CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214962Orig2s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 214962
Review # 1

Drug Product Name	Fingolimod
Dosage Form	Orally disintegrating tablets
Strength	0.25 mg (b) (4)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Handa Neuroscience, LLC
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sukhamaya (Sam) Bain	Donna Christner
Drug Product	Renishkumar Delvadia	Julia Pinto
Manufacturing	Prashanth Manda	Shujun Chen
Microbiology	--	--
Biopharmaceutics	Leah Falade	Ta-Chen Wu
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	--	--
Environmental	--	--

DOCUMENTS REVIEWED

Submission(s)	Document Date	Discipline(s) Affected
SD-1	12/18/2020	All
SD-7	2/4/2021	Drug product, manufacturing
SD-10	2/12/2021	Drug product, manufacturing
SD-12	3/2/2021	Drug substance, drug product
SD-14	3/10/2021	Drug substance, manufacturing
SD-15	3/25/2021	Drug product, manufacturing, biopharmaceutics
SD-19 Labeling – C/C draft	6/21/2021	
SD-20	6/25/2021	Manufacturing
SD-26	8/27/2021	Manufacturing
SD-27	09/02/2021	Biopharmaceutics

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II		(b) (4)	Adequate	(b) (4)	
	III			--	--	Adequate information in NDA, DMF not reviewed.

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

Document	Application Number	Description
pIND	130544	Handa sought feedback for fingolimod under this pre-IND. The pivotal bioequivalence was not performed under an IND.
NDA	22527	Novartis NDA for Gilenya (fingolimod) capsules is referenced under 505(b)(2) to support safety and efficacy of fingolimod.

2. CONSULTS

None.

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Pharmaceutical Quality recommends **APPROVAL** of NDA 214962 for fingolimod orally disintegrating tablets. From a quality perspective, the application, as amended during the review, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS). It was initially approved in 2010 and is marketed by Novartis under the trade name GILENYA. The innovator product is an immediate release capsule containing fingolimod hydrochloride equivalent to 0.25 mg or 0.5 mg fingolimod base.

In the current 505(b)(2) NDA, the applicant seeks approval of a fingolimod orally disintegrating tablet (ODT) formulation to be marketed in the same strengths as the innovator product.

(b) (4)

During the initial risk assessment, several critical quality attributes (CQAs), including content uniformity, physical (solid state) stability, dissolution, and palatability were identified as moderate risk CQAs. The remaining CQAs are considered low risk.

Proposed indication(s) including intended patient population	Treatment of relapsing forms of multiple sclerosis (b) (4)
Duration of treatment	Chronic
Maximum daily dose	(b) (4) mg
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: **Adequate**

Fingolimod HCl USP is manufactured by [redacted]. Information to support manufacture and control of the API is cross-referenced to [redacted]. The DMF was last reviewed on [redacted] and is adequate. [redacted] assigns a [redacted] retest date for fingolimod HCl when stored at [redacted] °C.

The NDA includes the applicant's controls of the API, which include compliance with USP monograph and relevant ICH guidelines for parameters such as residual solvents, impurities, etc. that are specific to the supplier's manufacturing process. The information provided in the NDA is consistent with information in the referenced DMF and adequate to support approval.

Drug Product: **Adequate**

The proposed drug product is manufactured using [redacted] for orally disintegrating tablets (ODT); [redacted]. All excipients in the proposed formulation meet pharmacopeial requirements and are present at levels that do not result in higher exposure than for previously FDA-approved solid oral products and the applicant has performed adequate product development studies to justify the selection of the excipients and to demonstrate their chemical compatibility with the drug substance. Adequate data has been submitted in the original submission and IR responses [redacted]

The proposed drug product specification, as amended during the review, includes appropriate tests and acceptance criteria to ensure product quality and suitability for use. Analytical procedures adequately described and validated. The applicant has provided adequate justification for not including [redacted] and elemental impurity testing in the specification.

Based on the long-term and accelerated stability data provided, the proposed shelf life of 24 months for product stored at 20°C – 25°C is granted.

Labeling: **Adequate**

No deficiencies were identified during review of the NDA. Based on the supporting data provided, the FLS [redacted] is considered the active ingredient in the product and will be included in labeling.

Manufacturing: **Adequate**

Fingolimod orally disintegrating tablets, 0.25 mg (b) (4) manufactured by Catalent Pharma Solutions (b) (4) The drug product is manufactured by the following processes: (b) (4) The applicant proposes using the same process steps and in-process controls for commercial batches as for the registration batches. (b) (4) The commercial process utilizes equipment of the same design and operating principle as those used to produce registration batches. All critical process parameters and in-process controls for commercial manufacturing were studied and established with data obtained from both the development line and the commercial line.

All facilities that will be responsible for commercial manufacturing or testing (b) (4) fingolimod orally disintegrating tablets are currently acceptable. Facility status should be verified prior to final action.

Biopharmaceutics: **Adequate**

The biopharmaceutics review evaluated the proposed dissolution method and acceptance criterion, formulation bridging, and biowaiver request.

The applicant's validated dissolution method [USP Apparatus 2 (Paddle) with sinkers at 50 rpm, with 500 mL 0.1 N HCl with 0.2% SDS/37°C] is adequately justified and considered acceptable for the proposed fingolimod ODT, 0.25 mg (b) (4) for batch release and stability testing. However, the proposed acceptance criterion, Q=(b) (4)% in (b) (4) minutes, was deemed overly permissive. in response to an IR and FDA-recommended acceptance criterion, the applicant proposed to revise the acceptance criterion to Q = (b) (4)% in 20 min. The Applicant's justification for the revised acceptance criterion is acceptable. The agreed-upon dissolution is summarized below.

FDA-Approved Dissolution Method and Acceptance Criterion for batch release and stability testing of the proposed (b) (4) *(fingolimod) Orally Disintegrating Tablets:*

Apparatus	Speed	Medium/Temperature	Volume	Acceptance Criterion
2 (Paddle) with sinkers	50 rpm	0.1 N HCl with 0.2% SDS/37°C	500 mL	Q= (b) (4)% in 20 min

The formulation of the 0.5 mg fingolimod ODT used in the pivotal clinical study is the same as the to-be-marketed (TBM) formulation (b) (4) Therefore, product bridging is not needed.

The pivotal clinical study using the 0.5 mg strength of the ODT product comparing it to the Gilenya® Capsules was found to be acceptable. The lower 0.25 mg strength is the same dosage form and has the same release mechanism (b) (4) as the 0.5 mg strength. The pharmacokinetics of fingolimod was dose-proportional after single dose within the dose range of 0.125 to 40 mg and multiple doses at doses at 0.5 mg per day and lower. Based on the supportive data, the biowaiver for the 0.25 mg strength of fingolimod ODT can be granted.

Environmental: **Adequate**

The applicant requested a categorical exclusion from environmental assessment under 21 CFR 25.31(a), since this proposed action will not increase the use of the active moiety. The applicant states that no extraordinary circumstances exist. The claim for categorical is acceptable.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay, stability	Formulation, container closure, moisture, process parameters	**Low**	Data from registration batches demonstrate high stability of the product.	**Adequate**	
Content Uniformity	API physical properties, formulation, process parameters, equipment, scale	**Moderate**	(b) (4)	**Adequate**	
Physical stability (solid state)		**Moderate**	(b) (4)	**Adequate**	
Disintegration		**Low**		**Adequate**	
Dissolution		**Moderate**	Adequate testing procedure and acceptance criterion to ensure quality.	**Adequate**	
Palatability	API organoleptic properties, formulation, raw materials, excipient changes, process parameters	**Moderate**	(b) (4)	**Adequate**	
Microbial limits	Formulation, raw materials, moisture, container closure	**Low**	Compendial testing at release and on stability. No further mitigation needed.	**Adequate**	

D. List of Deficiencies for Complete Response

Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
Senior Product Quality Assessor for Neurology Products
Office of New Drug Products

9/14/2021

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate; comments regarding prescribing information label have been conveyed to DMEPA to add in their PI version.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4)	
Established name(s)	(fingolimod) orally disintegrating tablets	
Route(s) of administration	Oral	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	0.25 mg orally disintegrating tablets (3) (b) (4)	Change to "Orally disintegrating tablets: 0.25 mg (b) (4)
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	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4) is available as: • 0.25 mg orally disintegrating tablets are white to off white with  debossing. (b) (4)	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Yes	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Yes	
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 labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Yes	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
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	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	Change (b) (4) to "Chemically, fingolimod lauryl sulfate is…" Comment conveyed to DMEPA
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Yes	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	
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	

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

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Protect from moisture. Store in sealed blister pack. Do not open blister until ready to administer	
If the product contains a desiccant, ensure the size and shape differ from the	N/A	

dosage form and desiccant has a warning such as “Do not eat.”		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
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	N/A	

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Handa Neuroscience, LLC San Jose, California 95112 USA	

2.0 PATIENT LABELING

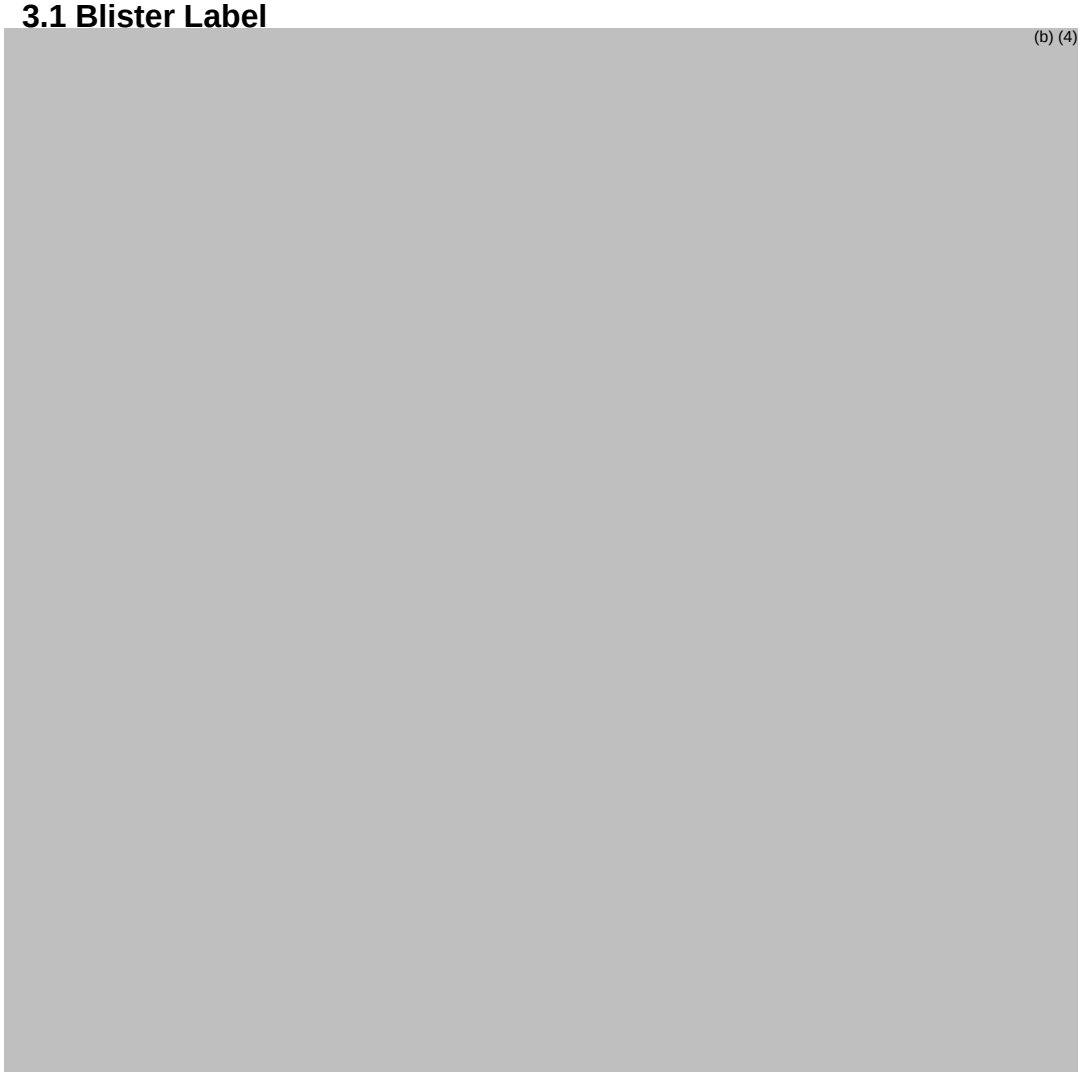
Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

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

3.0 CARTON AND CONTAINER LABELING

3.1 Blister Label

(b) (4)



3.2 Carton Labeling

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

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)	Yes	
No text on Ferrule and Cap overseal	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	None	

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

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

ITEMS FOR ADDITIONAL ASSESSMENT

Medication guide in SPL

(b) (4)

(fingolimod)
orally disintegrating tablets

Adequate

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Renishkumar Delvadia, 09/02/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed): Martha Heimann, 09/02/2021

Renishkumar Delvadia

Digitally signed by Renishkumar Delvadia
Date: 9/02/2021 10:48:51AM
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Martha Heimann

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-214962-ORIG-1
Drug Product Name/ Strength	(b) (4) (fingolimod) Orally Disintegrating Tablets/ 0.25 mg (b) (4)
Route of Administration	Oral
Applicant Name	Handa Neuroscience, LLC
Therapeutic Classification/ OND Division	Multiple Sclerosis/DN2
RLD/RS Number	Gilenya® (fingolimod) Capsules, NDA 022527
Proposed Indication	For the treatment of relapsing forms of multiple sclerosis (MS) (b) (4)
Primary Reviewer	Leah W. Falade, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

REVIEW SUMMARY

The Applicant is seeking approval for the proposed (b) (4) (fingolimod) Orally Disintegrating Tablets (ODT), 0.25 mg (b) (4) for the treatment of relapsing forms of multiple sclerosis (MS) (b) (4). The NDA is submitted for approval via the 505(b)(2) pathway and relying on the Agency's findings of safety and efficacy of the listed drug (LD) Gilenya® Capsules approved under NDA 022527.

The proposed drug product is an orally disintegrating tablet (b) (4) (b) (4) The drug product is designed to be bioequivalent to the listed drug (LD) Gilenya® (fingolimod) Capsules. The major differentiation of the proposed product and the LD capsule is its ability to be taken with and without water which offers better benefit for patients with difficulty swallowing.

The clinical package in support of this NDA includes two pivotal relative bioavailability (BA)/ bioequivalence (BE) studies conducted using the (b) (4) 0.5 mg strength comparing the proposed ODT product with Gilenya® Capsules. The studies were conducted with and without water under fasting and fed conditions. In support of the Biopharmaceutics program, a suitable dissolution method was developed for the proposed ODT product.

This review focuses on the Biopharmaceutics evaluation and acceptability of 1) the proposed dissolution method and acceptance criterion, 2) product bridging throughout the formulation development, and 3) biowaiver request for the lower strength, as summarized below.

1. **In Vitro Drug Release Method and Acceptance Criteria:**
   The Applicant's validated dissolution method [USP Apparatus 2 (Paddle) with sinkers at 50 rpm, with 500 mL 0.1 N HCl with 0.2% SDS/37°C] is adequately justified and considered acceptable for the proposed fingolimod ODT, 0.25 mg (b) (4) for batch release and

stability testing (see final approved dissolution method and acceptance criterion under **RECOMMENDATION** section). A data-driven acceptance criterion was recommended. The Applicant provided a counter proposal for (b) (4) acceptance criterion at 20-minute timepoint. The Applicant's justification for the newly proposed acceptance criterion of "Q= (b) (4)% in 20 min" is acceptable (See Dissolution section for justification).

2. **Bridging Throughout Product Development:**
   The ODT formulation used in the clinical pivotal studies for the 0.5 mg strength are identical in composition to the to-be-marketed (TBM) formulation. The commercial batches will be manufactured at the same site as the exhibit batches, Catalent Pharma Solutions in Wiltshire, UK. Therefore, bridging is not needed.

3. **Biowaiver Request:**
   The pivotal clinical study using the 0.5 mg strength of the ODT product comparing it to the Gilenya® Capsules was found to be acceptable. The lower 0.25 mg strength is the same dosage form and has the same release mechanism (b) (4) as the 0.5 mg strength. The pharmacokinetics of fingolimod was dose-proportional after single dose within the dose range of 0.125 to 40 mg and multiple doses at doses at 0.5 mg QD and lower. Based on the supportive data, the biowaiver for the 0.25 mg strength of fingolimod ODT can be granted.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA-214962-ORIG-1 for the proposed (b) (4) (fingolimod) Orally Disintegrating Tablets, 0.25 mg (b) (4) is recommended for **approval**.

FDA-Approved Dissolution Method and Acceptance Criterion for batch release and stability testing of the proposed (b) (4) (fingolimod) Orally Disintegrating Tablets**:**

Apparatus	**Speed**	**Medium/Temperature**	**Volume**	**Acceptance Criterion**
2 (Paddle) with sinkers	50 rpm	0.1 N HCl with 0.2% SDS/37°C	500 mL	Q= (b) (4)% in 20 min

BIOPHARMACEUTICS ASSESSMENT

LIST of SUBMISSIONS BEING REVIEWED

eCTD # (SND #)	Received date	Document
0001	12/18/2020	Original
0015	03/25/2021	Quality Response to IR
0027	09/02/2021	Quality Response to IR

BIOPHARMACEUTICS RELATED INFORMATION

BCS Class Designation	*None claimed in current submission. NDA review of RLD could not precisely assign a BCS class to fingolimod drug substance. However, this drug product is not eligible for a BCS waiver.*
Solubility	Soluble in water and pH 1.0. Low solubility in neutral and alkaline pH. (b) (4)
Permeability	OCP review had no reliable conclusions on Caco-2 cell monolayers.
In Vitro Drug Release	Very rapid
Particle Size (Drug substance)	N/A
Polymorphic form	(b) (4)
Particle Size (Microsphere)	N/A
Formulation	(b) (4) (b) (4) DP can be taken without water which offer benefit for patients who have difficulty swallowing.
Dosing	(b) (4) orally once-daily with or without food, with or without water. Place tablet directly on the tongue and allow it to dissolve before swallowing.
Absorption	The absolute oral bioavailability is 93%.

Dose Proportionality	The pharmacokinetics of fingolimod was dose-proportional after single dose within the range of 0.125 to 40 mg.[1]
BE	ODT is bioequivalent to LD under fasting and fed conditions.
Tmax	12-16 hours Steady-state blood concentrations are reached in 1 to 2 months following initiation of once-daily administration.
Food Effect	Food intake does not alter Cmax or (AUC) of fingolimod or fingolimod-phosphate. Biotransformation of fingolimod in humans can occur by reversible stereoselective phosphorylation to the pharmacologically active S-enantiomer of fingolimod-phosphate.

DISSOLUTION

Applicant's Proposed Dissolution Method and Acceptance Criterion:

Strengths/sample per vessel	Apparatus	Agitation Speed	Medium Volume	Temp.	Medium	Acceptance Criterion
1 ODT	2 (Paddles) with sinker	50 rpm	500 mL	37°C	0.1 N HCl with 0.2% SLS	Q (b) (4)% in (b) (4)min

Dissolution Method Development:

(b) (4)

[redacted]

[1] https://darrts fda.gov/darrts/faces/ViewDocument?documentId=090140af801e89bb&_afrRedirect=485149444193663

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Discriminating Capability of the Dissolution Method:

During the filing review, an Information Request (IR) was sent to the Applicant requesting rationale and justification on the suitability of the adopted method. Discriminating ability of the method was also requested. In response to the IR (Seq 0015), the Applicant provided simulation results to support their claim that the dissolution is not the determining factor of the in vivo PK profile. Considering that the dissolution does not reflect the in vivo performance, the discriminating ability of the method is not applicable for this case. (b) (4)

This reviewer agrees with the Applicant's justification due to the following reasons:

(b) (4)

Dissolution Acceptance Criterion:

Dissolution data from the following registration batches were submitted to support the proposed acceptance criterion: (b) (4) 2.5 mg strength: Lot #3741454, #3741455, and #3741456. The data for 12 units of each strength are summarized in the table and figures below.

Table 4. Summary of in Vitro Dissolution Studies (QC Method)

(b) (4)

Figure 2. (b) (4)

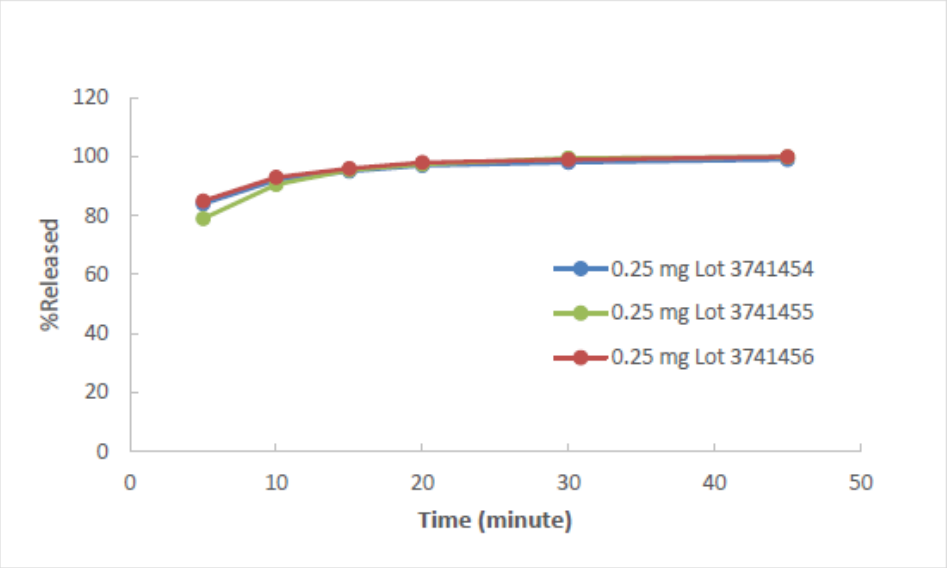

Figure 3. Dissolution Profile of Fingolimod ODT 0.25 mg Registration Batches, N=12

The Applicant proposed an acceptance criterion Q= (b) (4)% in (b) (4)min with the justification based on the FDA dissolution database method to ensure rapid drug release as appropriate for IR tablets. This Applicant's justification is not acceptable as the acceptance criterion should be set based on the data for the test product. The proposed acceptance criterion (b) (4). Based on the provided dissolution profile data of biobatch/registration batches, (b) (4) acceptance criterion "Q (b) (4)% in (b) (4)min" was recommended to the Applicant (date 08/31/2021). In response (date 09/02/2021), the Applicant counter proposed with an acceptance criterion of "Q= (b) (4)% in 20 min"

(see Appendix). This Reviewer finds the Applicant's counter-proposed specifications as quality control for batch release and stability testing acceptable based on the following reasons:

1. (b) (4)
2. The Applicant was not able to demonstrate discriminating ability of the proposed dissolution method.
3. (b) (4)

The 18-month stability data for all registration lots and clinical batch of the 0.25 mg (b) (4) show no downward trend.

BRIDGING THROUGHOUT PRODUCT DEVELOPMENT

The pivotal clinical studies (FGL-P01 and FGL-P02) were performed on the (b) (4) (b) (4) formulation/product (0.5 mg strength). The commercial batches will be manufactured at the same site as the exhibit batches, Catalent Pharma Solutions in Wiltshire, UK. Therefore, bridging is not needed.

BIOWAIVER REQUEST

In support of the waiver request for the 0.25 mg strength, the Applicant has submitted comparative dissolution data and formulation comparison. (b) (4) The quantitative and qualitative formulation compositions are presented in **Table *5***.

Table 5. Components and Quantitative Composition of Fingolimod Orally Disintegrating Tablets, 0.25 mg (b) (4)

Components listed as Compendial Name, Standard Name	Weight (mg) per Tablet		Weight (%) per tablet		Function	Maximum Daily Exposure by PRAL per FDA Website[2]
	0.25 mg	(b) (4)	0.25 mg	(b) (4)		(b) (4)
(b) (4)	(b) (4)		(b) (4)			
Gelatin, NF (b) (4)						
Mannitol, USP (b) (4)						
Sodium Lauryl Sulfate, NF (b) (4)						
Medium-Chain Triglycerides, NF (b) (4)						
(b) (4)	-	-	-	-		
Total (b) (4)					-	-
(b) (4)						

In vitro comparative dissolution profiles of fingolimod ODT, 0.5 mg (pivotal clinical batch 3741451) and 0.25 mg (exhibit batch 3741455) were submitted in three dissolution media (b) (4) The drug product was very rapidly dissolving in all media; therefore, the similarity factor calculation is not applicable. The Applicant also conducted multi-media dissolution testing using the reference product, Gilenya® Capsules. However, this information is not needed for the biowaiver and is only presented for information only.

The pivotal relative BA/BE study using the 0.5 mg strength of the ODT product comparing it to the Gilenya® Capsules was found to be acceptable (confirmed by Clinical Pharmacology reviewer Dr. Xiaohan Cai on 09/02/2021). The lower 0.25 mg strength is the same dosage form and has the same release mechanism (b) (4) as the 0.5 mg strength. The pharmacokinetics of fingolimod was dose-proportional after single dose within the dose range of 0.125 to 40 mg and multiple doses at doses at 0.5 mg QD and lower. Based on the totality of the supportive information/data, the biowaiver for the 0.25 mg strength of fingolimod ODT can be granted.

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Leah Falade

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Ta-Chen Wu

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MARTHA R HEIMANN
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