CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214938Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214938
PDUFA Goal Date	11/20/2021
OSE RCM #	2020-1757
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS[a]
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D., BCPS
Review Completion Date	November 19, 2021
Subject	Evaluation of Need for a REMS
Established Name	Vosoritide
Trade Name	Voxzogo
Name of Applicant	BioMarin Pharmaceutical, Inc.
Therapeutic Class	C type natriuretic peptide (CNP) analog
Formulation(s)	0.4 mg (lyophilized powder) single dose vial 0.56 mg (lyophilized powder) single dose vial 1.2 mg (lyophilized powder) single dose vial
Dosing Regimen	(b) (4) injected subcutaneously once daily

[a] Dr. Chapman was on extended leave from the Agency at the time this review was completed.

Table of Contents

EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, Voxzogo (vosoritide) is necessary to ensure the benefits outweigh its risks. BioMarin Pharmaceutical, Inc submitted a New Drug Application (NDA) 214938 for vosoritide with the proposed indication: for the treatment of achondroplasia in patients (b) (4) whose epiphyses are not closed. Achondroplasia is a serious condition with no currently FDA-approved treatment options and unmet medical need. Vosoritide met its primary endpoint of change from baseline in annualized growth velocity (AGV) and secondary endpoint of difference in height z-score but did not show significant improvement in change in upper to lower body ratio. (b) (4) the FDA-approved indication of vosoritide will be for the treatment of achondroplasia in pediatric patients who are 5 years or age and older. At the time of this review, the review team is recommending accelerated approval given that AGV is an intermediate clinical endpoint and verification of the clinical benefit on final adult height is needed. The Applicant will be required to conduct a post-approval trial to verify the clinical benefit of improved final adult height based on the intermediate clinical endpoint of improved annualized growth velocity.

Risks associated with vosoritide are primarily tolerability issues and include vomiting, transient decreases in blood pressure and injection site reactions. The prescribing information does not include a boxed warning for any risk, and the warnings and precautions section will be limited to the risk of transient decreases in blood pressure. The Applicant submitted a proposed pharmacovigilance and risk minimization plan for vosoritide that included labeling, routine pharmacovigilance, collection of safety data from ongoing clinical studies, and specific follow-up questionnaires for use in pregnancy. The Division of Risk Management (DRM) and the Division of General Endocrinology (DGE) agree that a REMS is not needed to ensure the benefits of vosoritide outweigh its risks. Based on the data available, the benefit-risk profile is favorable. Prescribers should be familiar with managing the adverse effects associated with vosoritide.

1 Introduction

This review by DRM evaluates whether a REMS for the NME, Voxzogo (vosoritide) is necessary to ensure the benefits outweigh its risks.[b] BioMarin Pharmaceutical, Inc submitted a NDA 214938 for vosoritide with the proposed indication: for the treatment of achondroplasia in patients (b) (4) whose epiphyses are not closed.[1] The FDA-approved indication will be: for the treatment of achondroplasia in pediatric patients who are 5 years or age and older. [2]

This application is under review in the DGE. The Applicant did not submit a REMS with this application but proposed a pharmacovigilance and risk minimization plan for vosoritide that included labeling, routine pharmacovigilance, collection of safety data from ongoing clinical studies to address long-term safety including skeletal effects, use in patients 2-5 years of age, and off-label use in patients less than 2 years old, and specific follow-up questionnaires for use in pregnancy.[3]

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

2 Background

2.1 Product Information

Voxzogo (vosoritide), an NME[c], is a C-type natriuretic peptide proposed for the treatment of achondroplasia in patients (b) (4) whose epiphyses are not closed. Vosoritide is proposed as a single-dose vial of lyophilized powder for reconstitution with sterile water for injection. Vosoritide is available in (b) (4) strengths: 0.4 mg, 0.56 mg, 1.2 mg, (b) (4). The recommended dose is (b) (4) once daily by subcutaneous injection.[2] See Table 1 in the appendix for detailed vosoritide dosing. Treatment with vosoritide should be stopped upon confirmation of no further growth potential, indicated by closure of epiphyses.[d] Vosoritide received marketing authorization on August 26, 2021 by the European Medicines Agency valid throughout the European Union.[4]

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 214938 relevant to this review:

- 08/20/2020: NDA 214938 submission for vosoritide for the treatment of achondroplasia in patients (b) (4) whose epiphyses are not closed received.
- 02/10/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no significant safety issues had been identified and a REMS is not being considered for vosoritide.
- 03/31/2021: Submission of efficacy data after two years of treatment in the Applicant's Phase 3 study as well as an additional follow-up in the Applicant's Phase 2 study received which constitutes a major amendment to this NDA . The goal date was extended by three months. The extended user fee goal date is November 20, 2021.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Achondroplasia is a serious, autosomal dominant condition caused by pathogenic variants in the fibroblast growth factor receptor 3 (*FGFR3*) gene.[5] It is the most common bone dysplasia in humans with a prevalence of approximately 1 in 20,000 to 1 in 25,000 live births.[6,e] The clinical manifestations of achondroplasia include distinctive craniofacial features (macrocephaly, frontal bossing, and midface retrusion), disproportionate short stature with rhizomelic shortening of the arms and the legs, brachydactyly (shortening of the fingers and toes), kyphoscoliosis, and accentuated lumbar lordosis.

Complications associated with achondroplasia include recurrent otitis media, sleep-disordered breathing, obesity, leg bowing, narrowing of the lumbar spine, and cervical medullary compression.[5] Cervical medullary compression is of concern because it is associated with significant morbidity and

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

mortality, including an increased risk of sudden infant death.[f] These complications can greatly impact a patient and caregiver's quality of life.

3.2 Description of Current Treatment Options

There are no FDA-approved pharmacologic therapies for the treatment of achondroplasia. The management of this condition focuses on maximizing functional capacity as well as monitoring, preventing, and treating complications.[5] Human growth hormone has been used off-label to treat achondroplasia. Use of growth hormone is not recommended and can potentially worsen the disproportion seen in these patients.[5]

Non-pharmacologic therapy for achondroplasia includes surgical limb lengthening. Surgical limb lengthening of the lower extremities may confer up to 15 to 30 cm of added standing height. However, it is associated with significant surgical complications (e.g., wound complications and complications related to stretching of non-skeletal tissue such as nerves and blood vessels) and requires repeated procedures and long-term use of orthopedic appliances.[6]

Due to the lack of a cure or specific treatment, there is an unmet medical need for the treatment for achondroplasia.

4 Benefit Assessment

The efficacy of vosoritide for the treatment of achondroplasia was demonstrated in one Phase 3, randomized, double-blind, placebo-controlled study, Study 111-301 (NCT# 03197766). This study was conducted in 121 subjects, ages 5 to 18 years, with genetically confirmed achondroplasia. Subjects were randomized to vosoritide 15 mcg/kg injected subcutaneously once daily (N = 60) or placebo (N = 61) for 52 weeks. The primary efficacy endpoint was change from baseline in annualized growth velocity (AGV) at Week 52. Key secondary endpoints included change from baseline in height Z-score at Week 52 and change from baseline in upper to lower body segment ratio at week 52.

For the primary endpoint, results showed the least square (LS) mean difference in AGV in those treated with vosoritide versus placebo was 1.57 cm/year (95% confidence interval: 1.22, 1.93; with a two-side p-value of < 0.0001) in favor of vosoritide. For the major secondary endpoints, results showed a LS mean difference in height Z-score between vosoritide and placebo at Week 52 was +0.28 in favor of vosoritide (95% CI 0.17, 0.39, two-sided p-value <0.0001). However, there was no change in upper to lower body segment ratio at 52 weeks.[6]

The review team concluded the vosoritide-treated group demonstrated superiority to placebo in terms of change in AGV from baseline to Week 52. Differences in AGV between the two groups were notable as early as the Week 13 visit. The difference was maintained until Week 52. The vosoritide-treated group also demonstrated superiority to placebo in terms of change in height Z-score from baseline to

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

Week 52.[6] Of note, AGV is considered an intermediate clinical endpoint. Verification of the clinical benefit on final adult height is needed, therefore, the Applicant will be required to conduct a post-approval trial using the accelerated approval pathway.

5 Risk Assessment & Safe-Use Conditions

The safety profile of vosoritide was derived from the 121 patients in the Phase 3 study, 111-301. No serious risks were determined to be associated with vosoritide.[g] The most common (greater than 10%) adverse reactions that occurred in subjects treated with vosoritide include injection site reactions, vomiting, and transient decreases in blood pressure.[2] Patients were excluded from the study if they had significant cardiac or vascular disease, as well as patients who were on anti-hypertensive medications. Eight (13%) of 60 patients that were treated with vosoritide had 11 events of transient decreases in blood pressure compared to 3 (5%) of 61 patients on placebo. These events were identified primarily during periods when vital signs were monitored at clinical visits over the 52-week treatment period. The median time to onset of hypotension was 31 minutes (range 18-120 minutes) with resolution within 31 minutes (range: 5-90 minutes). Two patients (3%) experienced symptomatic episodes of hypotension which included dizziness and vomiting in one patient, and dizziness alone in another patient. These events resolved within 5 minutes and 42 minutes respectively. No patients in the placebo arm had any symptomatic hypotensive events.[2] Recommendations in the draft label include monitoring for associated symptoms of decreases in blood pressure and ensuring that patients are hydrated at the time they receive vosoritide. The risk of low blood pressure is the only adverse event that is communicated in the warnings and precautions section of the prescribing information.

There were no deaths in the clinical trial program.

Based on data from Study 111-301 and the safety profile to date, the review team recommends accelerated approval of vosoritide for the treatment of achondroplasia in pediatric patients who are 5 years or age and older.

6 Expected Postmarket Use

Vosoritide will be prescribed and administered primarily in an ambulatory setting in which patients and/or their caregivers could administer the injections. The likely prescribers include pediatricians who specialize in treating patients with achondroplasia. These prescribers should be familiar with managing the adverse effects associated with vosoritide which may include injection site reactions, vomiting, and transient decreases in blood pressure.

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug*

7 Risk management activities proposed by the Applicant

The Applicant submitted a proposed pharmacovigilance and risk minimization plan for vosoritide that included labeling, routine pharmacovigilance, collection of safety data from ongoing clinical studies, and specific follow-up questionnaires for use in pregnancy.

8 Discussion of Need for a REMS

Achondroplasia is a serious, autosomal dominant condition caused by pathogenic variants in the fibroblast growth factor receptor 3 (*FGFR3*) gene. It is the most common bone dysplasia in humans with a prevalence of approximately 1 in 20,000 to 1 in 25,000 live births. Currently, there are no FDA-approved pharmacologic treatment options for achondroplasia. Growth hormone has been used off label for this condition, however, it is not recommended because treatment could worsen the patient's condition. Surgical limb lengthening is associated with significant surgical complications. There is an unmet medical need for treatment options for achondroplasia.

The review team recommends accelerated approval of vosoritide based on the clinical data that demonstrated an improvement in linear growth (AGV) compared to placebo and the favorable safety profile. Vosoritide will be the first pharmacologic treatment option for this patient population. Because approval is based on an intermediate clinical endpoint, verification of the clinical benefit will be determined in the Applicant's confirmatory trials under the following post-marketing requirement (PMR):

- To conduct an open-label, external-controlled trial in subjects with ACH 5 years of age and older, whose epiphyses are not closed, to measure the effect of vosoritide on final adult height. The trial should also evaluate disproportionality and bone age as secondary endpoints. The safety endpoints related to the drug (e.g., blood pressure) or to the disease itself that may improve or worsen with long-term treatment (e.g., neurological complications, bone deformities, sleep apnea) should also be included. The total exposure to vosoritide for each patient should be sufficient to meet the study's stated objectives. The vosoritide-treated trial population should include subjects who are already enrolled and treated with vosoritide in Studies 111-202/205 and 111-301/302 and/or treatment-naïve subjects with a genetically confirmed ACH diagnosis.

Furthermore, an additional PMR is required for the Applicant to conduct a Human Factors (HF) validation study using a redesigned product user interface that addresses the residual risks identified in the previous HF validation study. Results of the Applicant's original HF validation study demonstrated that trained and untrained participants experienced product-use errors, close calls, and use-difficulties, which indicated that the user interface is not optimized for safe and effective use. (b) (4)

No serious risks have been determined to be associated with vosoritide. Prescribers should be familiar with managing the common adverse effects associated with vosoritide which may include injection site reactions, vomiting, and decreased blood pressure. This reviewer recommends that, should vosoritide be approved, a REMS is not necessary to ensure its benefits outweigh its risk. These risks can be communicated in the prescribing information.[7]

9 Conclusion & Recommendations

Based on the integrated review, the benefit-risk profile is favorable, therefore a REMS is not necessary for vosoritide to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 Table 1:[2] Recommended Voxzogo Daily Dosage and Injection Volume

Body Weight	Dose	Injection Volume from Reconstituted Vial
10-11 kg	0.24 mg	**0.3 mL** from reconstituted **0.4 mg** vial
12-16 kg	0.28 mg	**0.35 mL** from reconstituted **0.56 mg** vial
17-21 kg	0.32 mg	**0.40 mL** from reconstituted **0.56 mg** vial
22-32 kg	0.40 mg	**0.50 mL** from reconstituted **0.56 mg** vial
33-43 kg	0.50 mg	**0.25 mL** from reconstituted **1.2 mg** vial
44-59 kg	0.60 mg	**0.30 mL** from reconstituted **1.2 mg** vial
60-89 kg	0.70 mg	**0.35 mL** from reconstituted **1.2 mg** vial
≥90 kg	0.80 mg	**0.4 mL** from reconstituted **1.2 mg** vial

10.2 References

1. Bio Marin Pharmaceutical Inc. Voxzogo (vosoritide). NDA 214938. Proposed Prescribing Information, draft. August 20, 2020.
2. Bio Marin Pharmaceutical Inc. Voxzogo (vosoritide). NDA 214938. Prescribing Information, FDA November , 2021.
3. Bio Marin Pharmaceutical Inc. Voxzogo (vosoritide). NDA 214938. Module 1.16 – Risk Management Plan - Proposed Pharmacovigilance and Risk Minimization Plans for Vosoritide (BMN 111). August 20, 2020.
4. Voxzogo (vosoritide). European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/voxzogo. Accessed October 7, 2021.
5. Bacino CA. Achondroplasia. *UpToDate.* December 15, 2020. Accessed October 7, 2021.

6. Food and Drug Administration. Division of General Endocrinology. Voxzogo (vosoritide). NDA 214938. Integrated review. accessed November 19, 2021
7. NDA 214938 Late-Cycle Meeting Minutes. September 9, 2021, Archived in DARRTS October 6, 2021

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/s/

NAOMI S BOSTON
11/19/2021 09:12:34 AM

LAURA A ZENDEL
11/19/2021 09:16:39 AM