CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216956Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216956
Applicant Name	Pfizer, Inc.; Collegeville, PA
Drug Product Name	Tradename (etrasimod) Tablets, 2 mg
Dosage Form.	Tablet
Proposed Strength(s)	2 mg
Route of Administration	Oral
Maximum Daily Dose	2 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Indicated for the treatment o [redacted] (b) (4) moderately to severely active ulcerative colitis (UC)
Drug Product Description	Tradename (etrasimod) Tablets, 2 mg is indicated for the treatment o [redacted] (b) (4) with active ulcerative colitis. The recommended dose is one tablet taken orally once daily. The tablet should be swallowed as a whole with or without food. The active ingredient, etrasimod is a synthetic small molecule sphingosine 1-phosphate receptor modulator. Etrasimod has not been previously approved or marketed in the United States and therefore, it has been classified a New Molecular Entity (NME). Tradename (etrasimod) tablets are green, round, film-coated immediate release tablets debossed with “ETR” on one side and “2” on the other side. Each tablet contains 2.762 mg of etrasimod arginine equivalent to 2mg of etrasimod as the active ingredient and magnesium stearate, mannitol, microcrystalline cellulose, and sodium starch glycolate, with a film coating containing FD&C blue #1/brilliant blue FCF aluminum lake, FD&C blue #2/indigo carmine aluminum lake, FD&C yellow #5/tartrazine aluminum lake, macrogol 4000

	JP/PEG 3350, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide as inactive ingredients. Tradename (etrasimod) Tablets, 2mg are supplied as 30 tablets in a child resistant 100 mL high density polyethylene (HDPE) white, round bottle with 4 g silica gel as desiccant integrated directly into the 45 mm white polypropylene (PP) closure. This drug product should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Based on the stability data provided in the application, an expiration dating period of 24 months has been granted to this drug product.		
Co-packaged product information	N/A		
Device information:	Description, performance attributes or N/A		
Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sharon Kelly, Ph.D.	Lawrence Perez, Ph.D.
	Drug Product/ Labeling	Hitesh Shroff, Ph.D.	Hamid Shafiei, Ph.D.
	Manufacturing	Mesfin Abdi, Ph.D.	Vaikunth, Prabhu, Ph.D.
	Biopharmaceutics	Leah Falade, Ph.D.	Tapash Ghosh, Ph.D.
	Microbiology	Mesfin Abdi, Ph.D.	Vaikunth, Prabhu, Ph.D.
	Other (specify): Environmental Assessment Labeling	 Hitesh Shroff, Ph.D. Hitesh Shroff, Ph.D.	 Hamid Shafiei, Ph.D. Hamid Shafiei, Ph.D.

	RBPM	Grafton Adams, RN, MS
	ATL	Hamid Shafiei, Ph.D.
Consults	N/A	

2. Final Overall Recommendation` - Approval

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, etrasimod arginine, and the drug product, Tradename (etrasimod) Tablets, 2 mg.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC PI labeling recommended changes as well as the recommended revisions for the container and carton labels have been communicated to the Clinical Review Team and are being conveyed to the applicant.
- The applicant's request for categorical exclusion from preparation of environmental assessment has been found adequate and is granted

Therefore, from the OPQ perspective this application is recommended for **approval** with an expiration dating period of **24 months** pending the submission of the negotiated PI labeling as well as container and carton labels to the application.

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	-	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. **Life-Cycle Considerations**

Established Conditions per ICH Q12: No
Comments:

N/A

Comparability Protocols (PACMP): No
Comments:

N/A

Additional Lifecycle Comments:

N/A

Hamid Shafiei

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CHAPTER IV: LABELING

(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)
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	**Revise as follows:** Tablets: 2 mg of etrasimod
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	

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

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	
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).	Adequate	The following equivalency statement is in Sec. 11 DESCRIPTION: (b) (4)

1.1 FULL PRESCRIBING INFORMATION

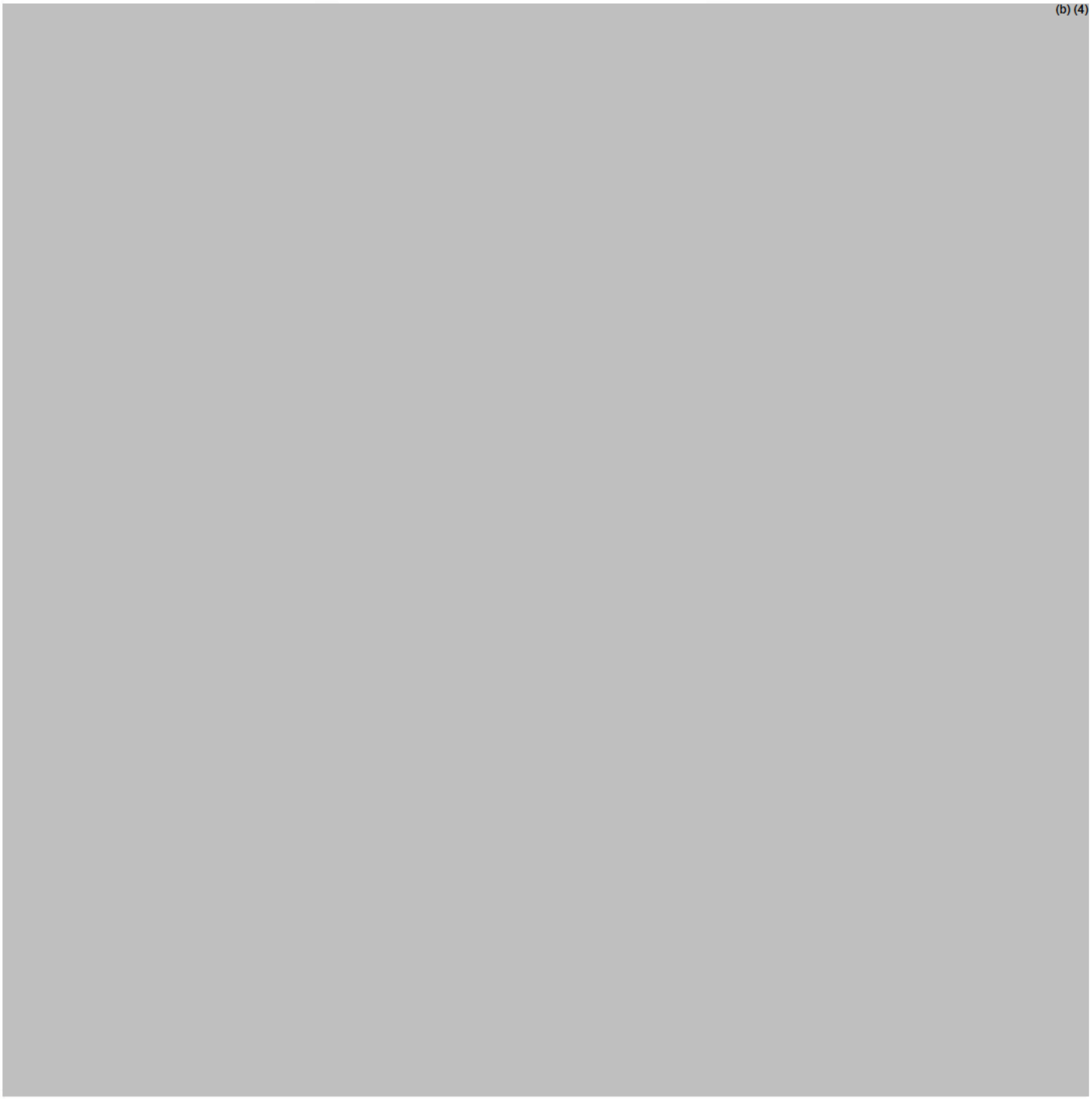
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(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	
Strength(s) in metric system	Adequate	
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).	Adequate The USP Salt Policy is adhered to. The tablet strength is based on the active moiety, etrasimod.	
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	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.2 Section 3 (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)"	Adequate	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Alphabetize the inactive ingredients names.
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	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	Revise the API name as shown below: L-Arginine, (3R)-7-[[4-cyclopentyl-3-(trifluoro ethyl)phenyl]methoxy]-1,2,3,4-tetrahydrocyclopent[b]indole-3-acetate (1:1)
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

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")	N/A	
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	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

[redacted]

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	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	• NDC number is provided. • **Add the following statement:** TRADENAME tablets are packed in a child-resistant 100 mL white, round, high-density polyethylene (HDPE) bottle containing 4 g of silica gel desiccant integrated directly into the 45 mm polypropylene (PP) cap.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple- dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
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.[X]" with x numerical citation to "OSHA Hazardous Drugs."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	Adequate	**Add the following information about the container/closure system:** TRADENAME tablets are packed in a child-

		resistant 100 mL white, round, high-density polyethylene (HDPE) bottle containing 4 g of silica gel desiccant integrated directly into the 45 mm polypropylene (PP) cap.

1.2.6 Manufacturing Information After Section 17 (for drug products)

(b) (4)

[redacted]

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	

2 Pages 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[2], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	N/A	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	Revise as follows: (b) (4)
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	
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	Location of bar code placement shown
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
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 Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

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[1]	Adequate	
Special preparation instructions (if applicable)	Adequate	
Storage and handling information (if applicable)	Adequate	
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	
Active ingredient(s) (if applicable)	Adequate	Replace "etrasimod" with "etrasimod arginine"
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

Assessment of PI: *ADEQUATE*

Assessment of Carton and Container Labeling: *ADEQUATE*

Assessment of Medication Guide: *ADEQUATE*

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

ITEMS FOR ADDITIONAL ASSESSMENT: *None*

Overall Assessment and Recommendation:

All PI, container/carton labels revisions and medication guide, shown in red, have been conveyed to the review team and will be conveyed to the applicant.

This NDA is recommended for "**Approval"** from the labeling perspective.

Primary Labeling Assessor Name and Date:
Hitesh Shroff
OPQ, ONDP, DNDP II, Branch 4
May 23, 2023

Secondary Assessor Name and Date
I concur with Dr. Shroff's assessment.

Hamid Shafiei, Ph.D.
ATL
OPQ, ONDP, DNDP II, Branch 4

Hitesh Shroff

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Hamid Shafiei

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-216956-ORIG-1
Assessment Cycle Number	1
Drug Product Name/ Strength	Velsipity® (etrasimod) Tablets/2 mg
Route of Administration	Oral
Applicant Name	Pfizer Inc.
Therapeutic Classification/ OND Division	Division of Gastroenterology
RLD/RS Number	N/A
Proposed Indication	For the treatment of moderately to severely active ulcerative colitis
Primary Reviewer	Leah W. Falade, Ph.D.
Secondary Reviewer	Tapash Ghosh, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant seeks approval for its Velsipity® (etrasimod) Tablets, 2 mg for the treatment of moderately to severely active ulcerative colitis (UC [redacted (b) (4)] Etrasimod is a sphingosine 1-phosphate receptor modulator (S1P1,4,5) developed as a once-daily oral medication for immune-mediated inflammatory disorders where new therapies, particularly oral therapies and therapies that act via novel mechanisms, are needed to treat these diseases. The clinical package in support of this NDA includes two pivotal Phase 3 studies that were performed using the to-be-marketed (TBM) IR tablet formulation.

The Biopharmaceutics review focuses on the evaluation and acceptability of 1) the proposed dissolution method and acceptance criterion, and 2) formulation bridging throughout product development, with key findings summarized below.

1) **Dissolution Method and Acceptance Criterion:**
   The Applicant proposed a dissolution method using USP Apparatus 2 (paddles) at 75 rpm in 900 mL of 0.05 M Phosphate Buffer with 0.2% Tween 20, 37°C. Etrasimod has low solubility [redacted (b) (4)]
   Aberrant formulations were manufactured with differing [redacted (b) (4)]
   levels, tablet hardnes [redacted (b) (4)]
   The target tablets have a dissolution profile that is very rapidly dissolving, and discrimination was seen at the 5-minute time point for the aberrant formulations.

The acceptance criterion was proposed based on the mean dissolution profile data of the pivotal clinical batch and registration batches at release. The proposed acceptant criterion of (b)(4) % in 30 min" is deemed appropriate based on the data.

The Applicant's proposed dissolution method and acceptance criterion is deemed acceptable for batch release and stability testing of the proposed drug product.

2) **Formulation Bridging:**
The drug product was originally developed as an IR capsule. An IR tablet was later developed and used in Phase 1 through Phase 3 studies. The to-be-marketed (TBM) formulation was bridged to the clinical IR tablet formulation in clinical study APD334-007. The pivotal Phase 3 clinical studies used the TBM formulation. The PK studies will be assessed by the Office of Clinical Pharmacology to bridge the formulations. All batches of the test product were manufactured at the same site, Penn Pharmaceutical Services Limited in Tredegar, UK. From a Biopharmaceutics perspective, additional formulation bridging is not needed.

Recommendation:
From the Biopharmaceutics perspective, NDA-216956-ORIG-1 for Velsipity® (etrasimod) Tablets, 2 mg, is recommended for **approval**.

The FDA-approved dissolution method and acceptance criteria for the proposed Velsipity® (etrasimod) Tablets, 2 mg, for batch release and stability testing:

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criterion
2 (paddles)	75 rpm	0.05 M Phosphate Buffer with 0.2% Tween 20/37°C	900 mL	Q (b)(4) % in 30 min

List Submissions being assessed:

Document(s) Assessed	Date Received
Seq 0001	10/14/2022
Seq 0005	12/21/2022

Highlight Key Issues from Last Cycle and Their Resolution:
This is the first review cycle.

Concise Description of Outstanding Issues:
None

B.1 BCS DESIGNATION

Assessment: Etrasimod can be classified as a BCS Class 2 compound with low solubility and high permeability.

Solubility:
The solubility of etrasimod is pH-dependent. It is believed that etrasimod begins to self-associate at pH.8.1 leading to increased solubility at higher pH.

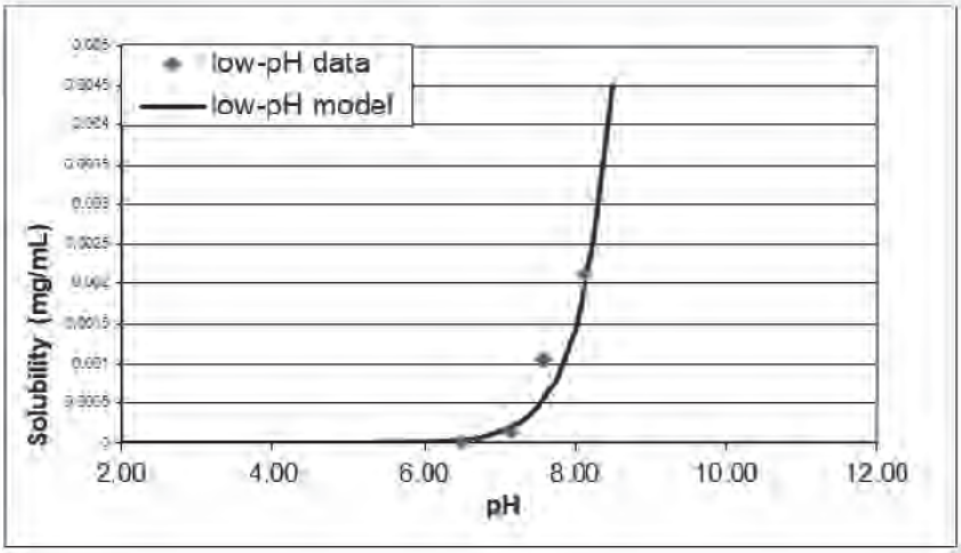

Figure 1. Etrasimod Low-pH Solubility Data Fit to Monoacidic Henderson-Hasselbalch Model

Permeability:
In a bidirectional Caco-2 study, etrasimod was highly permeable with P_{appAB}>20.6×10^{-6} cm/s which is consistent with the results from the human mass balance study showing at least 89% absorbed.

Dissolution:
See dissolution section below.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ***Adequate***

(b) (4)

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The optimized dissolution method is summarized in the table below:

USP Apparatus	Speed	Medium/Temperature	Volume
2 (Paddles)	75 rpm	0.05 M Phosphate Buffer with 0.2% Tween 20/37°C	900 mL

Discriminating Ability

Tablets were manufactured with different [redacted] (b) (4) levels. Both tablets were considered very rapidly dissolving but the tablets with 0% [redacted] (b) (4) had a lower % dissolved at 5 minutes.

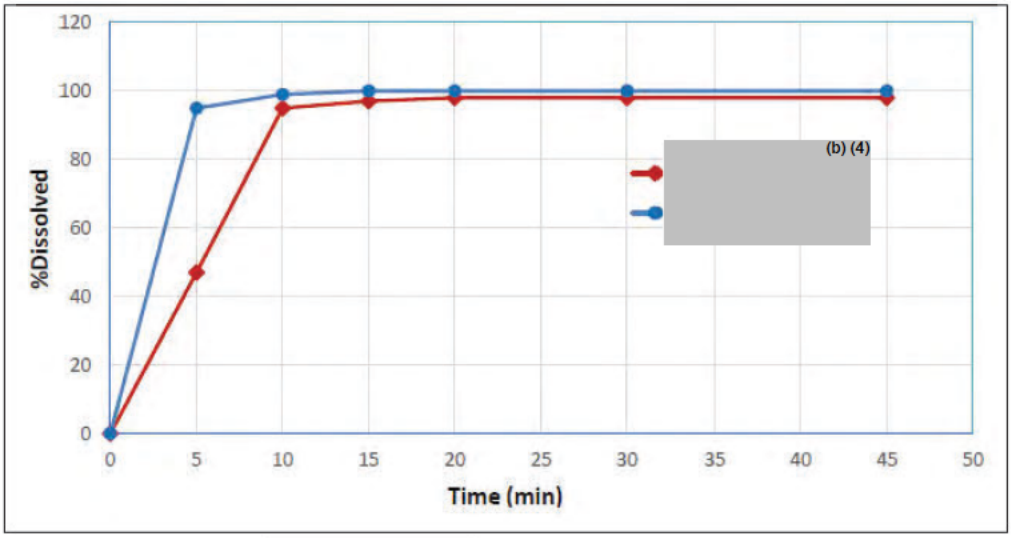

Figure 6. Effect [redacted] (b) (4) Level on the Dissolution of Etrasimod Commercial Tablets (n = 6)

Tablets were manufactured with different tablet hardness. All tablets were considered very rapidly dissolving [redacted] (b) (4)

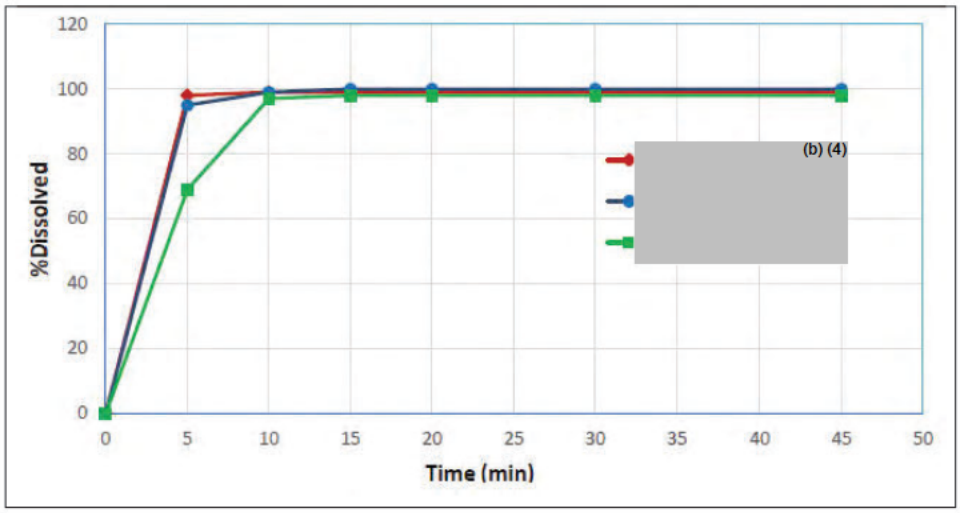

Figure 7. Effect of Tablet Hardness on the Dissolution of Etrasimod Commercial Tablets (n = 6)

Tablets were manufacture (b) (4) All tablets were considered very rapidly dissolving. (b) (4)

Although the drug product is considered very rapidly dissolving, there is some discrimination at 5 minutes for tablet hardness (b) (4) level, and (b) (4) level.

Acceptance Criterion

In response to an Information Request (IR), the Applicant clarified that the original dissolution data submitted used the dissolution method at the time of testing, which is not the same as the proposed commercial dissolution method. The paddle speed (b) (4) rpm was initially used for clinical tablets. The commercial tablets have a different composition (b) (4) was observed during testing. Therefore, the paddle speed of 75 rpm (b) (4) and was selected for the final dissolution method (**Figure 5**).

Time zero data from all packaged registration stability lots was submitted which was tested using the final dissolution method. Lot 020988 was used for the clinical PK studies. Three registration bathes were divided into a total of 9 packaging batches. This Reviewer used the data from the registration and PK batches to set the acceptance criterion (n=18 from each registration batch). The data meet the proposed acceptance criterion of "Q (b) (4) % in 30 min" and is acceptable.

Table 1. Dissolution Data from Registration and PK Biolot

Time (min) / Lot	5	10	15	20	30	45
1750452	(b) (4)					
1750452						
1750453						
020988 (Biolot)						
020989						
020990						
020991						
020992						
020993						
Mean	**79.11**	**97.33**	**99.22**	**99.11**	**99.11**	**98.78**
Std.Dev.	**3.86**	**2.55**	**2.49**	**2.37**	**2.37**	**2.17**
%CV	**4.87**	**2.62**	**2.51**	**2.39**	**2.39**	**2.19**

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

The drug product was originally developed as an IR capsule that was used in early Phase 1 and Phase 2 studies. An IR tablet formulation was developed and used in Phase 1 through Phase 3 studies. Clinical study APD334-007 bridged the IR capsule formulation with the clinical and commercial IR tablet formulations.

The to-be-marketed (TBM) commercial 2 mg IR Tablets was utilized in Study APD334-114 which was a bioequivalence and food effect study. This clinical PK study bridged the IR clinical tablet formulation to the IR commercial formulation. The IR commercial tablet formulation only differs from the to-be-marketed (TBM) formulation (b) (4) (b) (4) The phase 3 pivotal PK studies (APD334-301 and APD334-302) were performed using the TBM formulation. The PK studies will be assessed by the Office of Clinical Pharmacology to bridge the formulations. All batches of the test product were manufactured at the same site, Penn Pharmaceutical Services Limited in Tredegar, UK. From a Biopharmaceutics perspective, additional formulation bridging is not needed.

Primary Biopharmaceutics Assessor's Name and Date: Leah W. Falade, Ph.D.

Secondary Assessor Name and Date: Tapash Ghosh, Ph.D.

Leah Falade

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Tapash Ghosh

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