

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217159Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number.	217159		
Applicant Name	BioLineRx, Ltd.		
Drug Product Name	Aphexda (motixafortide)		
Dosage Form.	Injection, powder, lyophilized, for solution		
Proposed Strength(s)	62 mg		
Route of Administration	Subcutaneous		
Maximum Daily Dose	75 mg, see clinical review.		
Rx/OTC Dispensed	Rx		
Proposed Indication	Indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma.		
Drug Product Description	Lyophilized powder in a (b) (4) glass vial with (b) (4) rubber stopper and aluminum crimp seal.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	2°C to 8°C, Store in original carton to protect from light.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Daniel Jansen OPQ/ONDP/DNDAPI/NDB3	Zhengfu Wang OPQ/ONDP/DNDAPI/NDB3



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	<i>Drug Product/ Labeling</i>	George Ward OPQ/ONDP/DNDPIII/NDPB5	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5
	<i>Manufacturing</i>	Zhouxi Wang OPQ/OPMA/DPMIII/PMB9	Kamal Tiwari OPQ/OPMA/DPMIII/PMB9
	<i>Biopharmaceutics</i>	N/A	
	<i>Microbiology</i>	Yuansha Chen OPQ/OPMA/DMAI/MAB2	Nandini Bhattacharya OPQ/OPMA/DMAI/MAB2
	<i>Other (specify):</i>	N/A	
	<i>RBPM</i>	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	<i>ATL</i>	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: A shelf life of 24 months is granted for the drug product when stored at 2°C to 8°C.

b. Additional Comments for Action Letter: None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1.) Background

BioLineRx has submitted a 505(b)(1) NDA seeking marketing approval for motixafortide, a synthetic peptide indicated for use in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize (b) (4) hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma. In



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support of approval, the Applicant has submitted the results of a single pivotal Phase 3 study and other supporting clinical, nonclinical, and other studies.

2.) Drug Substance

The motixafortide drug substance is a synthetic amino acid cyclic peptide composed of fourteen amino acids (ten natural and four unnatural). The drug substance is manufactured as an acetate salt, (b) (4)

(b) (4) The peptide is acylated on the N-Terminus with a 4-fluorobenzoyl group and has a disulfide bridge between cysteine residues at positions 4 and 13.

Motixafortide drug substance is a white to off-white hygroscopic powder and is freely soluble in water. The drug substance manufacturing process, control strategy and specifications were found to be adequate to support the quality of the drug substance. A re-test period of (b) (4) months is proposed based on real time stability data.

3.) Drug Product

The drug product is manufactured as a single strength of 62 mg/vial, based with a gross content of 73 mg/vial. Prior to administration, the drug product is reconstituted with 2 mL of half normal saline that is not a part of the drug product, which includes an excess volume permitting withdrawal of up to 1.7 mL per vial of a solution containing 36.5 mg/mL motixafortide. The drug product is manufactured (b) (4) (b) (4) which contains 73 mg motixafortide and 26 mg mannitol in (b) (4) mL of water for injection, adjusted for pH. The drug product specification includes appropriate tests to ensure the quality and potency of the drug product. The drug product is packaged in (b) (4) glass vials with (b) (4) (b) (4) rubber stoppers. The Applicant provided up to 48 months stability data for the designated primary batches; however, due to a change in manufacturing (b) (4) the stability data for these batches was deemed to be supportive. Therefore, a shelf life of 24 months is granted based on 12 months of stability data for three batches manufactured using the commercial manufacturing process.

4.) Manufacturing

Process -The manufacturing of the drug product includes (b) (4) (b) (4) The proposed commercial manufacturing batch size is the same as the executed batches, i.e., approximately (b) (4) vials of drug product. After the Applicant responded to information requests, including issues related to the manufacturing process and controls, equipment, and leachables, the manufacturing process was found to be adequate.



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Facilities – All facilities except for the drug product manufacturing facility were found to be approvable based on previous inspection history. A preapproval Inspection (PAI) of the drug product manufacturing facility, BioConnection B.V. (FEI: 3011445650), was conducted from 2/27/2023-3/7/2023 with an inspection outcome of Voluntary Action Indicated (VAI). The overall recommendation for the manufacturing process and facilities is Approval.

5.) Microbiology

The motixafortide drug product is a sterile, single-dose, lyophilized powder without preservative (b) (4)

After review of the Applicant’s responses to information requests covering microbiological aspects of drug product manufacturing, including sterilization of equipment, stopper depyrogenation, validation studies and runs, and media fills, the NDA is recommended for approval from the microbiology perspective.

6.) Quality Labeling

The quality labeling was reviewed and found to be adequate after final revisions are implemented by the Applicant.

7.) Environmental Assessment

The Applicant claimed a categorical exclusion from the requirements for environmental assessment in accordance with 21 CFR 25.31(b). This request is supported by the calculated EIC-Aquatic of (b) (4) ppb, which is well below 1 ppb. Therefore, this request is granted.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

- Drug Substance** - Adequate
- Drug Product** - Adequate
- Quality Labeling** - Adequate
- Manufacturing** - Adequate
- Biopharmaceutics** - N/A
- Microbiology** - Adequate

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments: N/A



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Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments: None.



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Carver

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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:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

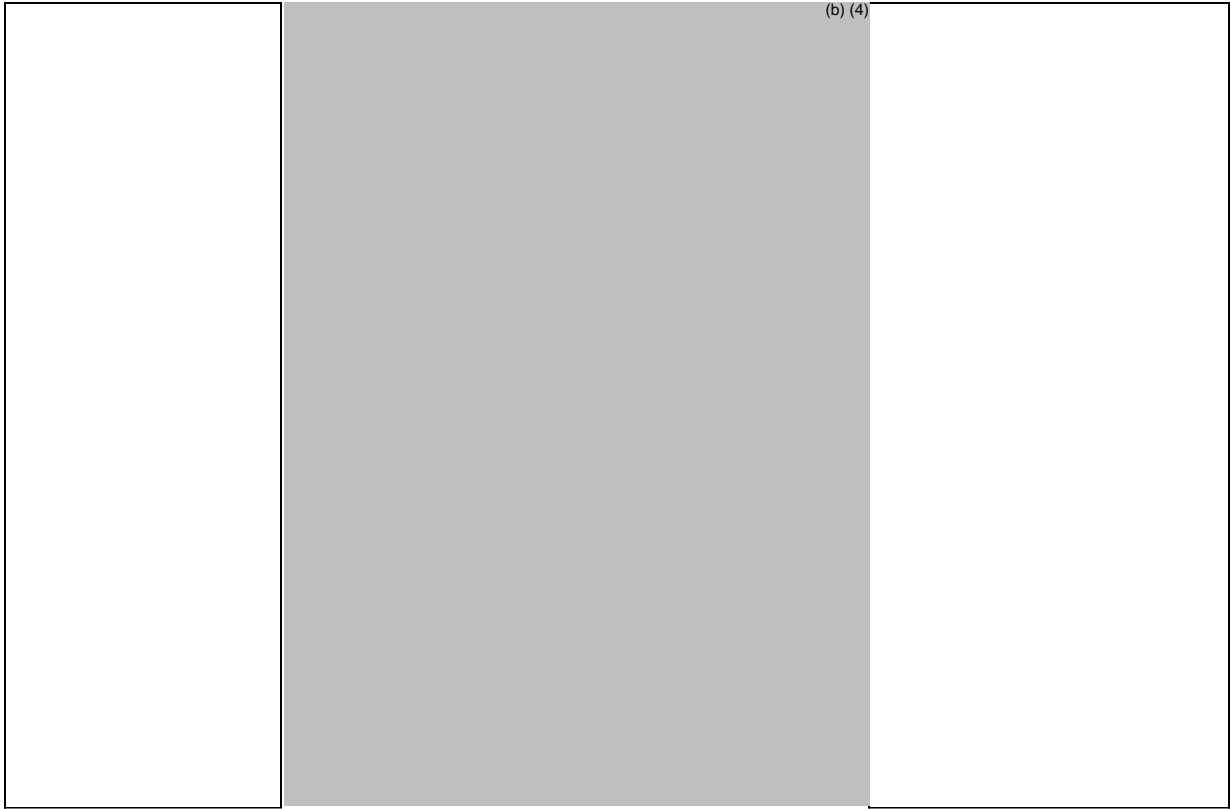
Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Aphexda	Adequate
Established name(s)	Aphexda, Motixafortide for Injection	Adequate
Route(s) of administration	Subcutaneous Injection	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	For Injection: (b) (4) mg (b) (4) (b) (4) as a lyophilized powder, in a single dose (b) (4) vial	Inadequate – update strength to 62 mg to reflect the change in total amount available to remove from the vial.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	N/A
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)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
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)	<i>Concomitant Medication</i> Administer (b) (4) 10 (b) (4) kg once daily for 4 days prior to the first dose of APHEXDA and on each day prior to each apheresis (b) (4)	Inadequate – Section 2 needs to be updated with new dosing directions. Only 1.7 mL should be removed from the reconstituted solution. The maximum dosage that can be taken from one vial is now 62 mg.



1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4) (b) (4) as a white to off-white lyophilized powder in a single-dose (b) (4) vial for reconstitution.	Inadequate – deleted (b) (4) Update with new strength of 62 mg
Strength(s) in metric system	Not stated	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Acetate salt; Strength is expressed (b) (4) per FDA Guidance.	Inadequate – edited to incorporate variable acetate salt amount in the drug substance.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	See above.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	N/A
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.	Single-dose	Adequate

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

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.	See first paragraph above	Inadequate – Change list of ingredients to list amounts first and list inactive ingredients in alphabetical order
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	Adequate	Adequate
Pharmacological/therapeutic class	Not provided	Inadequate – Lacking from section
Chemical name, structural formula, molecular weight	See above	Inadequate – Chemical name and molecular weight is not provided. Only linear amino acid structural formula.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A	N/A

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	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	N/A

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Lyophilized powder	Adequate
Strength(s) in metric system	Not listed in this section	Adequate
Available units (e.g., bottles of 100 tablets)	N/A	N/A
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White to off-white lyophilized powder in a single-dose (b) (4) vial	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
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.)	Protect from light	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	(b) (4)	Inadequate – (b) (4) (b) (4)
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.”	Not made with natural rubber latex	Adequate
Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 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 for: BioLineRx Ltd Modi'in, Israel Distributed by: BioLineRx USA Inc 625 Massachusetts Avenue Cambridge, MA 02139 USA	Adequate

2.0 PATIENT LABELING

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

The product is to be administered by healthcare professionals only.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Copy/paste or refer to a representative example of a proposed container)

(b) (4)

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3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

(b) (4)

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	APHEXDA, motixafortide for injection	Adequate
Dosage strength	(b) (4) mg per vial	Inadequate – update to state new label strength of 62 mg
Route of administration	For subcutaneous Use Only	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Missing	Inadequate
Net contents (e.g. tablet count)	N/A	N/A
“Rx only” displayed on the principal display	Yes	Adequate
NDC number	Yes, see above	Adequate
Lot number and expiration date	Yes	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4)	Inadequate – (b) (4)
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose vial	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	Adequate
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	Yes	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	N/A
And others, if space is available		

Assessment of Carton and Container Labeling: {Adequate/Inadequate}

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

After the recommended revisions are made, the sections herein will be adequate for approval.

Primary Labeling Assessor Name and Date: George Ward

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



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George
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CHAPTER VII: MICROBIOLOGY

Product Information	This drug product is a sterile, lyophilized powder provided as 73 mg in 6 mL vials. This drug product is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize (b) (4) (b) (4) hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma.
NDA Number	217159
Assessment Cycle Number	001
Drug Product Name/ Strength	Motixafortide (proprietary name: APHEXDA) 73 mg lyophilized powder in 6 mL vials
Route of Administration	Subcutaneous injection
Applicant Name	BioLineRx, Ltd.
Therapeutic Classification/ OND Division	CDER/OND/OCHEN/DNH
Manufacturing Site	BioConnection B.V. Kloosterstraat 9 (b) (4), (b) (4) Oss, AB, The Netherlands, 05349 FEI: 3011445650
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary: This drug product is a sterile, lyophilized powder (b) (4) (b) (4). The drug product is single-dose and is not preserved. The drug product is reconstituted before administration to patients.

List Submissions being assessed:

Document(s) Assessed	Date Received
Seq-0000 (SDN 1)	09 September 2022
Seq-0003 (SDN 4)	18 October 2022
Seq-0004 (SDN 5)	04 November 2022
Seq-0006 (SDN 7)	08 November 2022
Seq-0010 (SDN 10)	29 November 2022
Seq-0014 (SDN 15)	14 December 2022
Seq-0016 (SDN 18)	20 January 2023
Seq-0023 (SDN 24)	23 February 2023

Seq-0026 (SDN 27)	28 March 2023
Seq-0027 (SDN 28)	05 April 2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: Information requests were sent to the applicant on 06 October 2022 and on 09 February 2023. The applicant responded on 18 October 2022 in Seq-0003 and on 23 February 2023 in Seq-0023. This information is reviewed here.

Concise Description of Outstanding Issues: None.

Supporting Documents:

(b) (4) A letter of authorization (LOA) dated 17 November 2021 was provided referencing DMF (b) (4) (b) (4) DMA recently reviewed DMF (b) (4) (b) (4) dated 22 August 2022 (adequate) and this review supports this submission.

Product Quality Microbiology Assessment

S DRUG SUBSTANCE

The drug substance is not sterile and, therefore, is not reviewed here.

Note to reviewer: The specification for microbial enumeration tests of the drug substance is NMT (b) (4) cfu/g total aerobic microbial count and NMT (b) (4) cfu/g total combined yeasts and molds. The endotoxin specification is NMT (b) (4) EU/mg.

P DRUG PRODUCT

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

The drug product is a sterile, white to off-white lyophilized powder provided in 6 mL vials. This drug product is single-dose and is not preserved. The drug product is reconstituted with half normal saline (0.45% sodium chloride) before administration to patients (*note to reviewer:* the drug product is not packaged with half normal saline).

The composition of the drug product is described in the table below (copied from [Description and Composition of Drug Product](#)):

Component	Function	Grade	Weight [mg/vial]
Motixafortide drug substance	Active pharmaceutical ingredient	GMP	73 ¹
Mannitol (b) (4)	(b) (4)	USP/ Ph.Eur	(b) (4) 26
Hydrochloric Acid solution (b) (4)		USP/ Ph.Eur	q.s. to pH (b) (4)

(b) (4)

The container closure components are described in the table below (copied from [Container Closure System](#)):

Packaging Component	Packaging Material	DMF Number	Reference to Standard	Drawing	Manufacturer
Vial	(b) (4) glass	(b) (4)	Ph. Eur./USP/JP	Figure 1	(b) (4)
Stopper	(b) (4)		Ph. Eur./USP/NF	Figure 2	
Cap			Ph. Eur./USP/JP	Figure 3	

(b) (4)

Assessment: Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)



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