18] Confirmation of an achondroplasia diagnosis requires radiographic assessment.[18] Genetic testing is not typically necessary for diagnosis but can be obtained to confirm a prenatal diagnosis.[17] Almost all patients with achondroplasia will have a c.1138G>A gene mutation.[4]

Patients with achondroplasia are of normal intelligence and usually able to live independent, productive lives.[20] However, developmental milestones can be delayed, and some studies suggest that there may be a 10-year reduction in overall life-expectancy.[21] Therefore, early care management of patients with achondroplasia is often overseen by a pediatric neurologist or endocrinologist.[7] Prompt recognition of achondroplasia is important for effective management as early intervention strategies may minimize or even prevent serious health complications.[22] For example, acute brainstem compression may occur in infants with achondroplasia which puts them at increased risk of sudden death.[23] In these cases, it is recommended that a rapid neurologic history and neurologic examination is performed followed by imaging, polysomnography, and possible suboccipital decompression surgery.[24] Various growth curves specific to achondroplasia have been published which not only assist clinicians in tracking height and weight, but also help them anticipate and test for known complications at key stages in the disease.[13,25] Body mass is routinely monitored due to the potential for exacerbation of obstructive sleep apnea and spinal stenosis.[22] Other problems such as a rapidly enlarged head size or head size above the 95th percentile along with symptoms of increased pressure may indicate communicating hydrocephalus and warrant surgical shunting.[26] Surgical techniques to lengthen limbs have been employed, they are costly, not without risk, and often have significant social ramifications.[27] Newer techniques such as magnetic rodding technologies have been successful at reducing the risk of infection and scarring.[28] Therapy focused on improvements in linear height through surgical intervention or other means are still controversial as many individuals with

achondroplasia are taught to embrace and celebrate their uniqueness rather than looking at the condition as a disability.[28] Nonetheless, some patients with achondroplasia continue to suffer with depression, anxiety, and low self-image due to their condition. [15,29] The 36-item Short-Form Health Survey (SF-36) is an interview and self-administered questionnaire designed to assess health-related quality of life in healthy and unhealthy adult populations.[30] The complete SF-36 has eight scaled scores; the scores are weighted sums of the questions in each section and range from 0-100 where lower scores indicate more disability.[31] Some achondroplasia intervention studies have suggested SF-36 Physical Functioning domain scores improve with greater height, but the SF-36 has not been validated for use in patients with achondroplasia.[32,33] Cervical cord compression, cardiorespiratory function, metabolic monitoring, and neurocognitive development must all be closely monitored to prevent serious long-term complications in the patient with achondroplasia.[7]

There is currently no standard of care for the management of patients with achondroplasia, and there is limited evidence-based literature published to assist clinicians and caregivers. There is no known cure for achondroplasia, and 2020 practice guidelines from the American Academy of Pediatrics focus on identification of patients at high risk of developing complications.[34] Monitoring recommendations are stratified by age and include recommendations for diagnostic procedures, genetic counseling, and type of medical evaluation.[34] Most guideline recommendations were based on expert opinion. Other guideline limitations included lack of reporting for stakeholder involvement, method of consensus, search terms, detailed search strategy and inclusion/exclusion criteria. There was insufficient comparative evidence to guide recommendations on first-line medical therapy. The American Academy of Pediatrics noted that treatment guidance in the report does not indicate an exclusive course of treatment or serve as a standard of medical care so accounting for variations and individual circumstances may be appropriate.[34]

Clinical trials in patients with achondroplasia often evaluate outcomes such as improvements in final height, weight, and proportionality.[2] Disproportionality due to the extreme shortness of extremities compared to the trunk may be assessed using measurements of upper to lower body segment ratios.[1,19,25] For example, a larger ratio between sitting height and leg length may be associated with decreased mobility.[19] To monitor growth, specialized charts have been created for children with achondroplasia since their height advances considerably below normal curve area.[19] Deficits in growth in terms of annualized growth velocity (AGV) from infancy to adolescence are often tracked and compared to population norms.[19] Some studies have used these values and converted measurements to an age- and sex-appropriate score known as a height z-score which allows a comparison with normal references.[2,19] A negative z-score value such as -2 would be interpreted as a raw score 2 standard deviation lower than the mean average for a particular age and sex.[19] Clinically relevant outcomes in patients with achondroplasia include final height, functional improvement, and avoidance of long-term disease complications but no minimal clinically important difference has been established in these areas for this population. Research investigating whether there may be a correlation between height z-score and negative outcomes such as spinal cord compression or stenosis in patients with achondroplasia is ongoing.[35]

In 2022, vosoritide was FDA approved for achondroplasia based on the intermediate clinical endpoint of annualized growth velocity (AGV) and changes in height Z-scores. Vosoritide is a recombinant human C-type natriuretic peptide (CNP) that, when bound to NPR-B, helps regulate the overactive FGFR3 pathway which may stimulate chondrocyte proliferation and increase bone growth.[36-38] The effect of vosoritide on other clinically important endpoints related to abnormal bone growth have not been evaluated.[1]

In the Oregon Medicaid population between 1/1/2021 and 12/31/2021, there were fewer than 55 individuals with the diagnosis of achondroplasia (Q77.4), and approximately 15% of whom were part of the Fee-for-service (FFS) population.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Vosoritide 15 mcg/kg subcutaneous injection daily is indicated for the treatment of achondroplasia in pediatric patients who are 5 years of age or older with open epiphyses.[1] Vosoritide was studied in one 52-week, multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial (study 111-301) to determine efficacy and safety in the treatment of achondroplasia in 121 pediatric patients ages 5 to 17 years old.[1,2] Enrolled patients had completed a minimum 6-month lead-in observational growth study, were ambulatory, and had a diagnosis of ACH verified by genetic testing.[1,2] Patients were excluded if they had radiographic evidence of closed epiphyseal plates or growth velocity <1.5 cm/year, planned bone surgery, previous fracture of long bones or spine in prior 6 months, treatment with growth stimulant drugs in prior 6 months or oral corticosteroids in prior 12 months, symptomatic hypotension, chronic therapy with antihypertensive medications, diagnosed with cardiovascular disease, untreated sleep apnea, or any medical conditions known to affect growth.[1,2] The primary endpoint was the change from baseline in annualized growth velocity (AGV) at week 52.[1,2] Key secondary endpoints were change from baseline in height Z-score and upper to lower body segment ratio at week 52.[1,2] The upper to lower body segment ratio was calculated by the following: sitting height (cm)/[standing height (cm) – sitting height (cm)].[1] The mean age of enrolled patients was 8.7 years, and some differences were noted between groups for age ranges of 5 to 8-years (51% vosoritide vs. 39% placebo) as well as 8 to 11-years (28% vosoritide vs. 39% placebo).[1,2] Overall, characteristics were generally balanced between groups, and most subjects were prepubertal with Tanner Stage of 1 (79%), had a mean AGV of 4.16 cm/year, and had a standard deviation score (SDS)/height z-score of -5.13 at baseline.[1,2] Seventy-one percent of patients were white, almost 20% were Asian, and about 3-5% Black or African American.[1,2]

Vosoritide-treated patients demonstrated a statistically significant least-squares mean change in AGV of 1.4 cm/year compared to -0.17 cm/year in the placebo group (LS mean treatment difference 1.57 cm/year [95% CI, 1.22 to 1.93; p<0.0001]).[1,2] There was also a LS mean difference in SDS/height Z-score which favored vosoritide over placebo (0.28 [95% CI, 0.17 to 0.39; p<0.001]).[1,2] There was no statistically significant LS mean change in upper to lower body segment ratio compared to baseline.[1,2] The clinical significance of these relatively modest differences in height-related outcomes is unclear.

An ongoing, phase 3, open-label extension trial (study 111-302) was initiated for completers of study 111-301.[1,39] All participants received vosoritide at a dose of 15.0 µg/kg/day and were to be followed for either 5 years or until their near final adult height was reached. No prespecified statistical inference was performed, but trends in average AGV, height Z-score, and upper-to-lower body segment ratio were observed.[1,39] Fifty-six patients in the original vosoritide group continued vosoritide (vos/vos) treatment, while 61 subjects in the original placebo group were switched to vosoritide (pbo/vos).[1,39] Based on the FDA full analysis set, annualized growth velocity in the vos/vos arm was reported to increase from a baseline of 4.26 cm/year to 5.67 cm/year at week 52, followed by 5.57 cm/year at week 104.[1] For patients in the pbo/vos arm, baseline AGV was reported to decline from 4.06 cm/year to 3.94 cm/year at 52 weeks but after the switch to vosoritide the AGV increased to 5.43 cm/year at week 104.[1] Mean SDS/height z-scores for standing height was converted to an age- and sex-appropriate Z-score for comparison.[1,39] These results are summarized in **Table 1.**

Table 1. 12-month Interval AGV (cm/year) Over Time – Full Analysis Set[1]

	Week 0 (baseline)		Week 52		Week 104		Change from Baseline to 1 year		Change from 1 year to 2 years	
	Vosoritide (N=60)	Placebo (N=61)	Vosoritide (N=58)	Placebo (N=61)	Vos/Vos (N=52)	PBO/Vos (N=54)	Vosoritide	Placebo	Vos/Vos	PBO/Vos
Mean AGV (cm/year)	4.26	4.06	5.67	3.94	5.52	5.43	1.41 (0.96 to 1.86)*	-0.12 (-0.56 to 0.33)*	- 0.14 (-0.50 to 0.22)*	1.66 (1.22 to 2.10)*
Mean SDS/height Z-score	-5.13	-5.14	-4.85	-5.14	-4.54	-4.89	0.24 (0.15 to 0.32)*	-0.005 (-0.077 to 0.067)*	0.21 (0.11 to 0.30)*	0.23 (0.14 to 0.32)*

**=95% CI for mean change from baseline is from paired t-test between visits.*

Trial Limitations

The trial included the use of AGV and changes in height Z-scores which are intermediate clinical endpoints. It is unclear if a change of 1.57 cm in AGV is clinically significant and whether treatment with vosoritide for achondroplasia leads to sustained AGV improvements throughout a child's natural growth period. It is unknown to what extent age influenced clinical response rate as patients in the vosoritide group appeared to be slightly younger than those in the placebo group. The long-term effects of vosoritide on final height, proportional growth, or other areas of clinical significance such as reduced medical complications associated with achondroplasia, functionality, or activities of daily living are unknown. The results of the study are most applicable to patients with open epiphyses who are still growing as patients with AGV of <1.5cm/year were excluded. Also, it is unknown if the vosoritide study results would apply to those with more severe disease as patients were required to be ambulatory and not have a prior fracture. In addition, patients are typically diagnosed at birth (or prior) but vosoritide was not studied in those <5 years of age. There may be unknown mental health consequences of focused efforts to solely improve linear growth since children with achondroplasia are often able to live healthy and productive lives regardless of physical height and are frequently taught to think of their condition as a difference to be celebrated and not as a person with a disability or disease. Outcomes with a linear growth focus may need to be united with validated scales that assess health-related quality of life improvements to help determine the impact on mental health. Larger and longer trials are required before the long-term effects and potential risks of vosoritide therapy are known.

Clinical Safety:

Trial attrition was low overall with 2 discontinuations due to anxiety and pain in the vosoritide group (1.7%) and none in the placebo group.[1,2] Although there were no significant differences in discontinuations due to adverse events between groups, a higher rate of injection site reactions was observed in the vosoritide group compared to placebo (70% vs 43%, respectively).[1] Besides injection site reactions (erythema, swelling, and urticaria), the most common adverse events in vosoritide treatment compared to placebo were gastrointestinal events (vomiting, gastroenteritis, and diarrhea) arthralgia, hypotension, dizziness, ear pain, and influenza.[1-3] The incidence of serious adverse events were few and occurred at similar rates in vosoritide and placebo groups.[1-3] **Table 2** presents the frequency of common adverse reactions.[1,3]

Table 2. Adverse Reactions Occurring in ≥10% Vosoritide-Treated Patients and >5% More Frequently than in Placebo-Treated Patients[1,3]

	Vosoritide (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)
Hypotension	8 (13)	3 (5)
Gastroenteritis	8 (13)	5 (8)
Diarrhea	6 (10)	2 (3)
Dizziness	6 (10)	2 (3)
Ear Pain	6 (10)	3 (5)
Influenza	6 (10)	3 (5)

There were no deaths in either the vosoritide or placebo study groups.[1,3] The FDA labeling did not identify any contraindications to vosoritide therapy, however, there were many trial exclusions for patients with various cardiovascular risks, those on chronic therapy with antihypertensive medications, and patients with symptomatic hypotension.[3] Use of vosoritide in patients with eGFR less than 60 ml/min/1.73 m^2 is not recommended.[1,3] As a post-marketing condition of approval, the FDA has required that the manufacturer continue the long-term, open-label study to evaluate the effects of vosoritide on final adult height, disproportionality, bone age, and safety endpoints related to the drug (e.g. blood pressure effects) or to the disease that may improve or worsen with long-term treatment (e.g. bone deformities, neurological complications, sleep apnea, etc.).[1]

Look-alike / Sound-alike Error Risk Potential: None identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Final Height
2) Disease progression and complications (e.g., cervicomedullary compression, spinal stenosis, etc)
3) Health-related quality of life and function
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Annualized growth velocity (AGV; cm/year) at Week 52

Table 3. Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	Vosoritide is a modified recombinant human C-type natriuretic peptide (CNP) that inhibits the FGFR3 signaling pathway and consequently, stimulates chondrocyte proliferation and differentiation which promotes linear growth.
Oral Bioavailability	N/A
Distribution and Protein Binding	Vd: 2880 mL/kg to 3020 mL/kg; increases with increasing body weight; Protein Binding: Not available
Elimination	Not available
Half-Life	SubQ, multiple-dose, 15 mcg/kg: 21 minutes to 27.9 minutes
Metabolism	Catabolic pathways with degradation into small peptide fragments and amino acids

Abbreviations: FGFR3=fibroblast growth factor receptor 3; SubQ=subcutaneous; Vd=volume of distribution

Table 4. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.Savarirayan et al.[1, 2]	1. vosoritide 15 mcg/kg SC daily 2. placebo 52 weeks	Demographics: 1. Mean age: 8.7 years (range 5.1 to 14.9 years) 2. Ethnic group: -White/Caucasian 71% -Asian 19% -Black/African American 5% 3. Mean baseline AGV (cm/year): -Vosoritide: 4.26 -Placebo: 4.06 4. Mean baseline height SDS/Z-score: -Vosoritide: -5.13 -Placebo: -5.14 5. Mean Upper to lower body segment ratio: -Vosoritide: 1.98 -Placebo: 2.01 6. Sleep apnea -Vosoritide 45% -Placebo 51% 6.Cervical spinal stenosis -Vosoritide 12% -Placebo 3%	ITT: 1. 60 2. 61 Attrition: 1. 2 (2%) 2. 0 (0%)	Primary Endpoint: LS mean change from baseline in AGV (cm/year) 1. 1.4 2.- 0.17 LSMD 1.57 (95% CI, 1.22 to 1.93); p<0.0001 Secondary Endpoints: Change from baseline in height Z-score 1. 0.27 2. -0.01 LSMD 0.28 (95% CI 0.17 to 0.39); p <0.0001 LS mean change in upper to lower body segment ratio compared to baseline -No statistically significant difference between groups	N/A	Serious Adverse Events 1. 3 (5%) 2. 4 (7%) ARD -1.6 (95%CI, -9.9 to 6.7) Any Adverse Event 1. 59 (98%) 2. 60 (98%) ARD -0.1 (95% CI, -4.6 to 4.4) Injection site reaction 1. 42 (70%) 2. 26 (43%) ARD 27.4 (95% CI, 10.4 to 44.4)	NS NS NNH 4	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients were randomly assigned 1:1 to receive either vosoritide or matched, identical placebo. Randomization was done with the use of an interactive, automated voice-response or web response System. Baseline characteristics were similar between groups except higher percentage white and non-Hispanic/Latino patients in vosoritide group, and overall younger patients in vosoritide group. Performance Bias: Low. Participants, investigators, caregivers administering injections were all masked to group assignment. Electronic data capture system was used to collect study data at each site. Detection Bias: Low. Assessors analyzing outcome data were all masked to group assignment. Attrition Bias: Low. <5% attrition overall and in either group. All randomized and consented patients were included, and ITT analysis performed for both groups. Reporting Bias: Low. Trial protocol was followed. Other Bias: Unclear. Study was funded by manufacturer. Many major authors served as consultants for or received research funding from manufacturer.

		Key Inclusion Criteria: -completed 6-month growth study -ambulatory -genetically verified ACH diagnosis Key Exclusion Criteria: -evidence of closed growth plates or growth velocity <1.5 cm/year -planned bone surgery -severe untreated sleep apnea -medical conditions or treatments known to affect growth -previous fracture of long bones or spine in prior 6 months -treatment with growth stimulant drugs in prior 6 months or oral corticosteroids in prior 12 months -symptomatic hypotension -chronic therapy with antihypertensive medications -diagnosed with cardiovascular disease						**Applicability**: Patient: Results most applicable to white patients with achondroplasia ages 5 to 15 years. Extensive exclusion criteria. Unknown effects on patients with cardiovascular risks, on chronic therapy with antihypertensive medications, or patients with symptomatic hypotension, etc. Intervention: Vosoritide dose appropriately determined from a phase 2 study. Comparator: Placebo is appropriate comparator to determine efficacy. Outcomes: AGV surrogate marker to demonstrate drug efficacy in treatment of disproportional short stature at 52 weeks. The impact on long-term growth velocity, final height upon closed epiphyses, physical symptom or daily functioning improvement is unknown. Setting: 7 countries, 24 sites in 7 countries (Australia, Germany, Japan, Spain, Turkey, USA, and UK)
Abbreviations: ARD = absolute risk difference; ARR = absolute risk reduction; CI = confidence interval; ITT = intention to treat; LS = least squares; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; SC = subcutaneous; SDS = standard deviation score								

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VOXZOGO safely and effectively. See full prescribing information for *VOXZOGO*.

VOXZOGO (vosoritide) for injection, for subcutaneous use
Initial U.S. Approval: 2021

----------INDICATIONS AND USAGE----------
VOXZOGO is a C type natriuretic peptide (CNP) analog 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 based on an improvement in annualized growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). (1)

----------DOSAGE AND ADMINISTRATION----------
- Ensure adequate food and fluid intake prior to administration. (2.1)
- Recommended dosage is based on patient's weight. Administer subcutaneously once daily. (2.2)
- Reconstitute prior to use. The injection volume is based on both patient's weight and concentration of reconstituted VOXZOGO. (2.2)
- Monitor growth and adjust dosage according to body weight. Permanently discontinue upon closure of epiphyses. (2.3)
- See full prescribing information for preparation and administration instructions. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
For injection: 0.4 mg, 0.56 mg, or 1.2 mg lyophilized powder in a single-dose vial for reconstitution. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
Risk of Low Blood Pressure: Transient decreases in blood pressure have been reported. (5 1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>10%) are injection site erythema, injection site swelling, vomiting, injection site urticaria, arthralgia, decreased blood pressure, and gastroenteritis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Renal Impairment Not recommended in patients with eGFR < 60 mL/min/1.73 m^2. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2021

Vosoritide

Goal(s):

- Ensure medically appropriate use of approved agents for the treatment of achondroplasia in pediatric patients

Length of Authorization:

- Up to 12 months

Requires PA:

- Vosoritide

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1:

Actual Body Weight	Vial Strength for Reconstitution*	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 reconstituted 0.4 mg vial and 0.56 mg vial is 0.8 mg/mL.
The concentration of vosoritide in reconstituted 1.2 mg vial is 2 mg/mL.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication based on diagnosis and current age restrictions?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP
4. Is the prescribed agent being dosed according to actual body weight (ABW) as outlined in Table 1?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to Renewal Criteria	**No:** Go to #6
6. Is the agent prescribed by, or in consultation with, a pediatric endocrinologist, neurologist, or other prescriber specialized in the care of patients with achondroplasia or skeletal dysplasia?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there documented evidence of a baseline measurement of annualized growth velocity (AGV) within the last 90 days AND, if male $\geq$15 years or female $\geq$13 years old, evidence of non-closure of epiphyseal plates?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a history of bone-related surgery or fracture of long bone or spine within the previous 6 months or planned bone surgery?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Does the patient have a diagnosis of recurrent symptomatic hypotension with or without orthostasis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 6 months

Renewal Criteria		
1. Is this an FDA approved indication based on diagnosis and current age restrictions?	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is there documented evidence that the regimen is well tolerated with no adverse effects or drug toxicity?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is there documented evidence of adherence of at least 85% to the approved therapy regimen verified through claims history and/or provider assessment OR If adherence less than 85% of the time, there is documentation that the discontinuation was temporary due to the need for surgery or treatment of an infection?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is this the first renewal request?	**Yes:** Approve for 6 months	**No:** Go to #5
5. Is there documented evidence of an improvement in annualized growth velocity (AGV) ≥ 1.0 cm/year from baseline AND, if male ≥15 years or female ≥13 years old, evidence of non-closure of epiphyseal plates?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/22 (DE)
Implementation: 5/1/22