CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214938Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 214938
Review 1

Drug Name/Dosage Form	Vosoritide for injection
Trade Name	Voxzogo
Strength	0.4 mg/vial, 0.56 mg/vial, and 1.2 mg/vial
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	BioMarin Pharmaceuticals Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original and Amendments	8/20/2020 (original) and amendments dated 9/09/2020, 9/15/2020, 10/07/2020, 10/16/2020, 11/27/2020, 2/17/2021 2/26/21, 3/02/2021, 4/08/21, 4/26/2021, 5/19/2021	Quality (Module 3.2. and 1.1)

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber /Suong Tran	Division of New Drug API/ONDP
Drug Product	Ali Mohamadi/David Claffey	Division of New Drug Products III/ONDP
Process/Facility	Peter Krommenhoek/ Aditi Thakkar	Office of Pharmaceutical Manufacturing Assessment (OPMA)
Microbiology	Samata Tiwari/Neal Sweeney	Office of Pharmaceutical Manufacturing Assessment (OPMA)
Regulatory Business Process Manager	Hamet Toure	Regulatory Business Process Management/OPRO
Application Technical Lead	Muthukumar Ramaswamy	New Drug Products III/ONDP
Facility (CDRH)	Florence Wilson/Rumi Young	CDRH
Environmental Analysis (EA)	Muthukumar Ramaswamy	Division of New Drug Products III/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Sufficient information in the NDA	LOA 11/25/2019
	Type III				LOA 07/17/2017
	Type III				LOA 12/18/2019
	Type III				LOA 11/25/2019 and 12/13/2019
	Type V			Adequate. Refer to microbiology review dated June 16, 2020	LOA 11/25/2019
	Type V			Sufficient information in the NDA	LOA 12/12/2019
	-			CDRH consult review dated 1/8, 2021	LOA 3/5/20
	-				LOA 3/5/2020

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	111299 and Type C meeting written response dated 4/27/2020	Vosoritide for Injection

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/Toxicology	Complete	Acceptable (Impurities and Leachables via email)	1/4/2021-	Dr. Dan Minck
CDRH – Device related	Complete	Acceptable, See review in DARRTS 1/8/2021	1/8/2021	Florencia Wilson

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 214938 is approval. This recommendation includes acceptable recommendation for all the facilities listed in the application. At present, there are no outstanding deficiencies associated with drug substance, drug product, environmental assessment, process, facility, and microbiology sections of this application.

II. Summary of Quality Assessments

A. Product Overview

This NDA is a 505(b)(1) application for vosoritide for injection. Vosoritide is a 39 amino acid peptide. The BioMarin assigned code for vosoritide is BMN 111. Vosoritide is also known as C-type natriuretic peptide (CNP) analog.

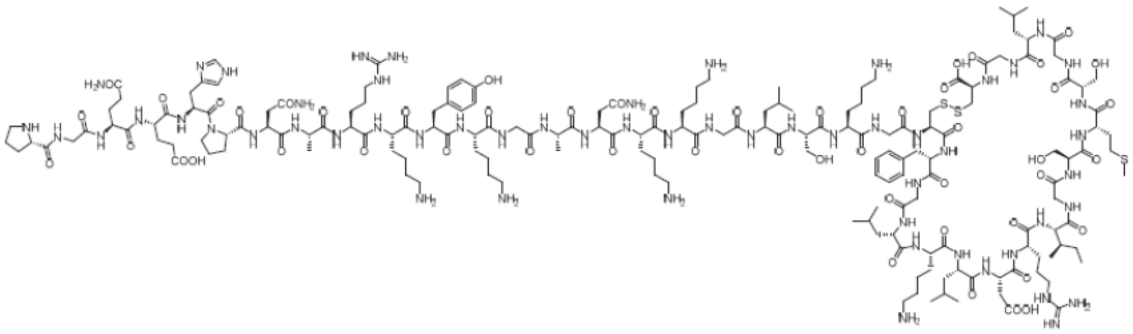
The drug product, Voxzogo (Vosoritide) for injection is a single-dose, sterile, white to yellow, lyophilized powder provided in a (b) (4) glass vial as 0.4 mg/vial, 0.56 mg/vial, and 1.2 mg/vial. Prior to use, the drug product is reconstituted with sterile water for injection provided in a diluent syringe. The reconstituted product is intended for subcutaneous administration using a dose administration syringe. The drug product is co-packaged with a pre-filled diluent syringe, diluent needle, and a dose administration syringe. Vosoritide is intended for the treatment of achondroplasia in patients (b) (4) whose epiphyses are not closed.

Proposed Indication(s) including Intended Patient Population	Treatment of achondroplasia in patients (b) (4) whose epiphyses are not closed
Duration of Treatment	CDTL review
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	Not applicable

B. Quality Assessment Overview

Drug Substance

Vosoritide is a 39 amino acid peptide (code: BMN111). The amino acid sequence of vosoritide includes the 37 C terminal amino acids of the human CNP53 sequence plus the addition of 2 amino acids (Pro-Gly) on the N terminus. Vosoritide contains one disulfide bridge between the cysteines (Cys23 and Cys39), which form a 17 membered cyclic peptide ring. This 17-membered ring is essential for biological activity. The molecular mass of Vosoritide is 4103 Da. The molecular formula of vosoritide is $C_{176}H_{290}N_{56}O_{51}S_3$. The structure of vosoritide is reproduced below form Module 3.



Vosoritide is produced in *Escherichia coli* [redacted] using recombinant DNA technology. The manufacturing process consists of [redacted]

[redacted] The applicant performed analytical comparability studies to demonstrate that all batches of vosoritide made by [redacted] (commercial process) conform to clinical and commercial release specifications. Comparability results are within historical ranges of [redacted] batches. Dr. Martin Haber reviewed the drug substance analytical comparability information and concluded that the structure characterization shows identical vosoritide structure irrespective of manufacturing process. Forced degradation studies show no differences in the degradation pathways or in the rate of degradation between [redacted] batches (Section 3.2.S.2.6 Comparability).

The structure and biological activity of vosoritide was characterized with respect to its molecular mass, primary amino acid sequence, the location of disulfide bond, secondary structure (by circular dichroism studies), purity and impurity profile using orthogonal methods, and biological activity (cell based assay) using a representative [redacted] commercial scale batch (P12003A-19101).

[redacted]

A cell-based activity assay was used during clinical development to measure potency. Due to variability associated with the bioassay, the bioassay was not retained for commercial [redacted] and drug product testing. RP-HPLC method offers a more precise measurement of active fraction (intact vosoritide).

Dr. Martin Haber reviewed the CMC information provided for the (b) (4) information including the description of the manufacturing process, process controls, critical quality attributes, starting materials, cell bank characterization and controls, hold time studies, structural characterization information for (b) (4) and impurities, analytical methods and their validation, the proposed specification of (b) (4), reference standards, (b) (4) storage container information and the available (b) (4) stability information.

Based on available stability data in the NDA, Dr. Haber granted a (b) (4) month retest period when the (b) (4) is stored (b) (4). Dr. Haber's review concluded that (b) (4) information provided in the NDA is adequate to support the application. Please refer to his review dated 3/21/2021 in Panorama.

Drug Product: Voxzogo (vosoritide) for injection is a sterile, white to yellow lyophilized powder provided in a clear 2mL (b) (4) glass vial sealed with (b) (4) rubber stopper, and aluminum seal with flip-off cap.

The drug product is reconstituted with diluent prior to use. In the original NDA, the applicant proposed to provide the drug product in a single-dose vial as 0.4 mg/vial, 0.56 mg/vial, 1.2 mg/vial, and (b) (4). On 0/31/2021, the applicant indicated that the (b) (4) presentation would no longer be commercialized and removed the presentation from the draft US prescribing information and Form 356h.

The vosoritide commercial drug product is co-packaged with the following components.
1) 10 lyophilized vosoritide single dose drug product vials.
2) 10 Pre-filled diluent syringes containing sterile Water for Injection (sWFI) for reconstitution.
3) 10 x 23G x1in (b) (4) diluent transfer needles for attachment to diluent syringe and 10 x 1mL (b) (4) administration syringes for injecting the reconstituted drug.

The diluent needle and the dose administration syringe are 510(k) cleared. The CMC information for diluent syringe, diluent needle and administration syringe was reviewed by CDRH and found acceptable.

The drug product contains the following inactive ingredients.

Strength	Inactive Ingredients per Vial
0.4 mg/0.5 mL per vial (0.8 mg/mL)	Trehalose dihydrate (29.01 mg), mannitol (7.5 mg), sodium citrate dihydrate (0.54 mg), methionine (0.36 mg), citric acid monohydrate (0.14 mg), and polysorbate 80 (0.025 mg). After reconstitution with 0.5 mL diluent, the nominal deliverable volume is 0.4 mL. This corresponds to a nominal dose of 0.32 mg
0.56 mg/0.7 mL per vial (0.8 mg/mL)	Trehalose dihydrate (40.61 mg), mannitol (10.50 mg), sodium citrate dihydrate (0.76 mg), methionine (0.51 mg), citric acid monohydrate (0.20 mg), and polysorbate 80 (0.035 mg). After reconstitution with 0.7 mL diluent, the nominal deliverable volume is 0.6 mL. This corresponds to a nominal dose of 0.48 mg.
1.2 mg/0.6 mL per vial (2 mg/mL)	Trehalose dihydrate (34.81 mg), mannitol (9 mg), sodium citrate dihydrate (0.65 mg), methionine (0.44 mg), citric acid monohydrate (0.17 mg), and polysorbate 80 (0.030 mg). After reconstitution with 0.6 ml diluent, the nominal deliverable volume is 0.5 mL. This corresponds to a nominal dose of 1.0 mg

The drug product formulation contains citric acid and citrate salt for buffering, trehalose and

mannitol for isotonicity. [redacted] The target pH of the reconstituted product is 5.5, [redacted] All excipients are USP-NF grade, and the proposed levels are within those of approved drugs.

During Phase 1 /2 clinical product development, the applicant utilized 10mL [redacted] glass sealed with [redacted] stopper for manufacturing the lyophilized product. For commercial, Phase 3 clinical studies, and registration stability studies, the applicant selected a 2 mL [redacted] glass and [redacted] stopper for lyophilized product manufacturing. The suitability and compatibility of the proposed container closure system is demonstrated by the available stability data. The packaging components meet requirements of USP<660> Glass and USP<381> Elastomeric closures for injection. The NDA includes adequate information on extractables and leachables, as confirmed by the Pharmacology Toxicology team. Please refer to Dr. Minck's review under OND integrated review for NDA 214938 under section 13.3 Impurities and degradants.

The drug product is tested for visual appearance, identity (Dot blot, HPLC retention time), moisture, reconstitution time, sub-visible particulate matter by light obscuration, uniformity of dosage units, pH, osmolality, polysorbate 80 content, sterility, endotoxin content, strength – (peptide concentration and intact peptide content), purity (multimer content by SEC, deamidated forms by SCX , main peak, total inactive fraction, [redacted] oxidation product, individual and total unidentified impurities). [redacted]

Dr. Ali Mohamadi reviewed the drug product information including drug product composition, drug product specification, excipient information, drug product specific analytical methods, container closure system, compatibility information, comparability protocol, and stability data. Dr. Mohamadi also reviewed the diluent specification, diluent syringe container closure information and stability.

Dr. Mohamadi's review concluded that the proposed specification is adequate to support the quality of the proposed product. Based on available stability data, Dr. Mohamadi granted an expiration period of 24 months for the product when stored at 2°C to 8°C (36°F to 46°F), during which the drug product can be stored at 25°C (77°F) for 3 months. Please refer to the drug product review dated 4/14/2021 for additional information.

[redacted]

Manufacturing Process and Control: [redacted]

(b) (4)

The composition of the drug product, the drug product manufacturing process, and the packaging system used to manufacture the drug product used in phase 3 clinical and registration stability studies are the same as that proposed for commercial use. (b) (4) For detailed information on the manufacturing process and process control, please refer to Dr. Krommenhoek's process review dated 4/13/2021 in Panorama. The process reviewer concluded that the proposed drug product manufacturing process controls are adequate to support the NDA.

Microbiological control information: Microbiology reviewer, Dr. Tiwari reviewed the microbiological controls used in the drug substance, drug product, and diluent manufacturing process. She reviewed the drug product, drug substance, and diluent specifications for endotoxin and sterility, container closure integrity testing, filter validation, (b) (4) , media fill studies and environmental monitoring, in-process testing ((b) (4) hold times for process intermediates, (b) (4) vials and rubber stoppers, diluent syringes, syringe stopper, and tip cap, process equipment (b) (4) information for diluent and post-approval stability commitment. Dr. Tiwari also reviewed the (b) (4) validation information provided in (b) (4) Her review concluded that the proposed microbiological controls are adequate to support the NDA. Refer to CMC (Microbiology) review by Dr. Tiwari's dated 3/31/2021 in Panorama.

Control Strategy: The critical quality attributes of the product are controlled (b) (4)

The proposed control strategy is adequate to assure the quality of the product. For

additional information, please refer to the following CMC reviews in Panorama: Dr. Martin Haber's drug substance review dated 3/21/2021, Dr. Tiwari 's microbiology review dated 3/31/2021, Dr. Mohamadi's reviews dated 4/14/2021 and 5/25/2021 and Krommenhoek' s process reviews dated 4/13/2021 in Panorama.

Facility compliance information: Facility compliance information for the drug substance, drug product and diluent manufacturing and testing facilities was reviewed by OPMA reviewer, Dr. Peter Krommenhoek. The facility recommendation for the Biomarin drug substance manufacturing facility located at Novato, CA (FEI 3004079983) is approve based on pre-approval inspection. The facility recommendation for the remaining facilities are based on previous history.

Time run: 5/24/2021 11:06:47 AM

Latest Submission Manufacturing Status for NDA-214938-Original-1

Latest Overall Manufacturing Inspection Recommendation
Approve
Completion Date: 04/12/2021
NDA-214938-ORIG-1

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Hint: Click Facility ID link to open Facility Program
Click Facility Name to open Facility Status View: Detail
To refresh the report, please click Refresh under Page Options.
Page Options can be found next to the "?" icon located at the top right

Facility ID	FEI	Facility DUNS	Facility Name	Latest Facility Status /As of Date / Recommendation Reason	Profile Code	Facility Drug Supply Chain Role	Compliance Status / Alert Date	Compliance Status Change Reason
110001856	3010885632	985066780	BIOMARIN INTERNATIONAL LIMITED	No Evaluation Necessary 1 /6 /2021	SVL SMALL VOLUME PARENTERAL, LYOPHILIZED	**Product Supply Chain:** LABELER: VOSORITIDE SECONDARY PACKAGER: VOSORITIDE RELEASE TESTER: VOSORITIDE	Compliant	
(b) (4)				Approve Facility 1 /6 /2021 Based on Profile	LBI LABORATORY, BIOLOGICAL TESTING	**Substance Supply Chain:** RELEASE TESTER: VOSORITIDE	Compliant	
				Approve Facility 1 /6 /2021 Based on Profile	LMN LABORATORY, MICROBIOLOGICAL - NON-STERILITY TESTING	**Substance Supply Chain:** RELEASE TESTER: VOSORITIDE	Compliant	
				Approve Facility 1 /5 /2021 District Recommendation	SVL SMALL VOLUME PARENTERAL, LYOPHILIZED	**Product Supply Chain:** MANUFACTURER: VOSORITIDE PACKAGER: VOSORITIDE SECONDARY PACKAGER: VOSORITIDE RELEASE TESTER(IN PROCESS): VOSORITIDE STABILITY TESTER: VOSORITIDE STERILITY TESTER: VOSORITIDE RELEASE TESTER: VOSORITIDE LABELER: VOSORITIDE	Compliant	
				Approve Facility 1 /6 /2021 Based on File Review	LBI LABORATORY, BIOLOGICAL TESTING	**Substance Supply Chain:** RELEASE TESTER: VOSORITIDE MANUFACTURER: VOSORITIDE STORER: VOSORITIDE	Compliant	
				Approve Facility 1 /6 /2021 Based on File Review	LMN LABORATORY, MICROBIOLOGICAL - NON-STERILITY TESTING	**Substance Supply Chain:** RELEASE TESTER: VOSORITIDE MANUFACTURER: VOSORITIDE STORER: VOSORITIDE	Compliant	
				Approve Facility 1 /6 /2021 Based on Profile	LBI LABORATORY, BIOLOGICAL TESTING	**Substance Supply Chain:** RELEASE TESTER: VOSORITIDE MANUFACTURER: VOSORITIDE STORER: VOSORITIDE	Compliant	
				Approve Facility 1 /6 /2021	LMN LABORATORY, MICROBIOLOGICAL - NON-STERILITY TESTING	**Substance Supply Chain:** RELEASE TESTER: VOSORITIDE MANUFACTURER: VOSORITIDE STORER: VOSORITIDE	Compliant	

(b) (4)	Based on Profile			
	Approve Facility 1/6/2021 Based on File Review	LCP LABORATORY, CHEMICAL/PHYSICAL TESTING	**Product Supply Chain:** RELEASE TESTER: VOSORITIDE RELEASE TESTER(IN PROCESS): VOSORITIDE STABILITY TESTER: VOSORITIDE STERILITY TESTER: VOSORITIDE	Compliant
	Approve Facility 1/6/2021 Based on File Review	LMN LABORATORY, MICROBIOLOGICAL - NON-STERILITY TESTING	**Product Supply Chain:** RELEASE TESTER: VOSORITIDE RELEASE TESTER(IN PROCESS): VOSORITIDE STABILITY TESTER: VOSORITIDE STERILITY TESTER: VOSORITIDE	Compliant
	Approve Facility 1/6/2021 Based on File Review	LMS LABORATORY, MICROBIOLOGICAL - STERILITY TESTING	**Product Supply Chain:** RELEASE TESTER: VOSORITIDE RELEASE TESTER(IN PROCESS): VOSORITIDE STABILITY TESTER: VOSORITIDE STERILITY TESTER: VOSORITIDE	Compliant
	Approve Facility 1/5/2021 District Recommendation	SVT TERMINALLY STERILIZED SMALL VOLUME PARENTERAL DRUG	**Product Supply Chain:** RELEASE TESTER(IN PROCESS): VOSORITIDE MANUFACTURER: VOSORITIDE STABILITY TESTER: VOSORITIDE PACKAGER: VOSORITIDE STERILITY TESTER: VOSORITIDE RELEASE TESTER: VOSORITIDE	Compliant
	Approve Facility 4/8/2021 District Recommendation	CFN NON-STERILE API BY FERMENTATION	**Product Supply Chain:** RELEASE TESTER: VOSORITIDE STABILITY TESTER: VOSORITIDE **Substance Supply Chain:** MANUFACTURER: VOSORITIDE RELEASE TESTER: VOSORITIDE STORER: VOSORITIDE	Compliant
	Approve Facility 1/6/2021 Based on Profile	LCP LABORATORY, CHEMICAL/PHYSICAL TESTING	**Product Supply Chain:** RELEASE TESTER: VOSORITIDE STABILITY TESTER: VOSORITIDE **Other Supply Chain:** RELEASE TESTER(PACKAGE)	Compliant
	Approve Facility 1/6/2021 Based on Profile	LCP LABORATORY, CHEMICAL/PHYSICAL TESTING	**Product Supply Chain:** RELEASE TESTER: VOSORITIDE STABILITY TESTER: VOSORITIDE	Compliant
	Approve Facility 1/6/2021 Based on Profile	IDD INJECTABLE DELIVERY DEVICE	**Other Supply Chain:** MANUFACTURER(PACKAGE)	Compliant

Thus, the overall manufacturing inspection recommendation (OMIR) from the Office of Process Manufacturing Assessment (OPMA) for this NDA is approval. The Panorama screen shot facility assessment recorded on 4/17/2021 is shown below. For additional details, please refer to Process/facility review in Panorama dated 4/13/2021.

Environmental assessment: The applicant sought exemption from environmental impact analysis per 21CFR 25.31(b) and 25.21 as the action on this NDA may not significantly affect the quality of the human environment. The estimated concentration of the drug substance at the point of entry into the aquatic environment would be below 0.1part per billion (0.1 ppb). Dr. Mohamadi granted categorical exclusion from submitting environmental assessment. Please refer to drug product review dated 4/14/21 for additional information.

Container and Carton Label Review: The drug product reviewer completed review of the container and carton label. Labeling comments will be resolved during OND labeling review. Refer to the Dr. Mohamadi's labeling review dated 4/14/2021 for additional information.

CDRH consult to review: A CDRH consult to review device related data and information in sections 3.2.P.7 and 3.2.R including user requirements, design control and verification, 510K clearance, biocompatibility, dose accuracy of administration syringe (b) (4) syringe with 30G (b) (4) retractable needle. (b) (4)), 1.5mL pre-filled diluent syringe. (b) (4) needle (b) (4) used for diluent syringe) and risk management. CDRH review concluded that the device part of the combination product is approvable for the proposed indication. There are no outstanding device related deficiencies. For details, please refer to Ms. Florencia Wilson's review in DARRTS dated 1/8/2021 under NDA 214938.

OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, process, facility, microbiology, and environmental analysis sections of this NDA. The OPQ overall recommendation for NDA 214938 is approval.

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Muthukumar Ramaswamy, Ph.D. 5/25/2021

Application Technical Lead Name and Date

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: This review is based on the most recent amendment, (0043(43) 04/08/2021), which may not reflect the final version of labeling. The labeling appears adequate after recommended changes are made.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	VOXZOGO	Adequate
Established name(s)	vosoritide	Adequate
Route(s) of administration	Injection	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	0.4 mg, 0.56 mg, and 1.2 mg lyopjilized powder in a single-dose vial	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		

APPEARS THIS WAY ON ORIGINAL

Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4)  • Check if correct VOXZOGO strength and prefilled diluent syringe co-pack is selected based on the patient's body weight. • Remove VOXZOGO vial and prefilled diluent syringe (Sterile Water for Injection, USP) from the refrigerator and let them reach room temperature before reconstituting VOXZOGO. • Attach the diluent needle provided with ancillary supplies to the diluent prefilled syringe (b) (4) • Inject the entire diluent prefilled syringe volume into the vial. • Gently swirl the diluent in the vial until the white powder is completely dissolved. Do not shake. • Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Once reconstituted VOXZOGO is a clear, colorless to yellow liquid. The solution should not be used if discolored or cloudy, or if particles are present. • After reconstitution, VOXZOGO can be held in the vial at a room temperature 68°F to 77°F (20°C to 25°C) for a maximum of 3 hours. • For administration, extract the required dose volume from the vial using the supplied administration syringe. Discard any unused portion. Do not pool unused portions from the vials. Do not administer more than 1 dose from a vial. Do not mix with other medications.	Adequate per revision: Change to: 20°C to 25°C (68°F to 77°F)

	Instructions for Subcutaneous Administration See Instructions for Use document for detailed, illustrated instructions. • (b) (4) • Slowly withdraw the dosing volume of the reconstituted VOXZOGO solution from the single dose vial into a syringe. • Rotate sites for subcutaneous injections. • The recommended injection sites for VOXZOGO are: the front middle of the thighs, the lower part of the abdomen at least 2 inches (5 centimeters) away from the navel, top of the buttocks or the back of the upper arms. The same injection area should not be used on two consecutive days. Do not inject VOXZOGO into sites that are red, swollen, or tender.	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

APPEARS THIS WAY ON ORIGINAL

<table>
<tr><th>Item</th><th>Information Provided in the NDA</th><th>Assessor's Comments</th></tr>
<tr><td colspan="3">DOSAGE FORMS AND STRENGTHS section</td></tr>
<tr><td>Available dosage form(s)</td><td>Lyophilized powder</td><td>Adequate</td></tr>
<tr><td>Strength(s) in metric system</td><td>For Injection: 0.4 mg, 0.56 mg, or 1.2 mg as a white to yellow lyophilized powder for reconstitution in a single-dose vial.</td><td>Adequate</td></tr>
<tr><td>If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance</td><td>N/A</td><td>Adequate</td></tr>
<tr><td>A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting</td><td>None</td><td>Adequate per revision

Adding:

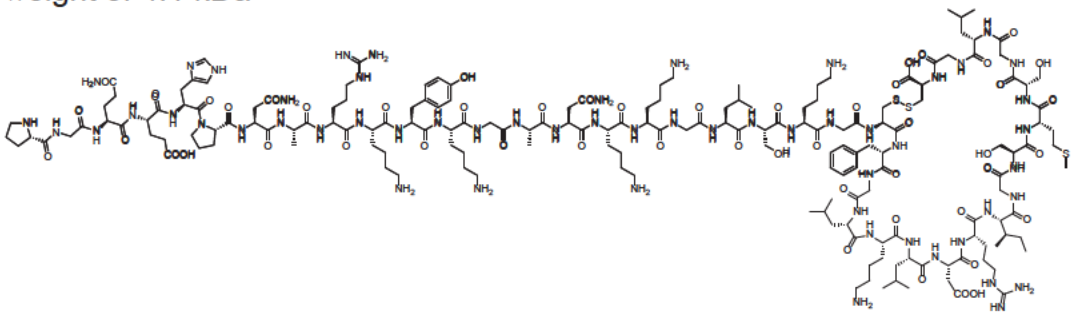
<table><tr><th>Strength (mg)</th><th>Diluent (mL)</th><th>Flip Cap Color</th></tr><tr><td>0.4</td><td>0.5</td><td>White</td></tr><tr><td>0.56</td><td>0.7</td><td>Magenta</td></tr><tr><td>1.2</td><td>0.6</td><td>Grey</td></tr></table></td></tr>
<tr><td>Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"</td><td>N/A</td><td>Adequate</td></tr>
<tr><td>For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.</td><td>Single-dose</td><td>Adequate</td></tr>
</table>

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

<table>
<tr><th>Item</th><th>Information Provided in the NDA</th><th>Comments</th></tr>
<tr><td colspan="2">DESCRIPTION section</td><td></td></tr>
<tr><td>Proprietary and established name(s)</td><td>VOXZOGO (vosoritide)</td><td>Adequate</td></tr>
<tr><td>Dosage form(s) and route(s) of administration</td><td>Injection</td><td>Adequate</td></tr>
<tr><td>If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.</td><td>N/A</td><td>Adequate</td></tr>
<tr><td>List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.</td><td>Trehalose dihydrate, mannitol, sodium citrate dihydrate, methionine, citric acid monohydrate, and polysorbate 80</td><td>Adequate</td></tr>
<tr><td>For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.</td><td>
<table>
<tr><th>Strength</th><th>Inactive Ingredients per Vial</th></tr>
<tr><td>VOXZOGO 0.4 mg/0.5 mL per vial (0.8 mg/mL)</td><td>Trehalose dihydrate (29.01 mg), mannitol (7.5 mg), sodium citrate dihydrate (0.54 mg), methionine (0.36 mg), citric acid monohydrate (0.14 mg), and polysorbate 80 (0.025 mg). After reconstitution the nominal deliverable volume is 0.4 mL.</td></tr>
<tr><td>VOXZOGO 0.56 mg/0.7 mL per vial (0.8 mg/mL)</td><td>Trehalose dihydrate (40.61 mg), mannitol (10.50 mg), sodium citrate dihydrate (0.76 mg), methionine (0.51 mg), citric acid monohydrate (0.20 mg), and polysorbate 80 (0.035 mg). After reconstitution the nominal deliverable volume is 0.6 mL.</td></tr>
<tr><td>VOXZOGO 1.2 mg/0.6 mL per vial (2 mg/mL)</td><td>Trehalose dihydrate (34.81 mg), mannitol (9 mg), sodium citrate dihydrate (0.65 mg), methionine (0.44 mg), citric acid monohydrate (0.17 mg), and polysorbate 80 (0.030 mg). After reconstitution the nominal deliverable volume is 0.5 mL.</td></tr>
</table>
</td><td>Adequate per revision:

Adding: Trehalose dihydrate and D-Mannitolis are used as a isotonic agent. Also, citric acid monohydrate and sodium citrate dihydrate are used as a buffering agent.</td></tr>
</table>

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Adequate
Statement of being sterile	Sterile	Adequate
Pharmacological/ therapeutic class	Missing	Adequate
Chemical name, structural formula, molecular weight	Vosoritide has a chemical formula of $C_{176}H_{290}N_{56}O_{51}S_3$ with a molecular weight of 4.1 kDa 	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	Adequate
Other important chemical or physical properties (such as pKa or pH)	N/A	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	Adequate
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X,"	N/A	Adequate

“structurally unique molecular entity”		

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

<table>
<tr><th>Item</th><th>Information Provided in the NDA</th><th>Assessor's Comments</th></tr>
<tr><td colspan="3">HOW SUPPLIED/STORAGE AND HANDLING section</td></tr>
<tr><td>Available dosage form(s)</td><td>Lyophilized powder for injection</td><td>Adequate</td></tr>
<tr><td>Strength(s) in metric system</td><td>
<table>
<tr><th>Strength (mg)</th><th>Diluent (mL)</th><th>Co-pack NDC Number</th><th>Flip Cap Color</th></tr>
<tr><td>0.4</td><td>0.5</td><td>NDC 68135-082-36</td><td>White</td></tr>
<tr><td>0.56</td><td>0.7</td><td>NDC 68135-119-66</td><td>Magenta</td></tr>
<tr><td>1.2</td><td>0.6</td><td>NDC 68135-181-93</td><td>Grey</td></tr>
</table>
</td><td>Adequate</td></tr>
<tr><td>Available units (e.g., bottles of 100 tablets)</td><td>VOXZOGO for injection is a lyophilized powder for reconstitution and is provided as a co-pack which includes ten; sterile, single-dose 2 mL glass vials containing VOXZOGO, either 0.5 mL, 0.6 mL or 0.7 mL diluent (Sterile Water for Injection, USP) in a single-dose prefilled syringe, diluent transfer needles (23 gauge) and single-dose administration syringes (30 gauge) both with needle retraction safety devices.</td><td>Adequate</td></tr>
<tr><td>Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number</td><td>
<table>
<tr><th>Strength (mg)</th><th>Diluent (mL)</th><th>Co-pack NDC Number</th><th>Flip Cap Color</th></tr>
<tr><td>0.4</td><td>0.5</td><td>NDC 68135-082-36</td><td>White</td></tr>
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</table>
</td><td>Adequate</td></tr>
</table>

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose	Adequate

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Reconstituted VOXZOGO must be administered within 3 hours of reconstitution Record the starting date of room-temperature storage clearly on the unopened product carton. Do not use beyond expiration date on the label. Store in the original package to protect from light.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant	N/A	Adequate

has a warning such as “Do not eat.”		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Refrigerate VOXZOGO vials at 36°F to 46°F (2°C to 8°C) VOXZOGO can be stored at room temperature 68°F to 77°F (20°C to 25°C); excursions permitted to 15°C to 30°C (59°F to 86°F) for 90 days. Do not return VOXZOGO to the refrigerator once stored at room temperature.	Adequate per revision change to Refrigerate VOXZOGO vials at 2°C to 8°C (36°F to 46°F) VOXZOGO can be stored at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) for 90 days. Do not return VOXZOGO to the refrigerator once stored at room temperature.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	Adequate
Include information about child-resistant packaging	N/A	Adequate

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by: BioMarin Pharmaceutical Inc. Novato, CA 94949	Adequate per revision. Change to: Manufactured for: BioMarin Pharmaceutical Inc. 105 Digital Drive, Novato, CA 94949

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): N/A

3.0 CARTON AND CONTAINER LABELING

(b) (4)

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	VOXZOGO™ (vosoritide) for injection	Adequate
Dosage strength	0.4, 0.56, and 1.2 mg per vial	Adequate
Route of administration	For injection	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	Adequate
Net contents (e.g. tablet count)	N/A	Adequate
"Rx only" displayed on the principal display	**Rx Only**	Adequate
NDC number	NDC 68135-181-93 lyophilized powder NDC 68135-158-17 Sterile water for injection	Adequate
Lot number and expiration date	PC 00368135181934 SN LOT EXP	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store in refrigerator at 36°F to 46°F (2°C to 8°C). Do not freeze. Voxzogo may be stored at room temperature between 68°F to 77°F (20°C to 25°C) for up to 90 days in the original carton to protect from light. Once stored at room temperature, do not return to the refrigerator. Discard if unused within 90 days.	Adequate after revision: Change to: 2 °C to 8 °C (36 °F to 46 °F), and 20 °C to 25 °C (68 °F to °77 F)

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Adequate
Bar code	(b) (4)  (b) (4)	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured by: BioMarin Pharmaceutical Inc Novato, CA 94949	Adequate per revision. Change to: Manufactured for
Medication Guide (if applicable)	(b) (4) See Prescribing Information. Reconstitute only with diluent provided. Contains no preservatives. After reconstitution use within 3 hours. Discard any unused solution.	Adequate
No text on Ferrule and Cap overseal	N/A	Adequate
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	Adequate
And others, if space is available	None	Adequate

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date:

Ali Mohamadi, Ph.D., 4/12/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):

128 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Ali Mohamadi

Digitally signed by Ali Mohamadi
Date: 4/14/2021 10:25:09AM
GUID: 508da6ea0002750ec7c6cb7cfc37f10e

David Claffey

Digitally signed by David Claffey
Date: 4/14/2021 11:09:08AM
GUID: 508da71e00029e20b201195abff380c2
Comments: labeling will undergo further review when amended labeling is submitted for team assessment

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MUTHUKUMAR RAMASWAMY
05/25/2021 02:51:36 PM