

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216578Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: February 22, 2023
From: Hamid Shafiei, Ph.D.
Application Technical Lead, Branch IV
Division of New Drug Products 2
Office of New Drug Products

To: To Executive Summary, IQA for Assessment # 1 of NDA 216578

Subject: Amendment #1: Final Recommendation of Approval

In the Integrated Quality Assessment #1 (IQA #1) dated November 25, 2022 the approval of this application was pending the labeling/label negotiation to address the deficiency noted in the CMC labeling review # 1 dated November 25, 2022. The applicant has satisfactorily addressed the CMC labeling/label deficiency (refer to the updated labeling review attached as the appendix).

Therefore, from the OPQ perspective this application is now recommended for **approval** with the expiration dating period of **30 months**.

Application Technical Lead:
Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

APPENDIX

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:

(b) (4)

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	Fezolinetant Tablets
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	Adequate	Fezolinetant Tablets, 45 mg

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

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”.	N/A	Not scored 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 injectable.
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 (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	Not a salt.

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,	N/A	Tablet doesn’t require special preparation.

storage conditions needed to maintain the stability of the reconstituted or diluted product)		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Do not crush, cut, or chew the tablets.
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 drug.
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 11).	N/A	No USP Monograph.
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.”</i> ^x with x numerical citation to “OSHA Hazardous Drugs”.	N/A	Not a hazardous product.
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1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)



(b) (4)

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	See above
Strength(s) in metric system	Adequate	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.
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	Round, light red, film-coated tablet, debossed with the company logo and '645' on the same side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not scored tablet.
For injectable drug products for parental 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.

Section 11 (DESCRIPTION)



(b) (4)

**QUALITY ASSESSMENT**

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	
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.	Adequate	Ferric oxide, hydroxypropyl cellulose, hypromellose, low-substituted hydroxypropyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.
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 an injectable.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	No alcohol.



QUALITY ASSESSMENT



Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	A (b) (4) small-molecule NK3 receptor antagonist.
Chemical name, structural formula, molecular weight	Adequate	(4-Fluorophenyl)[(8R)-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]methanone; C ₁₆ H ₁₅ FN ₆ O ₂ ; Mw 358.39.
If radioactive, statement of important nuclear characteristics.	N/A	Not a radioactive product.
Other important chemical or physical properties (such as pKa or pH)	Adequate	It is very slightly soluble in water (0.29 mg/mL).

Section 11 (DESCRIPTION) 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)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is	N/A	No USP Monograph.

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QUALITY ASSESSMENT



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fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

**QUALITY ASSESSMENT**

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	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	Bottles of 30 tablets Bottles of 90 tablets
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	round, light red, film-coated tablets, debossed with the Astellas logo and '645' on the same side. Bottles of 30 tablets with child resistant closure and desiccant, (NDC 0469-2660-30) Bottles of 90 tablets with child resistant closure and desiccant, (NDC 0469-2660-90)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a scored 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.



QUALITY ASSESSMENT



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	Tablet does not require special handling.
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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	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled 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: <i>"Not made with natural rubber latex. Avoid statements such as "latex-free."</i>	N/A	



QUALITY ASSESSMENT



Include information about child-resistant packaging	Adequate	child resistant closure
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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 review 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)

Distributed by:
Astellas Pharma US, Inc.
Northbrook, IL 60062

(b) (4) is a trademark of Astellas US LLC.

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	Distributed by: Astellas Pharma US, Inc. Northbrook, IL 60062

2.0 PATIENT LABELING



QUALITY ASSESSMENT



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

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**QUALITY ASSESSMENT**

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²	Adequate	(b) (4) (fezolinetant) tablets, for oral use
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	Store (b) (4) at room temperature between 68°F to 77°F (20°C to 25°C). (b) (4) (b) (4) Dispose of the unused medicine through a take-back option, if available. See www.fda.gov/drugdisposal.com for more information. Keep (b) (4) and all medicines out of the reach of children.
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.	Adequate	The applicant confirmed that desiccant bag has a “Do not eat” warning on it.
Active ingredient(s) (if applicable)	Adequate	fezolinetant

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



QUALITY ASSESSMENT



Alphabetical listing of inactive ingredients (if applicable)	Adequate	ferric oxide, hydroxypropyl cellulose, hypromellose, low-substituted hydroxypropyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Distributed by: Astellas Pharma US, Inc. Northbrook, IL 60062

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

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



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

**QUALITY ASSESSMENT**

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ³ , (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
“Rx only” displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	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, and these products require a “Not for direct infusion” statement.	N/A	

³ Established name = [Drug] [Route of Administration] [Dosage Form]

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QUALITY ASSESSMENT



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	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	



QUALITY ASSESSMENT



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
No text on Ferrule and Cap over seal, unless a cautionary statement is required.	Adequate	
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.	Adequate	

Assessment of Carton and Container Labeling: {Adequate}

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

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See [Carton/Container Labeling Specific Resources](#) for a presentation about inappropriate inconsistencies of product quality information between labeling.



QUALITY ASSESSMENT



If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

2.0 PATIENT LABELING

1. Provide a desiccant bag picture showing “Do not eat” warning and ensure the size and shape of the desiccant differs from the dosage form.

The applicant’s response:

The applicant confirmed that desiccant bag has a “Do not eat” warning on it. This is satisfactory.

Overall Assessment and Recommendation:

This application is deemed ready for approval in its present form per 21 CFR 314.125(b)(6) from the CMC labeling/labels perspective as the above deficiencies delineated under the “ITEMS FOR ADDITIONAL ASSESSMENT” are satisfactorily resolved.

Primary Labeling Assessor Name and Date: Baoqing Ma, Ph. D., 10/28/2022, 2/21/2023.

Secondary Assessor Name and Date: Hamid Shafier, Ph. D., 10/28/2022, 2/21/2023.



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Hamid
Shafiei

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Date: 2/22/2023 09:43:57AM
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/s/

HAMID R SHAFIEI
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RECOMMENDATION

☐ Approval
☒ Approval Pending Labeling Negotiations
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 216578 Assessment 1

Drug Product Name	Trade Name (fezolinetant)
Dosage Form	Tablet
Strength	45 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Astellas Pharma US, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA submission	06/22/2022	All
Labeling	07/21/2022	All
Labeling	07/28/2022	All
Response to Quality Information Request	08/11/2022	OPQ All
Response to Quality Information Request	10/03/2022	OPQ - ONDP
Proprietary Name Request	10/03/2022	All
Response to Quality Information Request	10/11/2022	OPQ – ONDP and OPMA
Proprietary Name Request	10/11/2022	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance Drug Product Manufacturing	Friedrich Burnett, Ph.D.	Lawrence Perez, Ph.D.
	Baoqing Ma, Ph.D.	Hamid Shafiei, Ph.D.
	Loqman Mohamed, Ph.D.	Vaikunth Prabhu, Ph.D.
Microbiology	Loqman Mohamed, Ph.D.	Vaikunth Prabhu, Ph.D.
Biopharmaceutics	Kalpna Paudel, Ph.D.	Tapash Ghosh, Ph.D.

Regulatory Business Process Manager	Dahlia Walter, M.S., PMP	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Xiaoqin Wu, Ph.D.	James Laurenson, Ph.D.



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Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
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NDA Executive Summary

1. Application/Product Information

NDA Number.	216578
Applicant Name	Astellas Pharma US, Inc.
Drug Product Name	Trade Name (fezolinetant)
Dosage Form.	Tablet
Proposed Strength(s)	45 mg
Route of Administration	Oral
Maximum Daily Dose	45 mg
Rx/OTC Dispensed	Rx
Proposed Indication	For the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause
Drug Product Description	Astellas Pharma US, Inc. has submitted the 505(b)(1) new drug application for Trade Name (fezolinetant) Tablets, 45mg. This drug product is intended for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. One 45mg tablet should be taken orally with or without food. The active ingredient, fezolinetant is a nonhormonal small molecule NK3 inhibitor. Fezolinetant has not been previously approved or marketed in the United States. Therefore, fezolinetant has been classified as a new molecular entity (NME). Trade Name (fezolinetant) is formulated as immediate release and is supplied round, light red, film-coated tablets, debossed with the Astellas logo and '645' on the same side. Each tablet contains 45mg of fezolinetant as the active ingredient and ferric oxide, hydroxypropyl cellulose, hypromellose, low-substituted hydroxypropyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide as inactive ingredients.



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	Trade Name (fezolinetant) will be packaged and marketed as 30 tablets and as 90 tablets with a desiccant in HDPE bottles with child-resistant caps. This drug product should be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature.” Based on the supporting stability data provided in the application, an expiration dating period of 30 months for this drug product is granted.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature.”		
Review Team	Discipline	Primary	Secondary
	Drug Substance	Friedrich Burnett, Ph.D.	Lawrence Perez, Ph.D.
	Drug Product/ Labeling	Baoqing Ma, Ph.D.	Hamid Shafiei, Ph.D.
	Manufacturing	Loqman Mohamed, Ph.D.	Vaikunth Prabhu, Ph.D.
	Biopharmaceutics	Kalpana Paudel, Ph.D.	Tapash Ghosh, Ph.D.
	Microbiology	Loqman Mohamed, Ph.D.	Vaikunth Prabhu, Ph.D.
	Environmental Assessment	Xiaoqin Wu, Ph.D.	James Laurenson Ph.D.
	RBPM	Dahlia Walter, M.S., PMP	
	ATL	Hamid Shafiei, Ph.D.	
Consults	N/A		



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2. Final Overall Recommendation -Approval pending successful labeling negotiations

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, fezolinetant and the drug product, Trade Name (fezolinetant) Tablets, 45mg.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC recommended changes to the labeling have been communicated to the Clinical Review Team and is pending the successful labeling negotiations with the applicant (see the CMC labeling deficiencies below).
- Based on the review of the applicant's environmental assessment report, the environmental assessment review team has concluded that no significant adverse environmental impacts are expected from the approval of this NDA. Therefore, FONSI is recommended for this application.

Therefore, this NDA is recommended for **approval** from the OPQ perspective the drug product expiration dating period of **30 months** pending successful labeling negotiations.

CMC labeling deficiencies pending the successful labeling negotiations:

Patient Labeling:

Provide a desiccant bag picture showing "Do not eat" warning and ensure the size and shape of the desiccant differs from the dosage form.

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



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Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Quality Labeling	-	Pending
Manufacturing	-	Adequate
Biopharmaceutics	-	Adequate
Microbiology	-	Adequate

Environmental Assessment: Review & FONSI - 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



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Shafiei

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QUALITY ASSESSMENT DATA SHEET

[IQA NDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)	(b) (4)	_____	_____	Adequate Information Provided in the NDA
	III			_____	_____	Adequate Information Provided in the NDA
	III			_____	_____	Adequate Information Provided in the NDA
	IV			_____	_____	Adequate Information Provided in the NDA

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B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description
N/A		

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

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CHAPTER III: ENVIRONMENTAL

[IQA NDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

Summary: During the IND phase (IND 130277), the applicant assessed the requirements for an environmental assessment (EA) of fezolinetant based on FDA's Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (USFDA 1998) and guidance on drugs with estrogenic, androgenic, or thyroid activity (USFDA, 2016), as well as several European Medicines Agency (EMA) guidances. Considering fezolinetant is expected to affect reproduction of vertebrate species, the applicant proposed to conduct a Tier 3 EA including a fish full life cycle study in zebrafish (*Danio rerio*). FDA agreed with the proposed plan. FDA then reviewed the subsequent full EA as well as the applicant's response to FDA information request (IR), and determined that the submitted information is sufficient to enable FDA to assess whether the proposed action to approve the application may significantly affect the quality of the human environment, per 21 CFR 25.15(a). FDA concludes that the proposed action would not significantly affect the environment. Thus, a finding of no significant impact (FONSI) is recommended. Due to the potential for adverse impacts, however, as well as uncertainties such as cumulative impact from other substances with a similar mechanism of action in the environment, the use of label/insert language addressing environmentally protective disposal practices is recommended for Sections 16 and 17 of the prescribing information, in the Medication Guide, and on relevant carton/container labels.

Environmental

Fezolinetant is a nonhormonal, selective neurokinin 3 (NK3) receptor antagonist for treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. By antagonizing NKB/NK3-mediated signaling, fezolinetant modulates kisspeptin, NKB and dynorphin (KNDy) neurons' activity in the thermoregulatory center in the hypothalamus. Fezolinetant is a new molecular entity, and is presented as 45 mg tablet to be administered orally.

The applicant filed an NDA for fezolinetant 45 mg tablet, on 22 June 2022. A full EA was submitted at that time pursuant to 21 CFR Part 25.

Prior to the NDA, under IND 130277, the applicant cited FDA's Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications

(USFDA 1998) and Guidance on Drugs with Estrogenic, Androgenic, or Thyroid Activity (USFDA, 2016), as well as several EMA guidances, and asked whether FDA agrees with a proposed study design of the fish study for the EA for fezolinetant, following a revised version of the Organization for Economic Co-operation and Development (OECD) 240 guideline. FDA agreed with the proposed plan.

In their original EA submitted under the NDA, the applicant provided experimental data obtained from OECD assays. They also provided additional information in their response to FDA IR. The following is a brief summary of the EA:

- The substance of interest for the EA was assessed. The applicant found that fezolinetant was extensively metabolized in humans. Only 1.1% of the administered dose was excreted unchanged (fezolinetant), while 61.7% of the administered dose was excreted as the major metabolite ES259564. This metabolite was found to have 9% the potency of the parent active substance (fezolinetant) at the hNK3 receptor, and has non-significant off-target activity. Four other minor metabolites were also identified in human urine and feces with minimal proportions and unknown pharmacological activities. Therefore, the EA only focused on fezolinetant.
- Physical and chemical characteristics and environmental depletion mechanisms were assessed in order to determine the predominant environmental compartment where the active substance would accumulate, and the extent of accumulation. Based on the physico-chemical properties as summarized in the table below, fezolinetant is predominantly present in neutral form over the environmentally relevant pH range. Exposure of the terrestrial compartment, sediment, and atmospheric compartment are expected to be negligible, and only the water compartment needs assessing. The biodegradation test results indicate that fezolinetant is not readily biodegradable in the environment. Its molecular structure also indicates that fezolinetant is unlikely to hydrolyze in the environment. The applicant concluded that no rapid, complete depletion mechanism was identified, and it is assumed that fezolinetant will persist in the environment.

Parameter	Result
Water solubility	0.29 mg/mL (pH 7.4)
Dissociation constant(s)	-1.58, 0.05, 0.87
Log octanol/water partition coefficient (Log K_{ow})	pH 5: 1.3; pH 7: 1.4; pH 9: 1.4

Vapor pressure (estimated)	1.21E-010 mm Hg (25°C); 1.61E-008 Pa (25°C)
Sorption/Desorption (K _{oc})	Sludge (n=2): 15.0 & 18.2 L/kg Soil (n=3): 145, 217 & 709 L/kg
Aerobic biodegradation	2-4% degradation in 28 days
Hydrolysis, photolysis, and metabolism	Not tested (not expected relevant)

- The expected introduction concentration (EIC) of fezolinetant into the aquatic environmental from patient use was calculated without including consideration of metabolism or environmental depletion mechanisms that could occur in the waste treatment process. The EIC was estimated to be (b) (4) ppb. The applicant also calculated the refined EIC by taking into consideration of the fraction of unchanged fezolinetant in excretion (1.1%) and the relative potency (9%) of its major metabolite which accounts for 61.7% of the administered dose in the excretion. The refined EIC was calculated to be (b) (4) ppb.
- The applicant evaluated the toxicity of the released fezolinetant to environmental organisms. Specifically, the zebrafish EOGRT assay ((b) (4)) concluded that among the obtained results, which revealed effects of fezolinetant on a range of endpoints and biomarkers assessed during the study, the F1 generation hatching success resulted in the lowest toxicity benchmark. A summary of the toxicity assays is shown in the following table:

Study	Test species	NOEC	EC ₅₀
Microbial Inhibition		1,000,000 µg/L	>1,000,000 µg/L
Algal growth inhibition	<i>Raphidocelis subcapitata</i>	10,000 µg/L	>10,000 µg/L
<i>Daphnia</i> reproduction	<i>Daphnia</i>	1,800 µg/L	>10,000 µg/L
Fish extended one generation reproduction test (EOGRT)	Zebrafish (<i>Danio rerio</i>)	0.1 µg/L	>1.0 µg/L
Sediment toxicity test	Midge	176 mg/kg dw	>346 mg/kg dw

- The applicant compared the EC₅₀ values derived from algae, *Daphnia*, fish, and sediment dwelling organisms to the refined EIC ((b) (4) ppb) for risk assessment. The EC₅₀/refined EIC ratios are all above the trigger of 10 for Tier 3 tests, with the lowest ratio being > (b) (4) for zebrafish EOGRT. Further, no effects were observed at the level of the refined EIC. The

applicant concluded that fezolinetant does not pose a risk to the environment and no further risk assessment is required.

Assessment: Adequate

The main goals of this review of the EA of fezolinetant, per 21 CFR 25.15(a) and (b), are to determine (1) whether the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment; and (2) if so, whether the proposed action will significantly affect the environment. Regarding the main findings of the EA:

- The substance of interest selection, which considered the extent of metabolism of the active moiety (fezolinetant) to less pharmacologically active compound (metabolite ES259564) and also provided a rationale for the decision as to which substance(s) will be studied, was appropriate based on FDA guidance (USFDA 1998), which notes that the EA should list the drug or biologic substance and the predominant structurally related substances (SRSs) expected to enter or exist in the environment.
- FDA agrees that based on the physical and chemical characteristics and environmental depletion mechanisms, neither a terrestrial or air environmental assessment is needed, and thus only the water compartment needs assessing. Fezolinetant was not considered to be readily biodegradable. One concern, therefore, is that the substance could persist and accumulate in the aquatic environment over a long term.
- The refined EIC (^{(b) (4)} ppb) of fezolinetant is reasonable based on the annual production and the pharmacological activity of the major metabolite relative to the active moiety, according to the Guidance for Industry (USFDA 1998).
- The summary of toxicity assays is reasonable, and FDA agrees with the NOEC data obtained from OECD assays to be used for risk assessment.
- The applicant concluded that fezolinetant does not pose a risk to the aquatic environment because the ratios of EC₅₀ values to the refined EIC are all higher than the assessment factor of 10 according to the Guidance for Industry (USFDA 1998). FDA notes, however, that the 1998 guidance, as with all FDA guidance documents, states that it is based on the current thinking at the time of publication, and that

alternative approaches can be used if such approaches satisfy the requirements of the applicable statute, regulations, or both. The 2016 FDA Questions and Answers guidance also provides updates in this regard. Using a standard assessment factor of 10 results in a predicted no-effect concentration (PNEC) of (b) (4) ppb. The applicant's refined EIC of (b) (4) ppb slightly exceeds this PNEC by a factor of (b) (4). Nevertheless, wastewater treatment and environmental dilution and degradation will result in lower actual concentrations in the aquatic environment downstream from wastewater treatment plant outfall areas, and at levels generally lower than the PNEC. Therefore, while there will likely be some impacts, FDA does not consider them to be significant.

- In conclusion, the reasonable worst-case analysis of the specific proposed action indicates that fezolinetant is not expected to significantly affect the quality of the human environment (per 21 CFR 25.21), as available data do not establish that, at the expected level of exposure, there is the potential for serious harm to the environment (per 21 CFR 25.21(a)). Nevertheless, the data indicate that some adverse environmental impacts might be possible from fezolinetant if used at the expected amount underlying the refined EIC, particularly in the wastewater treatment plant outfall areas of the aquatic environment where dilution and degradation are the lowest. In addition, there are uncertainties such as cumulative impact from other substances with a similar mechanism of action in the environment. Therefore, the use of label/insert language addressing environmentally protective disposal practices is recommended for Sections 16 and 17 of the prescribing information, in the Medication Guide, and on relevant carton/container labels.

Decision:

The EA is adequate. It contains sufficient information to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment. Based on an evaluation of the information provided in the EA and additional reports, and on the scientific validity of the conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA. Based on the information available to date, a FONSI is recommended for this application, along with recommendations for label/insert changes.

References

USFDA. 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application. Page 39 in Center for Biologics Evaluation and Research, editor. US Food and Drug Administration, Rockville, MD. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/environmental-assessment-human-drug-and-biologics-applications>

USFDA. 2016. Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity. Center for Drug Evaluation and Research. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/environmental-assessment-questions-and-answers-regarding-drugs-estrogenic-androgenic-or-thyroid>

Primary Environmental Assessor Name and Date: Xiaoqin Wu, November 22, 2022

Secondary Assessor Name and Date (and Secondary Summary, as needed): James P. Laurenson



James
Laurenson

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Wu

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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:

(b) (4)

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	Fezolinetant Tablets
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	Adequate	Fezolinetant Tablets, 45 mg

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

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”.	N/A	Not scored 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 injectable.
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 (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	Not a salt.

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,	N/A	Tablet doesn’t require special preparation.

storage conditions needed to maintain the stability of the reconstituted or diluted product)		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Do not crush, cut, or chew the tablets.
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 drug.
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 11).	N/A	No USP Monograph.
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.”</i> with x numerical citation to “OSHA Hazardous Drugs”.	N/A	Not a hazardous product.
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1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)



(b) (4)

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	See above
Strength(s) in metric system	Adequate	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.
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	Round, light red, film-coated tablet, debossed with the company logo and '645' on the same side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not scored tablet.
For injectable drug products for parental 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.

Section 11 (DESCRIPTION)



(b) (4)

**QUALITY ASSESSMENT**

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	
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.	Adequate	Ferric oxide, hydroxypropyl cellulose, hypromellose, low-substituted hydroxypropyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.
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 an injectable.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	No alcohol.



QUALITY ASSESSMENT



Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	A (b) (4) small-molecule NK3 receptor antagonist.
Chemical name, structural formula, molecular weight	Adequate	(4-Fluorophenyl)[(8R)-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]methanone; C ₁₆ H ₁₅ FN ₆ O ₅ ; Mw 358.39.
If radioactive, statement of important nuclear characteristics.	N/A	Not a radioactive product.
Other important chemical or physical properties (such as pKa or pH)	Adequate	It is very slightly soluble in water (0.29 mg/mL).

Section 11 (DESCRIPTION) 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)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is	N/A	No USP Monograph.

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QUALITY ASSESSMENT



Center for Drug Evaluation and Research

fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).



(b) (4)

**QUALITY ASSESSMENT**

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	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	Bottles of 30 tablets Bottles of 90 tablets
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	round, light red, film-coated tablets, debossed with the Astellas logo and '645' on the same side. Bottles of 30 tablets with child resistant closure and desiccant, (NDC 0469-2660-30) Bottles of 90 tablets with child resistant closure and desiccant, (NDC 0469-2660-90)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a scored 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.



QUALITY ASSESSMENT



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	Tablet does not require special handling.
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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	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled 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: “ <i>Not made with natural rubber latex. Avoid statements such as “latex-free.”</i> ”	N/A	



QUALITY ASSESSMENT



Include information about child resistant packaging	Adequate	child resistant closure
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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 review 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)

Distributed by:
Astellas Pharma US, Inc.
Northbrook, IL 60062

(b) (4) is a trademark of Astellas US LLC.

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	Distributed by: Astellas Pharma US, Inc. Northbrook, IL 60062

2.0 PATIENT LABELING



QUALITY ASSESSMENT



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

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**QUALITY ASSESSMENT**

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²	Adequate	(b) (4) (fezolinetant) tablets, for oral use
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	Store (b) (4) at room temperature between 68°F to 77°F (20°C to 25°C). (b) (4) (b) (4) Dispose of the unused medicine through a take-back option, if available. See www.fda.gov/drugdisposal.com for more information. Keep (b) (4) and all medicines out of the reach of children.
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	To include a desiccant warning, e.g., "Do not eat."
Active ingredient(s) (if applicable)	Adequate	fezolinetant

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



QUALITY ASSESSMENT



Alphabetical listing of inactive ingredients (if applicable)	Adequate	ferrie oxide, hydroxypropyl cellulose, hypromellose, low-substituted hydroxypropyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Distributed by: Astellas Pharma US, Inc. Northbrook, IL 60062

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

3.0 CONTAINER AND CARTON LABELING

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(b) (4)

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**QUALITY ASSESSMENT**

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ³ , (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	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, and these products require a "Not for direct infusion" statement.	N/A	

³ Established name = [Drug] [Route of Administration] [Dosage Form]

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QUALITY ASSESSMENT



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	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	



QUALITY ASSESSMENT



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	
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.	Adequate	

Assessment of Carton and Container Labeling: {Adequate}

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

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See [Carton/Container Labeling Specific Resources](#) for a presentation about inappropriate inconsistencies of product quality information between labeling.



QUALITY ASSESSMENT



If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

2.0 PATIENT LABELING

1. Provide a desiccant bag picture showing “Do not eat” warning and ensure the size and shape of the desiccant differs from the dosage form.

Overall Assessment and Recommendation:

This application is not deemed ready for approval in its present form per 21 CFR 314.125(b)(6) from the CMC labeling/labels perspective until the remaining deficiencies delineated under the “ITEMS FOR ADDITIONAL ASSESSMENT” above are satisfactorily resolved.

Primary Labeling Assessor Name and Date: Baoqing Ma, Ph. D., 10/28/2022.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Hamid Shafier, Ph. D., 10/28/2022.



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BIOPHARMACEUTICS**Product Background:****NDA: 216578****Drug Product Name / Strength:** Fezolinetant Tablet/45 mg**Indication:** Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.**Route of Administration:** Oral**Applicant Name:** Astellas Pharma US, Inc.***Review Recommendation: ADEQUATE******Review Summary:***

Fezolinetant is a small-molecule, nonhormonal, selective neurokinin-3 (NK3) receptor antagonist indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. Fezolinetant is a potential first-in-class product with a new mechanism of action, that blocks NKB binding on the KNDy neuron to modulate neural activity in the thermoregulatory center.

In order to ensure rapid drug dissolution in vivo, Fezolinetant Tablets 30 mg and 45 mg are developed as immediate release tablets with film-coating. However, the Applicant has proposed only 45 mg dosage strength for approval at this time. (b) (4)

(b) (4)

(b) (4)

Biopharmaceutics review is focused on the evaluation and acceptability of bridging of formulations, dissolution method, and dissolution acceptance criterion.

In Vitro Dissolution Method and Acceptance Criterion: ADEQUATE

The following dissolution method and acceptance criterion for the release of fezolinetant from the tablets are deemed acceptable:

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
Apparatus 1	100	0.1N HCl/37°C ± 0.5°C	500	Q= (b) (4)% in 30 minutes

The dissolution method and acceptance criterion are aligned with the FDA guidance (2018) on dissolution testing of immediate-release solid oral dosage forms containing high solubility drug substances.

Formulation development and bridging: ADEQUATE from Biopharm perspective

The applicant conducted Study 2693-CL-0009 that assessed the relative bioavailability of the tablet formulation (Phase 3) compared with the capsule formulation (Phase 1 and 2) and a bioequivalence Study 2693-CL-0010 between phase 3 tablets and the to-be-marketed tablets. Assessment of all in vivo BA and BE studies are under the purview of Office of Clinical Pharmacology.

Two minor adjustments were conducted in the formulation development from the phase 3 to the to-be marketed tablet. Compared to the phase 3 tablets, (b) (4)

(b) (4), respectively. The second adjustment is related to the tablet color shade. Comparative dissolution data between tablet formulation used in Pivotal Phase 3 clinical studies and the TBM tablets showed more than 85% dissolution at 15 min in all three evaluated pH media.

Biowaiver Request: Not Applicable

Only one strength is proposed for approval.

List of Submissions being reviewed:

Application 216578 - Sequence 0001 Original

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: None.

From Biopharmaceutics perspective, NDA 216578 for Fezolinetant tablets (45 mg) is recommended for APPROVAL.

BCS Designation**Reviewer's Assessment:**

The Applicant considers fezolinetant as a BCS I drug substance as it has both high aqueous solubility and high permeability. However, no request for BCS designation has been made.

Solubility:

Solubility profiles of fezolinetant were investigated in 0.1 N HCl, pH 4.5 and pH 6.8 at $37 \pm 1^\circ\text{C}$ [Module 3.2.S.1.3]. The solubility of fezolinetant was 0.44, 0.40, 0.37 mg/mL in 0.1 N HCl, USP pH 4.5 and USP pH 6.8, respectively. Based on "ICH Harmonised Guideline, Biopharmaceutics Classification System-based Biowaivers: M9" (ICH M9 Guideline, Nov 2019), fezolinetant can be considered as a highly soluble compound because the highest single therapeutic dose of fezolinetant, 45 mg, is soluble in no more than 250 mL of aqueous media over the pH range of 1.2 to 6.8 at $37 \pm 1^\circ\text{C}$. The average solubility results are shown in the table below.

Table 1: Solubility of fezolinetant in Different Media

Table 1 General Properties of Fezolinetant

Attribute	Results
Description	White powder
Dissociation Constant (pKa)	Not found in a range of pH 1.1 to 12.9
Partition Coefficient (Log P _{ow})	2.0
Solubility Profile at 20 ± 5°C (JP)	
Water	0.293 mg/mL (Very slightly soluble) ³
Ethanol (99.5)	10.3 mg/mL (Sparingly soluble) ³
Aqueous solution (pH 1) ¹ (After dissolution: pH 1.1)	0.221 mg/mL (Very slightly soluble) ³
Aqueous solution (pH 3) ² (After dissolution: pH 3.0)	0.324 mg/mL (Very slightly soluble) ³
Aqueous solution (pH 5) ² (After dissolution: pH 5.0)	0.279 mg/mL (Very slightly soluble) ³
Aqueous solution (pH 7) ² (After dissolution: pH 7.0)	0.250 mg/mL (Very slightly soluble) ³
Aqueous solution (pH 9) ² (After dissolution: pH 9.0)	0.227 mg/mL (Very slightly soluble) ³
Aqueous solution (pH 11) ² (After dissolution: pH 11.0)	0.211 mg/mL (Very slightly soluble) ³
Solubility Profile at 37 ± 1°C (ICH M9, 24 hours)	
0.1N hydrochloric acid	0.44 mg/mL (Highly soluble) ⁴
pH 4.5 acetate buffer	0.40 mg/mL (Highly soluble) ⁴
pH 6.8 phosphate buffer	0.37 mg/mL (Highly soluble) ⁴
Gastric Fluid, Simulated	Stable
Intestinal Fluid, Simulated	Stable
Hygroscopicity	Not hygroscopic
Melting Point (USP <741>)	171°C
Polymorphs	Two polymorphs have been observed.
Optical Rotation (JP)	[α] _D ²⁰ + 10.6 (0.30 g, methanol, 20 mL, 100 mm)

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, JP: Japanese Pharmacopoeia, USP: United States Pharmacopoeia

¹ 0.1 mol/L hydrochloric acid was used.² Carmody buffer (a mixture of 0.2 mol/L boric acid, 0.05 mol/L citric acid and 0.1 mol/L trisodium phosphate) was used. This pH value was measured before dissolution.³ Classified according to JP⁴ Classified according to ICH M9**Permeability:**

The permeability of fezolinetant was evaluated in Caco-2 permeability study. The permeability of [14C]-fezolinetant across Caco-2 cell monolayers was assessed at apical pH 6.5/basal pH 7.4. After incubation for 4 h, [14C]-fezolinetant did not show significant efflux, and the Papp values were 27.1, 28.0 and 28.8 x 10⁻⁶ cm/s for the apical to basal direction at 2, 20 and 200 μmol/L, respectively. The mean Papp values of fezolinetant in the absorptive apical-to-basolateral direction were more than 28.0 x 10⁻⁶ cm/s and approximately twice or more than the Papp value of propranolol (13.6 x 10⁻⁶ cm/s), indicating that fezolinetant is a high permeability compound [Study 2693-ME-0011, Module 2.7.2]. The applicant stated that the results of solubility and Caco-2 permeability studies suggest that fezolinetant is BCS Class 1 (high solubility, high permeability).

Dissolution: See below.**1. Composition of proposed drug product:**

The quantitative composition of the Fezolinetant Tablets 30 mg and 45 mg is listed in the table below.

Table 2: Compositions of Fezolinetant Tablets 30 mg and 45 mg

Component	Function	Reference to Quality Standard	Quantity (mg/tablet)	
			30 mg	45 mg
Fezolinetant	Active ingredient	In-house	30.0	45.0
Mannitol	(b) (4)	USP		(b) (4)
Hydroxypropyl Cellulose		NF		(b) (4)
Low-Substituted Hydroxypropyl Cellulose		NF		(b) (4)
Microcrystalline Cellulose		NF		(b) (4)
Magnesium Stearate		NF		(b) (4)
Total				(b) (4)

NF: National Formulary, USP: United States Pharmacopoeia, N/A: Not applicable

(b) (4)

2. In vitro dissolution method and acceptance criterion:

As mentioned earlier, fezolinetant can be considered as a highly soluble compound. Hence, the Applicant proposed the dissolution method (Apparatus 1, 100 rpm in 500 mL of 0.1N HCl) recommended in FDA guidance 2018 (Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances). The Applicant chose Basket Method (b) (4) The (b) (4) Fezolinetant Tablets 30 mg and 45 mg showed rapid and complete dissolution with Basket Method as shown in the figures below.

(b) (4)

The Applicant provided a brief dissolution method development report. No discriminating data was provided. The drug substance is highly soluble and rapidly dissolving per the adopted method in the 2018 FDA guidance. A detailed method development report and discriminating data is, therefore, not needed. Hence, the Applicant's proposed dissolution method is deemed acceptable.

Method Validation

The analytical method for the dissolution was fully validated by performing the specificity, linearity, precision, accuracy, range, robustness, and solution stability. This information will be

reviewed by Drug Product reviewer. Please refer to the DP review in Panorama for additional details.

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Dissolution data

The Applicant provided batch analysis data for the To-be-marketed 30 mg and 45 mg strengths generated using the currently proposed QC method (Apparatus 1, 100 rpm, 500 mL, 0.1 N hydrochloric acid). Data are shown in tables below.

Table 3: Dissolution profile data for the To-be-marketed Fezolinetant Tablets

Product Name		Fezolinetant Tablets 30 mg	Fezolinetant Tablets 30 mg	Fezolinetant Tablets 30 mg	Fezolinetant Tablets 45 mg	Fezolinetant Tablets 45 mg	Fezolinetant Tablets 45 mg
Formulation		To-be marketed	To-be marketed	To-be marketed	To-be marketed	To-be marketed	To-be marketed
DP Batch No. (Bulk)		20021	20022	20023	20024	20025	20026
Dissolution (%) ²	15 min	95	96	96	92	93	92 (b) (4)
	20 min	98	98	98	96	96	96 (b) (4)
	30 min	99	99	99	99	99	98 (b) (4)

Product Name		Fezolinetant Tablets 30 mg	Fezolinetant Tablets 45 mg	Fezolinetant Tablets 30 mg	Fezolinetant Tablets 45 mg
Formulation		To-be marketed	To-be marketed	To-be marketed	To-be marketed
DP Batch No. (Bulk)		21F30	21F45	G03417E	G03517E
Dissolution (%) ²	15 min	98	96	99	95 (b) (4)
	20 min	100	99	100	98 (b) (4)
	30 min	101	101	102	99 (b) (4)

Before implementation of the currently proposed dissolution method, the Applicant used a different method (^{(b) (4)}) for Phase 3 clinical batches and a To-be-marketed batch as shown in the table below. As can be seen, Phase 3 clinical batches of various strengths and To-be-marketed 45 mg Fezolinetant Tablets showed rapid dissolution with complete release in 15 minutes as with the currently proposed method.

Table 4: Dissolution profile data for the Phase 3 clinical batches

Product Name		Fezolinetant Tablets 120 mg	Fezolinetant Tablets 30 mg	Fezolinetant Tablets 30 mg	Fezolinetant Tablets 30 mg	Fezolinetant Tablets 15 mg	Fezolinetant Tablets 30 mg	Fezolinetant Tablets 15 mg	Fezolinetant Tablets 30 mg	Fezolinetant Tablets 45 mg
Formulation		Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	To-be marketed
DP batch No. (Bulk)		18026	18078	18079	19006	19008	19043	20015	20016	19058
Dissolution (%) ^{3,4}	15 min	97	99	100	99	98	100	101	100	99 (b) (4)
	20 min	99	100	100	100	98	101	101	100	99 (b) (4)
	30 min	99	100	100	100	98	101	100	100	99 (b) (4)

Stability data

The applicant submitted multi-point dissolution data at each stability months is provided in the link below:

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Per the Applicant, tablets without debossing are used for the stability studies. The data shows that the drug product is highly dissolving similar to the To-be-marketed product (debossed, Table 7) and meet the proposed acceptance criteria.

In vitro dissolution acceptance criterion

The Applicant's proposed dissolution acceptance criterion for fezolinetant tablet is $Q = \frac{(b)}{(4)}\%$ in 30 minutes which complies with the recommendation in the above FDA guidance and is acceptable.

Formulation development and bridging

Fezolinetant was initially developed as immediate-release hard gelatin capsules for oral administration of 3, 10, 15, 30, 60, 90, 120 and 180 mg strengths which was used in the initial phase 1 and 2 studies. A new tablet formulation at 15, 30, and 120 mg dose strengths was developed for phase 3 studies. The composition of the phase 3 tablet is proportionally similar among 15, 30 and 120 mg dose strengths of which the 15 mg and 30 mg tablets were used in the phase 3 studies; the 120 mg strength tablet was only used in the relative bioavailability Study 2693-CL-0009. Subsequently, the to-be-marketed tablet with 45 mg dose strength was developed for commercial use. The applicant conducted Study 2693-CL-0009 that assessed the relative bioavailability of the tablet formulation (Phase 3) compared with the capsule formulation (Phase 1 and 2) at 120 mg dose strength and a bioequivalence Study 2693-CL-0010 between phase 3 tablets and the to-be-marketed tablets. The assessment of these clinical studies is under the purview of Office of Clinical Pharmacology.

Two minor adjustments were conducted in the formulation development from the phase 3 to the to-be marketed tablet. Compared to the phase 3 tablets, the weight percentages of (b) (4) (b) (4) (b) (4), respectively. The second adjustment is related to the tablet color shade.

Dissolution Comparison Between Different Dose Strengths of Phase 3 Tablets and To-be-Marketed Tablets:

The dissolution profiles of tablet formulations used in Pivotal Phase 3 clinical studies and between the To-be-marketed tablets (SUPAC level 2 changes) were evaluated in multi pH media with dissolution conditions shown below. Dissolution was conducted in Apparatus 1, 100 rpm and as recommended in SUPAC IR guidance (Dissolution of 85% in 15 minutes in 900 mL of 0.1N HCl for high solubility/high permeability drugs).

Table 5: Dissolution conditions in each pH media

Medium pH	Dissolution Medium	Medium Volume	Apparatus	Sampling Points	Vessel Number
1.2	0.1 mol/L hydrochloric acid	900 mL	Apparatus I Rotation speed 100 rpm	15 minutes, 30 minutes	n = 12
4.5	USP acetate buffer				
6.8	USP phosphate buffer				

rpm: rotation per minute; USP: United States Pharmacopeia.

Source: Module 3.2.P.2.2, Table 21

Comparative in vitro dissolution data between tablet formulations used in Pivotal Phase 3 clinical studies and between the TBM tablets (SUPAC level 2 changes) showed more than 85%

dissolution at 15 min in all three evaluated pH media as shown in figures below. Additionally, the combination of one 15 mg and one 30 mg tablet was evaluated at the dose level of 45 mg, which was the highest dose level assessed in the phase 3 studies.

Considering all of the above, the to-be-marketed tablets are expected to perform similarly across different dose strengths. However, at this time, the Applicant has proposed only 45 mg strength for approval.

Table 6: Dissolution results of Phase 3 studies at each dose in each medium

Dissolution Medium Evaluated Doses	Dissolution Rate % (min - max)	
	15 minutes	30 minutes
0.1 mol/L hydrochloric acid, pH 1.2		
15 mg	99 (b) (4)	101 (b) (4)
30 mg	100	102
120 mg	95	98
45 mg (15 + 30 mg)	98	101
USP acetate buffer, pH 4.5		
15 mg	98	100
30 mg	98	101
120 mg	95	98
45 mg (15 + 30 mg)	97	100
USP phosphate buffer, pH 6.8		
15 mg	97	99
30 mg	99	101
120 mg	95	98
45 mg (15 + 30 mg)	98	101

max: maximum; min: minimum; USP: United States Pharmacopeia.

Source: Module 3.2.P.2.2, Table 22 through Table 24

Table 7: Dissolution results of To-be-Marketed tablet at each dose in each medium

Dissolution Medium Evaluated Doses	Dissolution Rate % (min - max)	
	15 min	30 min
0.1 mol/L hydrochloric acid, pH 1.2		
30 mg	96 (b) (4)	100 (b) (4)
45 mg	98	100
USP acetate buffer, pH 4.5		
30 mg	96	100
45 mg	97	99
USP phosphate buffer, pH 6.8		
30 mg	96	100
45 mg	97	99

max: maximum; min: minimum; USP: United States Pharmacopeia.

Source: Module 3.2.P.2.2, Table 25 through Table 27

Biowaiver Request: Not Applicable

Only one strength is proposed for approval.

Primary Biopharmaceutics Reviewer Name: Kalpana Paudel, Ph.D.

Secondary Reviewer Name: Tapash Ghosh, Ph.D.



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