

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218709Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	4		



Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number.	218709		
Applicant Name	X4 Pharmaceuticals		
Drug Product Name	XOLREMDI (mavorixafor)		
Dosage Form.	Capsule		
Proposed Strength(s)	100 mg		
Route of Administration	Oral		
Maximum Daily Dose	(b) (4)		
Rx/OTC Dispensed	Rx		
Proposed Indication	Indicated for the treatment of Warts, Hypogammaglobulinemia, Infections and Myelokathexis (WHIM) syndrome in (b) (4) patients 12 years of age and older.		
Drug Product Description	size 1 opaque hard gelatin capsules with white body and light blue cap. The white capsule body is axially imprinted with "100 mg" in black ink, and the light blue capsule cap is axially imprinted with "MX4" in black ink.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	2 °C to 8°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Stephanie Springer	Sithamalli Chandramouli
	<i>Drug Product/ Labeling</i>	Akm Khairuzzaman	Theodore Carver
	<i>Manufacturing</i>	Xueli Zhu	Erin Kim



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	4		



Template Revision: 03

	<i>Biopharmaceutics</i>	Min Sung Suh	Kevin Wei
	<i>Microbiology</i>	N/A	
	<i>Other (specify):</i>	N/A	
	<i>RBPM</i>	Mikee Aguirre	
	<i>ATL</i>	Theodore Carver	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

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

b. Additional Comments for Action

None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1. Background

X4 Pharmaceuticals has submitted NDA 218709 seeking marketing approval for mavorixafor (XP-001) 100 mg capsules, in accordance with Section 505(b)(1) of the Food, Drug, and Cosmetics Act. Mavorixafor is indicated for the treatment of Warts, Hypogammaglobulinemia, Immunodeficiency and Myelokathexis (WHIM) syndrome in (b) (4) patients 12 years of age and older, and this NDA has been granted Orphan Drug, Breakthrough Therapy, and Fast Track designations.



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	4		



Template Revision: 03

2. Drug Substance (Mavorixafor)

The drug substance is a synthetic small molecule with one stereocenter and is manufactured (b) (4). The synthesis, processes, and purification of the drug substance were found to be adequately controlled. The specification, analytical methods, and batch and stability data were found to support the drug substance quality. The limit for a single specified related substance, (b) (4), in the drug product specification is (b) (4)%, and this limit was confirmed to be qualified by the nonclinical review team. The stability data for three batches support a retest date of (b) (4) months.

3. Drug Product (Mavorixafor capsules)

The drug product is an immediate-release capsule containing 100 mg mavorixafor drug substance and several compendial excipients (USP/NF), including microcrystalline cellulose, dibasic calcium phosphate dihydrate, croscarmellose sodium, sodium stearyl fumarate, colloidal silicon dioxide, and sodium lauryl sulfate, gelatin capsules, titanium dioxide colorant, and ink, which are all present in acceptable amounts from the CMC perspective. The capsules are packaged in HDPE bottles containing a desiccant canister, (b) (4) child-resistant plastic screw cap. The drug product specification and analytical methods were found to be adequate, with acceptable batch analyses provided for a total of 13 drug product batches including three primary batches, and a total of ten clinical and supportive batches. Up to twenty-four (24) months of stability data (18 months from primary batches and 24 months from supportive batches) are submitted from long-term condition (5°C ± 3 °C), and six (6) months of accelerated data (25°C ± 2°C / 60% ± 5%) were provided for each batch. Based on these data, a shelf life of 24 months can be granted for the drug product when stored at 2° to 8°C (36° to 46°F).

4. Manufacturing

Process – The manufacturing process for the drug product consists of (b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4) the process information was

deemed adequate.

Facilities – All facilities are recommended for approval based on their previous inspection histories.



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	4		



Template Revision: 03

5. Biopharmaceutics

The biopharmaceutics review focused on the adequacy of the dissolution method and acceptance criteria in the drug product specification to support the quality of the drug product. Per BCS criteria, the drug substance is considered high solubility, and the final proposed (b) (4) dissolution method and acceptance criteria were deemed acceptable for quality control of the drug product.

6. Quality Labeling

Recommended changes in the drug product labeling that were identified have been communicated to the Applicant, and implementation of these changes will be confirmed in the final labeling.

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 - Adequate**
- Microbiology - N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

None.



Theodore
Carver

Digitally signed by Theodore Carver

Date: 3/05/2024 08:49:25PM

GUID: 5d963967007fd4bc3c9fab2a6c3eaded

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

CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s) ¹	Adequate	Proposed name: XOLREMDI™ (mavorixafor) capsules, for oral use
Route(s) of administration	Adequate	Oral
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Inadequate	(b) (4) Should be revised to: "Capsules: 100 mg mavorixafor"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	Not a tablet
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.	N/A	Not an injectable product
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient	Adequate	Strength is based on the active moiety

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

(e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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)	N/A	None
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	None
For parenteral products: include statement: <i>"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"</i>	N/A	Not a parenteral product.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another	N/A	There is no USP monograph.

section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	Not a radioactive product.
For hazardous products, include the statement <i>“DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.^x”</i> with x numerical citation to <i>“OSHA Hazardous Drugs”</i> .	N/A	Not applicable.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	The following information is provided: “Capsules: 100 mg (b) (4) ■ opaque hard gelatin capsules with white body and light blue cap. The white capsule body is (b) (4) imprinted with “100 mg” in black ink, and the light blue capsule cap is (b) (4) imprinted with “MX4” in black ink.”
Strength(s) in metric system	Adequate	Please see above
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	Not a salt

Continued on next page.....

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	See above in this table
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a tablet dosage form
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	Not an injectable product.

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	Provided as follows: "XOLREMDI is a hard gelatin capsule for oral administration."
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	Not a salt
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inadequate	Provided but not in alphabetical order
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.	N/A	Not a parenteral injectable dosage form.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	There is no alcohol in the formulation.
Sterility statement (if applicable)	N/A	Not a sterile product.
Pharmacological/Therapeutic class	Adequate	Provided as follows: "Mavorixafor is an orally (b) (4) CXC Chemokine Receptor 4 (CXCR4)"
Chemical name, structural formula, molecular weight	Adequate	Provided under section 11
If radioactive, statement of important nuclear characteristics.	N/A	Not a radioactive compound.

Other important chemical or physical properties (such as pKa or pH)	Adequate	provided under section 11 as follows: <i>“Mavorixafor is optically active and is a white to pale yellow to light brown solid. Mavorixafor is hygroscopic above relative humidities of 70%.</i> <i>Mavorixafor is freely soluble in methanol, 95% ethanol and n-octanol, soluble in toluene, sparingly soluble in DMSO and acetonitrile, and very slightly soluble in HPLC grade water according to the USP solubility criteria.</i> <i>Mavorixafor is soluble in pH 1.2 to 5.5 aqueous buffers and in pH 6.0 aqueous buffer, sparingly soluble in pH 6.8 aqueous buffer and slightly soluble in pH 7.5 aqueous buffer, according to the USP solubility criteria.”</i>
For oral prescription drug products, include gluten statement (if applicable)	N/A	None
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”)	N/A	None
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	There is no USP monograph.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Provided as follows: "XOLREMDI (b) (4) is supplied as a (b) (4) opaque white, hard gelatin capsule with a light blue cap, containing 100 mg of the active ingredient mavorixafor. The white capsule body is axially imprinted with "100 mg" in black ink, and the light blue capsule cap is axially imprinted with "MX4" in black ink."
Strength(s) in metric system	Adequate	Provided as follows: "XOLREMDI is (b) (4) (b) (4)"
Available units (e.g., bottles of 100 tablets)	Adequate	Provided as follows: 60 count (b) (4) – NDC 83296-100-60 120 count (b) (4) – NDC 83296-100-12
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Provided. See above in this table.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a tablet
For injectable drug products for parenteral 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.	N/A	Not an injectable product.

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.). For hazardous drugs, state “DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.” with x numerical citation to “OSHA Hazardous Drugs.”	Adequate	Provided as follows: (b) (4) <i>Keep bottle tightly closed. Store in and dispense from original container”</i>

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

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	The following statements are provided. “Store XOLREMDI refrigerated at 2° to 8°C (36° to 46°F)”
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: “<i>Not made with natural rubber latex. Avoid statements such as “latex-free.”</i>”	N/A	There is no “latex-free” statement in the labeling.
Include information about child-resistant packaging	Adequate	The container closure is child resistant.

1.2.5 Other Sections of Labeling

There is no other sections of labeling that contain product-quality related information such as warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenteral, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol].

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Container labeling has the following information: Manufactured for: X4 Pharmaceuticals, Inc. Boston, MA 02134

2.0 PATIENT LABELING

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

None

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels



3.2 Carton Labeling

There is no carton

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ² , (font size and prominence)	Adequate	(b) (4)
Strength(s) in metric system	Adequate	See above
Route(s) of administration	Adequate	(b) (4)
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	Adequate	Not a salt
Net contents (e.g., tablet count, volume of liquid)	Adequate	Provided
"Rx only" displayed on the principal display	Adequate	Provided
NDC	Adequate	Provided
Lot number and expiration date	Adequate	Provided
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Provided as follows: Store at 2° to 8°C (36° to 46°F). (b) (4) (b) (4) Keep bottle tightly closed. Store in and dispense from original container.
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	Inadequate	The product contains desiccant, but the bottle label does not include any warning.
For injectable drug products for parenteral 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, and these products require a "Not for direct infusion" statement.	N/A	Not a parenteral product
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Not a parenteral product

² Established name = [Drug] [Route of Administration] [Dosage Form]

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	
Name of manufacturer/distributor /packer	Adequate	Manufactured for: X4 Pharmaceuticals, Inc. Boston, MA 02134
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
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	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: {Inadequate}

Applicant should be informed to change their container labeling as follows:

1. Change your container label to include a statement as follows:
2. Include the following statement on the desiccant, (b) (4)

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

The overall labeling will be “Adequate” once the PI is updated with the recommended changes and the container label is updated with the suggested warning regarding the desiccant.

Primary Labeling Assessor Name and Date: Akm Khairuzzaman, Ph.D. 12/05/2023

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Theodore Carver, Ph.D., 12/05/2023*



Akm
Khairuzzaman

Digitally signed by Akm Khairuzzaman
Date: 2/27/2024 10:04:18AM
GUID: 502d1ab500002aef5afaa6f74ddf7e69



Theodore
Carver

Digitally signed by Theodore Carver
Date: 2/27/2024 10:38:02AM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

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

CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see [Chapter VI \(Biopharmaceutics\) of the NDA IQA Guide](#)

Product Information	
NDA Number	218709
Assessment Cycle Number	1
Drug Product Name/ Strength	Mavorixafor Capsule, 100 mg
Route of Administration	Oral
Applicant Name	X4 Pharmaceuticals Inc.
Therapeutic Classification/ OND Division	Division of Non-Malignant Hematology
RLD/RS Number	N/A, 505 (b)(1)
Proposed Indication	Treatment of Warts, Hypogammaglobulinemia, Infections and Myelokathexis (WHIM) syndrome in (b) (4) patients 12 years of age and older

Assessment Recommendation: Adequate

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #1	Comments



(b) (4)

(b) (4)

Mavorixafor is intended to treat (b) (4) patients with Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) syndrome and was granted orphan drug designation (10/10/2018), breakthrough therapy (11/08/2019), fast track (10/01/2020), and rare disease (12/04/2020). The recommended dose of mavorixafor is 400 mg (4×100mg) once a day for over 50 kg for (b) (4) patient 12 years and older and (b) (4) mg (b) (4) once a day for (b) (4) patients weighing ≤ 50 kg.

The clinical development program of mavorixafor includes 12 clinical studies. The 100 mg capsule formulation used in Phase 2 (X4P-001-MKKA) and 3 (X4P-001-103) clinical studies is the same as the proposed commercial formulation except for capsule color/print changes as shown in Table below.

Summary of capsule color and marking changes

Attribute	Phase 3 Clinical Studies	Primary Stability Batches	Commercial
Color	Cap: (b) (4) Body: white opaque	1 lot (bulk M11636): Cap: (b) (4) Body: white opaque	Cap: light blue opaque Body: white opaque
		2 lots (bulk M11789 and M11801): Cap: light blue opaque Body: white opaque	
Markings	(b) (4)	1 lot (bulk M11636): (b) (4)	MX4 100 mg
		2 lots (bulk M11789 and M11801): (b) (4)	

This Biopharmaceutics review was focused on the following aspects:

Quality control (QC) dissolution method and acceptance criterion: In the NDA, the Applicant proposed a dissolution method of USP Apparatus 2 (paddle) at (b) (4) 37°C for QC of mavorixafor capsules to ensure batch-to-batch consistency. The following critical bioavailability attributes (CBAs) were investigated to support the discriminating ability of the proposed method.

- Effect of process parameters (b) (4)
- Effect of changes in formulation
- Effect of particle size of drug substance

The discriminating ability of the proposed method was shown (b) (4) however, no significant effects of (b) (4) and particle size of drug substance on dissolution were observed. Based on the provided solubility data, mavorixafor is a high solubility drug substance as per BCS criteria. The Applicant was requested to provide complete dissolution profiles using USP Apparatus 2 (Paddle) at 50 rpm in 500 mL of 0.1N HCl at 37°C and batch information tested in the study via Information Request 1 (IR#1). In response to the IR#1 date 12/08/2023, the submitted dissolution data showed that the proposed drug product met the standard dissolution test (method (b) (4)) as per the 2018 FDA Dissolution Guidance. Therefore, the following standard method (b) (4) were determined appropriate for the proposed drug product.

- Dissolution method: USP Apparatus 2 (Paddle) at 50 rpm in 500 mL of 0.1N HCl at 37°C

The Applicant was recommended to implement the above standard methodology for the quality control of the proposed drug product via Information Request 2 (IR#2). The Applicant accepted and implemented the recommended dissolution method (b) (4) in response to the IR#2 dated 12/22/2023.

Overall, from a Biopharmaceutics perspective, NDA 218709 for Mavorixafor 100 mg Capsules is adequate and recommended for approval. The approved dissolution method and acceptance criterion are as follows.

Apparatus	USP Apparatus 2 (Paddle)
Medium	0.1N HCl
Volume	500 mL
Vessel Temperature	37 ± 0.5 °C
Paddle Speed	50 rpm
Acceptance Criterion	Q = (b) (4)% in 30 minutes

List of Submissions Being Assessed:

Document(s) Assessed	Date Received
Orig-1 NDA	08/31/2023
Response to IR#1 ¹	12/08/2023
Response to IR#2 ²	12/22/2023

Highlight Key Issues from Last Cycle and Their Resolution: None. This is the first review cycle.

¹ <\\CDSESUB1\EVSPROD\nda218709\0009\m1\us\response-to-information-request.pdf>

² <\\CDSESUB1\EVSPROD\nda218709\0017\m1\us\x4-response-to-information-request.pdf>

Concise Description of Outstanding Issues (list bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment: Adequate

Solubility: High

Mavorixafor has pH dependent solubility as shown in Table 1. It is highly soluble over the pH range (pH 1.2-6.8) and least soluble in pH 7.5 buffer (3.3 mg/mL).

Table 1. Solubility of mavorixafor at 37°C

Buffer	Solubility (mg/mL)
pH 1.2 HCl/KCl	> 70
pH 3.0 Acetate	> 70
pH 3.5 Acetate	> 70
pH 4.0 Acetate	> 70
pH 4.5 Acetate	> 70
pH 5.0 Acetate	> 70
pH 5.5 Acetate	> 70
pH 6.0 Acetate	56
pH 6.8 Phosphate	22

NOTE: Buffer systems which were clear solutions when samples for HPLC are reported as > 70.0 mg/mL

Permeability: Low

No permeability data of mavorixafor was provided but the pharmacokinetic parameter data in dogs and humans show slightly longer median T_{max} values (1.5-3.3 hrs) compared to BCS 1 drugs.

Based on the solubility data and Log P values of mavorixafor, the Applicant claims that Mavorixafor is a BCS Class 3 compound.

Dissolution: See “B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA”

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

➤ **Drug Product Background**

The proposed drug product is an immediate-release capsule that contains 100 mg of mavorixafor drug substance with mixing of excipients, dibasic calcium phosphate dihydrate (b) (4), microcrystalline cellulose (b) (4), croscarmellose sodium (b) (4), colloidal silicon dioxide (b) (4), sodium lauryl sulfate (b) (4) and sodium stearyl fumarate (b) (4) in a hard gelatin capsule. (b) (4) of mavorixafor has been identified, and mavorixafor drug substance is manufactured (b) (4)

revised the relevant sections of the original submission accordingly in response to IR#2 (12/22/2023).

Overall, based on the totality of the provided information and data, the standard method (b) (4) as per the 2018 FDA Dissolution Guidance are deemed acceptable for the quality control of Mavorixafor Capsules, 100 mg.

➤ **Dissolution Variability**

Variabilities in the dissolution data meet the recommendations (%CV < (b) (4)% at early time point and < (b) (4)% at other time points).

➤ **Dissolution Acceptance criteria**

The Applicant originally proposed a dissolution acceptance criterion of NLT (b) (4)% in 30 minutes that is in line with the recommended acceptance criterion of Q= (b) (4)% in 30 minutes (b) (4). The proposed acceptance criterion is found acceptable for the quality control of Mavorixafor Capsules, 100 mg as shown in Table 10.

Table 10. Recommended and proposed dissolution acceptance criteria

	Recommended	Proposed
Dissolution Acceptance Criterion	Q= (b) (4)% in 30 minutes	NLT (b) (4)% in 30 minutes

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Assessment: N/A

Mavorixafor Capsules, 100 mg comply with the standard methodology as per the 2018 FDA Guidance because of high solubility of mavorixafor drug substance.

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – In-Vitro Alcohol Dose Dumping

Assessment: N/A

The proposed drug product is an immediate-release capsule formulation.

B.11 EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Assessment: N/A

The proposed drug product is an immediate-release capsule formulation.

B.12 BRIDGING OF FORMULATIONS**Assessment: Adequate**

There are no significant differences between the clinical (used in Phase 2 and 3 clinical studies), registration/primary stability batches and commercial products (except for capsule color/print changes). No additional bridging is needed.

B. 13 BIOWAIVER REQUEST**Assessment: N/A**

The Applicant proposes only one strength (100 mg).

BIOPHARMACEUTICS LIST OF DEFICIENCIES**None**

Primary Assessor's Name and Date: Min Sung Suh, Ph.D. 02/10/2024

Secondary Assessor's Name and Date: Kevin Wei, Ph.D. 02/17/2024



Min Sung
Suh

Digitally signed by Min Sung Suh
Date: 2/16/2024 02:26:56AM
GUID: 5d418e82002882e44eb53342e324cad8



Kevin
Wei

Digitally signed by Kevin Wei
Date: 2/16/2024 07:56:23AM
GUID: 59e9fc4600508706ab6b474203201f10



Theodore
Carver

Digitally signed by Theodore Carver

Date: 3/05/2024 09:17:27PM

GUID: 5d963967007fd4bc3c9fab2a6c3eaded

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/

THEODORE E CARVER
03/05/2024 09:24:28 PM