CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-527

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22527 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Gilenia Established/Proper Name: fingolimod Dosage Form: capsules Strengths: 0.5 mg		
Applicant: Novartis Agent for Applicant (if applicable):		
Date of Application: December 21, 2009 Date of Receipt: December 21, 2009 Date clock started after UN:		
PDUFA Goal Date: June 21, 2010	Action Goal Date (if different):	
Filing Date: February 19, 2010	Date of Filing Meeting: 1/20/2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): relapsing forms of multiple sclerosis		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☒ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):				
List referenced IND Number(s):				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	✓			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	✓			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***			✓	
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*	

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		✓		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		✓		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		✓		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		✓		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		✓		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		✓		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			✓	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	✓			
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	✓			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*		✓		**Abuse Liability Consult sent at request of CDTL**
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	✓			
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	✓			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	✓			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	✓			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	✓			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	✓			

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	✓			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	✓			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			✓	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	✓			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***			✓	

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***		✓		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	✓			
Is the PI submitted in PLR format?	✓			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?				
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)				
REMS consulted to OSE/DRISK?	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?				
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	✓			

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	✓			
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	✓			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	✓			

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***				See NDA History
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***				See NDA History
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***				See NDA History

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/20/2010

BLA/NDA/Supp #: NDA 22527

PROPRIETARY NAME: Gilynia

ESTABLISHED/PROPER NAME: fingolimod

DOSAGE FORM/STRENGTH: 0.5mg tablet

APPLICANT: Novartis

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):
The treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of relapses and to delay the accumulation of physical disability.

BACKGROUND:
Novartis submitted a new drug application (NDA) to support the marketing of fingolimod (Gilenya), the first oral drug to be indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Fingolimod is a new molecular entity, and a first in class sphingosine 1 phosphate (S1P) receptor modulator. The proposed mechanism of action in MS is that fingolimod induces a reversible retention of CD4 and CD8 T-cells and B-cells into lymph nodes and Peyer's patches, which in turn reduces the number of these cells that may have access to sites of MS related inflammation in the brain.

REVIEW TEAM:

Discipline/Organization	Names		
Regulatory Project Management	RPM:	Hamet Toure	
	CPMS/TL:	Jackie Ware	
Cross-Discipline Team Leader (CDTL)	Eric Bastings		
Clinical	Reviewer:	Heather Fitter (efficacy) Lourdes Villalba (safety)	
	TL:	Eric Bastings (efficacy) Sally Yasuda (safety)	
Clinical Pharmacology	Reviewer:	Ju-Ping Lai, Jagan Parepally, PeiFan Bai, Darrell Abemethy, Joo-Yeon Lee	
	TL:	Angela Men, Yaning Wang	

Biostatistics	Reviewer:	Sharon Yan	
	TL:	Kun Jin	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Richard Siarey	
	TL:	Lois Freed	
Statistics (carcinogenicity)	Reviewer:	Matthew Jackson	
	TL:	Karl Lin	
Product Quality (CMC)	Reviewer:	Wendy Wilson	
	TL:	Martha Heimann	
Ophthalmology	Reviewer:	Wiley Chambers	
Liver Toxicity	Reviewer:	John Senior	
Cardiology	Reviewer:	Shari Targum	
	TL:	Norman Stockbridge	
Pulmonary	Reviewer:	Brian Porter	
	TL:	Susan Limb	
	Supervisor:	Badrul Chowdhury	
OSE	PM	Laurie Kelly	
OSE/DMEPA (proprietary name)	Reviewer:	Denise Baugh	
	TL:	Todd Bridges	
OSE/DMEPA (labeling)	Reviewer:	Felicia Duffy	
	TL:	Zachary Oleszczuk	
OSE/DRISK (REMS)	Reviewer:	Yasmin Choudhry, Marcia Britt, Brian Gordon, Kendra Worthy	
	Supervisor:	Claudia Karkowsi	
OSE/DRISK (labeling)	Reviewer:	Robin Duer, LaShawn Griffiths	
	Supervisor:	Mary Willy	
Bioresearch Monitoring (DSI)	Reviewer:	Antoine El-Hage	
	TL:	Tejashri Purohit-Sheth	
DSTP	Marc Cavaille-Coll		

AC Staff	Diem-Kieu Ngo	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: none	☐ Not Applicable
CLINICAL **Comments**: MRI data; Echo data small; Patient profiles problematic; request group D tables	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: June 2010 ☐ NO ☐ To be determined Reason: NME with safety issues

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: Unable to open data file; will contact firm.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**: SAP not found; contact firm	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Robert Temple **21st Century Review Milestones: Mid-cycle: March 21, 2010** **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELINE H H WARE
09/21/2010

Gilenya PMR 1679-2

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Postmarketing observational safety study in relapsing multiple sclerosis patients

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	1/31/2011
Study/Clinical trial Completion Date:	5/15/2020
Final Report Submission Date:	12/15/2020
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   This is appropriate for a PMR because the adverse events to be further evaluated will be described in labeling.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Serious adverse events of eye toxicity, cardiac and vascular toxicity, pulmonary toxicity, seizures, serious and opportunistic infections, malignancies, liver toxicity, and atypical multiple sclerosis relapse are of concern. Additional information is needed, including the potential for these adverse events in patients who were excluded form the clinical trials population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☒ Assess a known serious risk related to the use of the drug?
     ☒ Assess signals of serious risk related to the use of the drug?
     ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A postmarketing observational prospective, parallel cohort study in relapsing multiple sclerosis patients to assess the potentially serious risk of: eye toxicity, cardiac and vascular toxicity, pulmonary toxicity, seizures, serious and opportunistic infections, malignancies, liver toxicity and atypical multiple sclerosis relapse. Specific outcomes examined should include, but not be limited to, macular edema, symptomatic bradycardia, second and third degree atrioventricular block, and lymphoma. The two observed cohorts should consist of 1) patients newly prescribed fingolimod and 2) patients receiving another disease modifying therapy. The study population should be representative of patients with relapsing multiple sclerosis who take disease modifying therapies and should include patients with a history of diabetes or other cardiovascular risk factors. The study design should minimize differences between the cohorts by defining the populations in both cohorts so that they will be similar, by ensuring that both cohorts have similar clinical assessments, and by ensuring that patients who discontinue treatment have continued follow-up. In addition, the study protocol should account for duration of exposure, treatment changes, and loss to follow-up. Sample size should be supported by estimates of the rates of the events of interest.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)

Observational prospective, parallel cohort study

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

   ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☒ Are the objectives clear from the description of the PMR/PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Gilenya PMR 1679-3

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Pregnancy Registry

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	12/21/2010
Study/Clinical trial Completion Date:	03/31/2017
Final Report Submission Date:	10/31/2017
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☒ Unmet need
   ☐ Life-threatening condition
   ☒ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☒ Theoretical concern
   ☐ Other

   Pregnancy registries are conducted post-marketing to obtain safety data on drug use during pregnancy including maternal and infant outcomes. Historically, pregnancy registries are not conducted during the pre-marketing period, because except in unusual circumstances, it is ethically and medically important to demonstrate safety and efficacy in nonpregnant women before studying the drug in pregnant women.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   During the clinical development program for fingolimod adverse developmental outcomes occurred in animal reproductive and developmental toxicology studies, and the receptor affected by fingolimod (sphingosine-1-phosphate receptor) is involved in vascular and neural development during embryogenesis. However, while adverse developmental outcomes in other species raise the likelihood of adverse developmental outcomes in human pregnancy, these data can not reliably predict the type or frequency of adverse developmental outcomes in humans. Therefore, the goal of the pregnancy registry is to obtain data on fingolimod exposure during pregnancy including maternal and infant outcomes to inform prescribing for and counseling with women affected by multiple sclerosis who are pregnant and of childbearing potential.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the maternal, fetal, and infant outcomes of women exposed to fingolimod during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes will be assessed through at least the first year of life.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Prospective, observational pregnancy exposure registry study

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

GILENYA PMR 1679-4

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: An *in vitro* study to evaluate the potential for fingolimod-P to induce CYP450 isoenzymes.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	02/01/2011
Study/Clinical trial Completion Date:	09/01/2011
Final Report Submission Date:	12/1/2011
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☒ Theoretical concern
   ☐ Other

   The study to evaluate the potential for fingolimod-P to induce CYP450 isoenzymes can be done postmarketing as the uncertainty is described in the label.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   The sponsor did not conduct an in vitro study to determine potential for FTY720-P to induce CYP450 isozymes. There is a theoretical concern of decreased exposure of CYP450s substrates which may result in efficacy issues, if FTY720-P is an inducer of CYP450 isozymes. The goal of this study is to evaluate the potential for FTY720-P to induce these isozymes. Based on the results of the study, an in vivo study may be required.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An *in vitro* study to evaluate the potential for fingolimod-P to induce CYP450 isoenzymes.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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GILENYA PMR 1679-5

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: An *in vitro* study to evaluate the potential for fingolimod to inhibit CYP2C8 and for fingolimod-P to inhibit CYP2B6.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	10/15/2010
Study/Clinical trial Completion Date:	7/15/2010
Final Report Submission Date:	10/15/2010
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

This study to determine potential for fingolimod to inhibit CYP2C8 and for fingolimod-P to inhibit CYP2B6 can be done postmarketing as the uncertainty is described in the label.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The sponsor did not conduct an in vitro study to determine the potential for fingolimod to inhibit CYP2C8 or the potential for fingolimod-P to inhibit CYP2B6 (Guidance: Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro). There is a theoretical concern of increased exposure of CYP2C8 and CYP2B6 substrates, which may result in safety issues, if fingolimod and fingolimod-P are inhibitors of CYP2C8 and CYP2B6, respectively. The goal of this study is to evaluate the potential inhibitory effect of fingolimod and fingolimod-P on these two enzymes. Based on the results of the study, an in vivo study may be required.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An *in vitro* study to evaluate the potential for fingolimod to inhibit CYP2C8 and for fingolimod-P to inhibit CYP2B6.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

GILENYA PMR 1679-6

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: An *in vitro* study to evaluate the potential for statins (e.g. simvastatin, lovastatin) to induce CYP4F2.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	2/1/2011
Study/Clinical trial Completion Date:	9/1/2011
Final Report Submission Date:	12/1/2011
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   We request the sponsor to conduct an in-vitro study to determine the induction potential of statins on CYP4F2 (± 100 folds of clinical therapeutic concentrations). This is appropriate as a PMR because of the low risk for clinically significant interaction.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   FTY720 is mainly metabolized by CYP4F2. One publication in the literature reported that statins could induce the enzyme activity of CYP4F2 (Reference: Regulation of Human Cytochrome P450 4F2 Expression by Sterol Regulatory Element-binding Protein and Lovastatin. THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 282, NO. 8, pp. 5225–5236, February 23, 2007.). There is a concern of decreased exposure of FTY720 and/or FTY720-P, if statins are inducers of CYP4F2. The goal of this study is to evaluate the potential for statins to induce CYP4F2. Based on the results of the study, an in vivo study may be required.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An *in vitro* study to evaluate the potential for statins (e.g. simvastatin, lovastatin) to induce CYP4F2, an enzyme that metabolizes fingolimod.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Gilenya PMR 1679-7

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: An integrated summary of safety for Studies FTY720D2301, FTY720D2302, and FTY720D2309 (upon completion of Study FTY720D2309).

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	12/21/2010
Study/Clinical trial Completion Date:	06/30/2011
Final Report Submission Date:	01/30/2012
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   This is appropriate as a PMR because there is a substantial safety database already available to support labeling. The ISS will include a final analysis of all of the safety data, after completion of study 2309 that will be ongoing at the time of approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Study 2309 will be ongoing at the time of approval. The required ISS will include updated exposure and analysis of safety following the standard format of a 4-month NDA safety update report, and will provide for additional evaluation of risk.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An integrated summary of safety for Studies FTY720D2301, FTY720D2302, and FTY720D2309 (upon completion of Study FTY720D2309). The summary should include updated exposure and analyses of safety following the format of a 4-month NDA safety update report, for the double-blind portion of the studies (Pool D + FTY7202309) and all studies (Pool E + 2309 double blind and extension).

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

ISS to include ongoing clinical study 2309 and already completed studies

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Gilenya PMR 1679-8

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Juvenile rat toxicology study to evaluate effects of fingolimod on growth, reproductive development, and neurological and neurobehavioral development.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	01/31/2011
	Study/Clinical trial Completion Date:	10/29/2011
	Final Report Submission Date:	03/31/2012
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This product is ready for approval for use in adults and pediatric studies have not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A juvenile rat toxicology study under PREA to identify the unexpected serious risk of adverse effects of fingolimod on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study must evaluate effects of fingolimod on growth, reproductive development, and neurological and neurobehavioral development.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A juvenile rat toxicology study. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study should evaluate effects of fingolimod on growth, reproductive development, and neurological and neurobehavioral development.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Gilenya PMR 1679-9

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A drug interaction clinical trial to evaluate the effect of carbamazepine on fingolimod pharmacokinetics.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	02/01/2011
Study/Clinical trial Completion Date:	04/01/2012
Final Report Submission Date:	07/01/2012
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   An in vitro DDI study showed that carbamazepine increased the metabolism of FTY720 by 2.3 and 1.8-fold at 10 and 50 μM, respectively. There is a concern of decreased exposure of FTY720 and/or FTY720-P which will result in reduced clinical efficacy. However, a population PK analysis did not show a significant effect. Based on that, this can be conducted postmarketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   An in vitro DDI study showed that carbamazepine increased the metabolism of FTY720 by 2.3 and 1.8-fold at 10 and 50 μM, respectively. There is a concern of decreased exposure of FTY720 and/or FTY720-P which will result in reduced clinical efficacy. Thus, a clinical drug-drug interaction study is required to characterize the effect of carbamazepine on FTY720 exposure when coadministered.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A drug interaction clinical trial to evaluate the effect of carbamazepine on fingolimod pharmacokinetics.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Gilenya PMC 1679-10

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A prospective, randomized, controlled study of fingolimod 0.5 mg, fingolimod 0.25 mg, and an appropriate control, of at least one year duration, to evaluate the efficacy and safety of the drug.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	09/30/2011
Study/Clinical trial Completion Date:	03/30/2015
Final Report Submission Date:	07/30/2015
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is appropriate as a PMC because there is a substantial safety database already available to support labeling.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

It is not known whether a lower dose would still be effective and would be associated with less toxicity. There is a dose-response relationship for adverse events, particularly for macular edema, bradycardia, and AV block, as well as in liver enzyme elevations and decrease in pulmonary function tests. The safety profile of the 0.5 mg/day dose was more favorable than the 1.25 mg dose. The expert panel at the advisory committee recommended evaluation of the 0.25 mg dose to see whether this is the case.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective, randomized, controlled study of fingolimod 0.5 mg, fingolimod 0.25 mg, and an appropriate control, of at least one year duration, to evaluate the efficacy and safety of the drug.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

ISS to include ongoing clinical study 2309 and already completed studies

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☒ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

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/s/

SALLY U YASUDA
09/21/2010
PMR/PMC development template

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: September 16, 2010

To: Hamet Toure
Senior Regulatory Health Project Manager
DNP

CC: Mary Dempsey
Project Management Officer
OSE, DRISK

Robin Duer
Senior Patient Labeling Reviewer
OSE, DRISK

From: Sharon Watson, PharmD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: Drug: Gilenya (fingolimod) capsules
NDA: 022527

DDMAC has reviewed the 9/15/10 DRISK review of the proposed Medication Guide (Med Guide) for Gilenya in comparison with the proposed FDA-approved product labeling (PI), file named "022527_Near final PI_091510.doc", and we offer the following comments. DDMAC's comments are provided directly on the clean version of this proposed Med Guide document, attached below.

Thank you for the opportunity to comment on this proposed Med Guide.

If you have any questions or concerns regarding these comments, please contact me.

5 page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

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/s/

SHARON M WATSON
09/16/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9858

Maternal Health Team Review

Date: September 16, 2010 **Date Consulted:** June 6, 2010

From: Richardae Araojo, PharmD
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: The Division of Neurology Products (DNP)

Drug: Gilenya (fingolimod) capsules; NDA 22-527

Subject: Labeling Review

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Gilenya labeling.

Consult Question: Please comment on the Pregnancy and Nursing Mothers subsections of Gilenya labeling and the need for postmarketing requirements for a pregnancy registry and/or a clinical lactation study.

INTRODUCTION

On December 18, 2009, Novartis submitted a new drug application (NDA 22-527) for Gilenya (fingolimod) capsules. The sponsor's proposed indication for Gilenya is a disease modifying therapy for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. The Division of Neurology Products (DNP) consulted the Maternal Health Team (MHT) to review the Pregnancy and Nursing Mother's subsections of the sponsor's proposed labeling and to determine if postmarketing requirements (PMR) for a pregnancy registry and/or a clinical lactation study are needed.

BACKGROUND

Fingolimod is a first in class sphingosine-1-phosphate receptor modulator with a proposed indication for the treatment of patients with relapsing forms of multiple sclerosis (MS). Fingolimod is metabolized by sphingosine kinase to the active metabolite fingolimod-phosphate. Fingolimod-phosphate, binds to sphingosine-1-phosphate receptors (S1PR) 1, 3, and 4 located on lymphocytes, and readily crosses the blood brain barrier to bind to S1PR 1, 3, and 5 located in the central nervous system. By acting as a functional antagonist of S1PR on lymphocytes, fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. This redistribution reduces the infiltration of pathogenic lymphocyte cells into the central nervous system where they would be involved in nerve inflammation and nervous tissue damage.[1]

The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the Pregnancy and Nursing Mothers labeling subsections. In addition, the MHT works with the pharmacology/toxicology reviewers to present animal data, in the Pregnancy subsection, in a clear, organized way to make it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, animal dose including human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For the Nursing Mothers subsection, when animal data are available, only the presence or absence of drug in milk is presented in the label.

This review provides suggested revisions to the sponsor's proposed Gilenya labeling and recommendations on PMRs related to pregnancy and lactation.

SUMBMITTED MATERIAL

Sponsor's Proposed Labeling Related to Pregnancy and Nursing Mothers (submitted on July 9, 2010)

[1] Novartis proposed labeling submitted on July 9, 2010.

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(b) (4)

Reviewer comments:
The MHT's recommended revisions to the sponsor's proposed labeling are provided on page nine of this review.

Postmarketing Requirements related to Pregnancy and Lactation

Pregnancy:
The sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) identified reproductive toxicity as an area of risk. In reproductive and developmental toxicology studies, fingolimod caused adverse developmental outcomes including persistent truncus arteriosus (rats), ventricular septum defect (rats), and embryolethality (rats and rabbits). These effects were observed in rats at doses less than the recommended human dose of 0.5 mg/day based on body surface area (mg/m^2) and at doses greater than 20 times the recommended human dose in rabbits. These outcomes raise concerns, because the receptor bound by fingolimod (sphingosine-1-phosphate receptor) is involved in vascular and neural development during embryogenesis.

In response to an information request from DNP on July 30, 2010, Novartis provided an update on the number of pregnancies reported in fingolimod clinical trials for multiple sclerosis. As of July 28, 2010, the sponsor reported a total of 60 pregnancies in women participating in fingolimod clinical trials for multiple sclerosis (see Table 1 below).[2]

[2] Novartis Response to FDA Information Request dated July 30, 2010.

Table 1 Pregnancies in MS studies

	Pregnancy outcome					
Treatment	Normal birth	Abnormal offspring	Elective abortion	Spontaneous abortion	Ongoing	Total
Fingolimod	13 [3]	1	9	6	5 [3]	34
Interferon beta-1a	2 [1]	0	2	0	0	4
Placebo	0	0	7	1	0	8
Still blinded	6	0	4	0	4	14
Total	21	1	22	7	9	60

[] = patient had already discontinued treatment by the time the pregnancy was detected.

Among these, 34 pregnancies occurred in women treated with fingolimod and the following outcomes were reported:

- 13 normal offspring (for three women, pregnancy was detected two to nine months after fingolimod discontinuation)

- 6 spontaneous abortions

- 9 elective terminations
  - One termination was a therapeutic abortion performed for an abnormal fetus. A 15-day MedWatch report dated June 1, 2010 described a women who became pregnant while participating in Study CFTY720D2301 E1 [a 24-month extension, double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing efficacy and safety of fingolimod (FTY720) 1.25 and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis]. The mother's medical history included anemia, a legal abortion, and two previous pregnancies resulting in healthy babies. The mother entered the initial study phase on March 5, 2007 and entered the extension phase on March 26, 2009. Study medication was discontinued on January 26, 2010 when pregnancy was detected. The mother's last menstrual period was December 12, 2009. The mother used a condom for contraception. An ultrasound of the fetus performed on May 3, 2010 revealed partial ventricular septal defect, overriding aorta, a slight right ventricular hypertrophy, and pulmonary artery stenosis. Tests for Trisomy 21 and CATCH-22 were negative. The mother underwent a therapeutic abortion at week 21 (May 11, 2010). The investigator suspected a causal relationship between the event and study medication. The mother's concomitant medications included Imacillin[3] from November 10-19, 2009 for upper respiratory infection, swine flu influenza inoculation on October 20, 2009, and Duroferon[4] from January 16, 2010 to February 28, 2010 for low hemoglobin.

- 1 abnormal birth:

[3] Form of amoxicillin marketed outside the United States.
[4] Form of ferrous sulfate marketed outside the United States.

- A 29-year-old woman treated with fingolimod 0.5 mg for nine months delivered a premature baby with a congenital shortening of the right leg with deformity of the tibia, unilateral congenital posteromedial bowing of the tibia. There were no other abnormalities reported.

- 5 pregnancies ongoing.

In addition to the pregnancy outcomes reported above, the sponsor's Summary of Clinical Safety submitted on December 21, 2009, describes the following fingolimod pregnancy exposures:

- The wife of a patient participating in fingolimod clinical trials became pregnant. At approximately 14 weeks of pregnancy, an ultrasound examination revealed a fetus with absence of extremities, and the woman underwent therapeutic abortion. The sponsor states that this abnormality was not thought to be related to fingolimod because in animal studies fingolimod did not cause adverse effects on sperm morphology, did not elicit any known genotoxic effect, and potential exposure of a partner to fingolimod via seminal fluid was estimated to be many thousand folds lower than doses at which teratogenicity was observed in rats.

- The sponsor conducted a search of their clinical database for fingolimod (FTY720) transplant studies on June 30, 2008. Three pregnancies during fingolimod treatment were identified and no congenital malformations were reported.

Because limited human data are available on fingolimod exposure during pregnancy and adverse developmental outcomes were observed in animal studies, the sponsor states that women of childbearing potential should be counseled on potential fetal risk and advised to use effective contraception during and for at least two months after fingolimod treatment. In addition, the sponsor plans to conduct a post-marketing pregnancy registry to evaluate the pregnancy outcomes of women exposed to fingolimod during pregnancy.

Reviewer comments:

- *The MHT agrees that the sponsor should conduct a prospective pregnancy exposure registry as a postmarketing requirement to determine the effects of fingolimod use during pregnancy including maternal and infant outcomes. However, the registry should not be included as an element of the sponsor's proposed REMS. A pregnancy registry is a study conducted to determine the effects of a product's use during pregnancy. In this case, the registry is not an element to assure safe use or to mitigate risk; therefore it should be conducted separate from the sponsor's REMS.*

- *The pregnancy registry should be a prospective, observational cohort study conducted in the United States that compares the maternal, fetal, and infant outcomes of women exposed to fingolimod during pregnancy to an unexposed control population. The registry should detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, and any other adverse pregnancy outcomes. These events should also be assessed among infants through at least the first year of life.*

- *Because adverse developmental outcomes occurred in animal studies, and the receptor affected by fingolimod (sphingosine-1-phosphate receptor) is involved in vascular and neural development during embryogenesis, the MHT agrees that labeling should include language recommending contraception use in women of childbearing potential.*

Lactation:
There are no human data available on fingolimod exposure during human lactation. Based on animal studies, fingolimod was excreted into rat milk. While the presence of drug in rat milk does predict that the drug may be present in human milk, the concentration of drug in rat milk is a poor predictor of drug concentration in human milk. Because of the potential for serious adverse reactions from fingolimod in nursing infants, the sponsor states that lactating women should not breastfeed while on fingolimod and for two months after fingolimod discontinuation. In addition, the sponsor does not plan to conduct a post-marketing clinical lactation study.

Reviewer comments:
- *Because of the potential for serious adverse reactions from fingolimod in nursing infants, the MHT does not recommend that the sponsor conduct a clinical lactation study as a postmarketing requirement.*

DISCUSSION AND CONCLUSIONS
Fingolimod is a first in class sphingosine-1 phosphate receptor modulator with a proposed indication for the treatment of patients with relapsing forms of multiple sclerosis (MS). For this review, the MHT revised sections of Gilenya labeling related to pregnancy and lactation. In addition, the MHT reviewed sections of the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) related to pregnancy.

The sponsor's proposed REMS identified reproductive toxicity as an area of risk because adverse developmental outcomes occurred in animal studies and the sphingosine-1-phosphate receptor affected by fingolimod is involved in vascular and neural development during embryogenesis. Therefore, the sponsor's proposed REMS includes a pregnancy exposure registry that will be conducted as a PMR. The MHT agrees that a prospective, observational, pregnancy exposure registry should be conducted to determine the effects of fingolimod use during pregnancy. However, the Gilenya REMS should not include the pregnancy registry PMR since a pregnancy registry is a study and not an element to assure safe use or to mitigate risk. In addition, because of the potential for serious adverse reactions from fingolimod in nursing infants, the MHT does not recommend that the sponsor conduct a clinical lactation study as a PMR.

The MHT's recommendations for labeling and post-marketing requirements are provided below.

RECOMMENDATIONS

1. As proposed, the sponsor should conduct a prospective pregnancy registry for fingolimod as a PMR. The study should not be included in the Gilenya REMS. The following language can be used in the approval letter for the pregnancy registry PMR.

Develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the maternal, fetal, and infant outcomes of women exposed to fingolimod during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes will be assessed through at least the first year of life.

2. For guidance on how to establish a pregnancy exposure registry, the sponsor should review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071639.pdf.

3. The MHT recommends the following language for the Highlights, Warning and Precautions, Pregnancy, Nursing Mothers, and Medication Guide sections of Gilenya labeling. A track changes, word version of labeling will be forwarded to the division.

(b) (4)

[redacted]

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/s/

RICHARDAE T ARAOJO
09/16/2010

Karen B FEIBUS
09/17/2010
I agree with the content and recommendations contained in this review.

LISA L MATHIS
09/20/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 15, 2010
To:	Russell Katz, M.D., Director **Division of Neurology (DNP) Products**
Through:	Mary Willy, PhD, Deputy Director **Division of Risk Management (DRISK)** LaShawn Griffiths, MSHS-PH, BSN, RN Senior Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Robin Duer, MBA, BSN, RN Senior Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name:	GILENYA (fingolimod) capsules
Application Type/Number:	NDA 22-527
Applicant/sponsor:	Novartis
OSE RCM #:	2010-155

1 INTRODUCTION

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Risk Management and Evaluation Strategy (REMS) for Gilenya (fingolimod) capsules. DRISK provided an interim review of the Applicant's proposed REMS under separate cover on September 2, 2010.

Novartis submitted NDA 22-527 on June 15, 2009 as a "fast track rolling submission" indicated for the treatment of patients with relapsing remitting multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. During the review of this NDA the Agency requested that additional information concerning severe adverse events be submitted. In response to FDA's request, that amendment was submitted by Novartis on April 2, 2010 and was considered to be a major amendment. The FDA's review clock was extended to September 21, 2010.

During the review of the Gilenya MG, the DRISK reviewer noted that Section 17 of the prescribing information (PI), Patient Counseling was not developed by the Applicant. DRISK frequently refers to Section 17 of the PI while reviewing patient labeling. During a review team meeting with DNP on August 23, 2010 DRISK discussed the Patient Counseling section of the PI with DNP. DNP stated that the Applicant would be advised to submit a revised PI with a fully developed Patient Counseling section. DRISK was advised to wait to finalize the MG review until the revised PI was received by the Agency. The revised PI was received by the Agency on September 7, 2010.

During an initial team meeting for Gilenya, DNP advised DRISK to use the approved Tysabri MG as a comparator for the MG review of Gilenya. The most recently approved Tysabri MG dated October 3, 2008 was not representative of current recommended patient labeling, so we minimally referred to the approved Tysabri MG for our review of Gilenya.

Please send these comments to the Applicant and let us know if DNP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIALS REVIEWED

- Draft GILENYA (fingolimod) capsules Prescribing Information (PI) submitted on September 7, 2010 and received by DRISK on September 7, 2010.
- Draft GILENYA (fingolimod) capsules Medication Guide (MG) submitted on July 9, 2010 and received by DRISK on August 18, 2010

- TYSABRI (natalizumab) injection for intravenous use Medication Guide approved on October 3, 2008

3 RESULTS OF REVIEW

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- compared the approved Tysabri MG to the proposed Gilenya MG

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

14 page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBIN E DUER
09/15/2010

MARY E WILLY
09/15/2010
I concur

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 10, 2010

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Lori A. Love, M.D., Ph.D. , Lead Medical Officer
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: NDA 22,527 Gilenia (fingolimod hydrochloride)
Indication: Treatment of patients with relapsing-remitting form of multiple sclerosis to reduce the frequency of exacerbations
Dosages: 0.5 mg daily capsules for oral administration
Company: Novartis Pharmaceutical

Materials reviewed: NDA 22-527 (December 21, 2009) is located in the EDR
\\cdsesub1\evsprod\nda022527\022527.enx
Response to FDA request for information on the abuse potential of Fingolimod on Feb 19, 2010 \\CDSESUB1\EVSPROD\NDA022527\0025
Clinical Pharmacology Review, Dec 9, 2009
http://darrts.fda.gov:7777/darrts/ViewDocument?documentId=090140af801b821c

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I. Summary

A. Background

This is our response to the DNP consult regarding the abuse potential risks of fingolimod hydrochloride (FTY720), a new molecular entity (NME). Fingolimod hydrochloride (FTY720, Gilenia) is a novel sphingosine analogue developed by Novartis. The drug acts as a sphingosine 1-phosphate receptor modulator that reversibly traps certain lymphocytes in the lymph nodes, thereby reducing peripheral recirculation, including in the central nervous system. FTY720 was initially studied as prophylaxis for renal transplant rejection, but failed to demonstrate efficacy in Phase 3 trials. Novartis subsequently developed FTY720 for treatment of relapsing-remitting multiple sclerosis (RRMS). Fast-track review status was granted for the RRMS indication with a 6-month goal date of June 21, 2010, which was extended to September 21, 2010.

B. Conclusions:

1. Other than receptor binding studies, the usual array of preclinical abuse potential studies (self administration, drug discrimination, or condition place preference) was not performed. We relied primarily upon analysis of the abuse-related adverse events for assessment of the abuse potential of this drug in humans.
2. The current safety profile of this drug as well as the proposed population of use may likely limit the abuse potential of this drug product. No cases of overdose have been reported to date.
3. The withdrawal AEs from the safety studies D2301 and D2302 show some neurologic and psychiatric AEs which could potentially indicate physical dependence. However they also may be indicative of delayed toxicity of the drug and possibly symptoms related to MS itself.
4. Collection and analysis of postmarketing safety data are necessary to identify any signals related to the abuse and misuse of fingolimod.

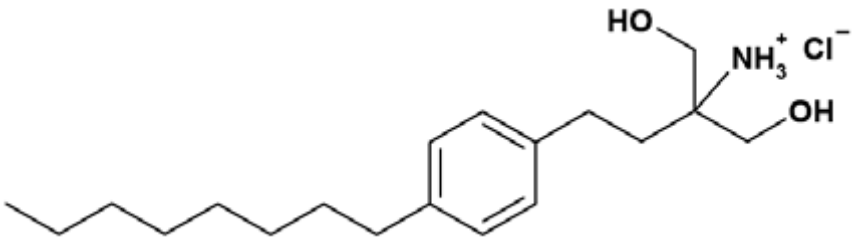
C. Recommendations:

1. The Sponsor should submit all reports of abuse related events and evaluation of these events after marketing of the product.

II. Review

A. Chemistry

The fingolimod hydrochloride, is a small molecule with molecular formula $C_{19}H_{33}NO_2$•HCl. The chemical name is 2-amino-2-[2-(4-octylphenyl)ethyl]-1,3-propandiol, hydrochloride. There are no chiral centers. The structural formula of fingolimod hydrochloride is:



The drug substance is a white powder. It is freely soluble in water, 0.9% saline and aqueous buffers at or below pH 2.0. It is very slightly soluble or almost insoluble in aqueous buffers above pH 3.0. The final commercial product is an immediate release capsule containing 0.5 mg fingolimod as the hydrochloride salt, and the inactive ingredients, mannitol and magnesium stearate.

B. Pharmacology of drug substance and active metabolites

Fingolimod FTY720 is a novel immunosuppressive drug that is structurally similar to sphingosine, a sphingolipids. Fingolimod-P, FTY720-P (but not parent fingolimod FTY720) is a sphingosine-1-phosphate (S1P) receptor modulator. Fingolimod is phosphorylated to the active moiety, S-enantiomer fingolimod-P. The proposed therapeutic mechanism of action of fingolimod in MS is down-modulation of sphingosine 1-phosphate receptors which retains lymphocytes within lymph nodes and Peyer's patches and subsequently reduces number of circulating lymphocytes. This mechanism prevents auto-aggressive T-cells that are implicated in the MS inflammatory disease process from recirculating to blood, tissue and the CNS. Fingolimod-P is reversibly dephosphorylated back to the inactive form fingolimod and in steady state fingolimod and fingolimod-P are in dynamic equilibrium.

Fingolimod and its metabolites in the CNS

FTY720 and its metabolites profiles were examined in the CNS (cerebral cortex and spinal cord) in rats after 14 days of treatment with oral dose of 7.5 mg/kg of [14C] FTY720. In the CNS mainly FTY720 and FTY720-P were present, and FTY720 predominated in the cerebral cortex, whereas FTY720-P predominated in the spinal cord [1]. The concentration of FTY720 in the cerebral cortex was found to be 28 times higher than in blood [2]. The high brain concentration of FTY-720 could have an effect on the activity of some receptors related to abuse such as dopaminergic and serotonergic according to the results of the receptor binding study # *RD-2006-50119.*

1. In vitro studies

Receptor binding studies study # RD-2006-50117 (for FTY720-P) and # RD-2006-50119 (for FTY720)

FTY720 (parent compound) was tested across a radioligand binding assay panel of 66 targets including GPCRs, transporters, ion channels and enzymes. Significant affinities were found for a number of targets: hr Ad_3, hr $Alpha_{2A}$, hr $Alpha_{2B}$, hr $Alpha_{2C}$, hr $Beta_1$, hr CB_1, hr CCKb, hr D_1, hr D_{2L}, hr D_3, hr D_5, hr H_1, hr H_2, hr H_3, hr Motilin, hr M_5, hr MC_3, hr MC_4, hr NT1, hr NK1, hr Opiate κ, hr Opiate μ, hr $5HT_{1A}$, hr $5HT_{2A}$, hr $5HT_{2B}$, hr

[1] EDR. NDA 22-527. CTD 2.6.4 PK Written Summary, page 40.
[2] EDR. NDA 22-527. CTD 2.6.5 PK Tabulated Summary, Table 2.6.5.5L, page 218.

5HT2C, hr DAT, hr NET, h PDE4d (see Table 1). All pKi values for these targets were between 5 and 6 (i.e. Ki between 10 µM and 1 µM), with the exception of the histamine H2 receptor where the affinity was slightly higher: pKi = 6.3 (Ki = 0.50 µM). No follow-up functional assays were performed to test whether FTY720 acts as an agonist or antagonist.

Table 1. Receptor binding results for selected receptors for FTY720 (parent compound).

Receptor profile for PKF117-812-AA-1: Summary of all targets where an activity was found with an IC_{50} of less than 10 microM

Target	% inh 10 µM	n	IC_{50} (µM)	pK_i
hr Ad_3	74	1	6.74	5.19
hr $Alpha_{2A}$	73	3	2.42	5.96
hr $Alpha_{2B}$	77	3	3.64	5.58
hr $Alpha_{2C}$	63	3	6.11	5.59
hr $Beta_1$	40	3	8.27	5.25
hr CB1	66	3	4.43	5.43
hr CCKb	68	1	7.18	5.18
hr D_1	87	3	3.42	5.6
hr D_{2L}	61	3	2.93	5.62
hr D_3	74	3	3.58	5.56
hr D_5	78	2	3.83	5.67
hr DAT	66	3	8.51	5.11
hr H_1	48	3	5.9	5.42
hr H_2	97	2	0.48	6.3
hr H_3	27	2	8.6	5.2
hr 5-HT_{1A}	66	3	5.29	5.87
hr 5-HT_{2A}	73	3	4.86	5.55
hr 5-HT_{2B}	54	4	2.78	5.51
hr 5-HT_{2C}	73	3	2.38	5.70
hr M_5	72	2	6.90	5.32
hr MC_3	105	1	2.06	5.79
hr MC_4	93	1	2.72	5.65
hr Motilin	52	2	8.64	5.12
hr NET	66	3	5.25	5.35
hr NT1	83	2	4.44	5.42
hr NK_1	36	2	9.23	5.47
hr Opiate κ	61	3	5.83	5.36
hr Opiate µ	45	3	5.83	5.65
h PDE4d	54	1	5.89	

% inh 10 µM – inhibition of radioligand binding by PKF117-812 (FTY720) at 10 micoM[5]; IC_{50} - concentration at which 50% inhibition of control value is achieved; pKi – negative log of Ki; Ki – inhibition constant; hr- human recombinat

Modified from Table 3-2, study *# RD-2006-50119 (for FTY720)* from page 20

FTY720-P (active metabolite) was tested across an assay panel for 65 targets including GPCRs, transporters, ion channels and enzymes and no activity was seen at any of the targets up to 10 µM.

As shown in Table 1 (above), FTY720 binds to multiple receptors related to abuse within dopaminergic, serotonergic, opioid, and cannabinoid systems. At 1.25 mg, the highest dose used in Phase III MS clinical trials, a steady state Cmax of approximately 7 ng/ml (20 nM) (page 7, above cited study) was achieved. The volume of distribution of this drug is ~1509 L, indicating a potential for high CNS concentrations. High tissue concentrations of FTY720 were noted in a vitro study in rat where the concentration of the parent compound in the cerebral cortex was 30 times higher than in blood [3]. The estimated FTY720 level in the human brain at the dose of 0.5 mg is 1055 ng/mL (table 2). Therefore, potential activity of FTY720 on some of the above cited receptors can not be excluded. Table 2 comprises comparisons of the brain/blood concentration ratio of FTY720 at steady state (24-hour post dose) following oral administration in rats, cynomolgus monkeys, and dogs.

Table 2. Predicted concentrations of FTY720 in the brain of different species after administration of doses: 0.125 – 5 mg (Study # 00-2265, table 6-4, page 11)[4].

	Daily Dose (mg)					
	0.125	0.25	0.5	1	2.5	5
Observed blood concentrations)(ng/mL) [a)]	0.69	1.36	3.05	5.22	9.13	24.38
Predicted brain concentrations (ng/mL) (Based upon dog brain/blood ratio = 255)	176	347	778	1331	2328	6217
Predicted brain concentrations (ng/mL) (Based upon monkey brain/blood ratio = 346)	239	471	1055	1806	3159	8435

a) Mean observed FTY720 blood concentrations at 24 h after 28 times repeated dosing (B102, Post-text Table 1).

2. Functional tests - Animal behavioral studies

No significant behavioral and physiological effects were observed in the Irwin test in mice, using doses of 0.1 – 10 mg/kg (study # R-7690). Avoidance testing in rats (study # R-7757) at low and high doses showed decreased number of avoidance responses in low dose group but not in high dose group. There was also significant body weight reduction and splenic atrophy in both drug schedules. Decreased adipose tissue was noted in the high dose group. In a rotarod mouse study (# R-7695), oral doses of 0.1, 1.0, 3.0, mg/kg did not produce significant effects compared to vehicle. The dose of 10 mg/kg produced impairment; and mephenesin produced significant impairment.

[3] EDR. NDA 22-,27. CTD 2.6.5 PK Tabulated Summary, Table 2.6.5.5L. Page 218.
[4] EDR. NDA 22,527. Study # 00-2265. Comparison of brain/blood concentration ratio of FTY720 at steady state (24-hour post dose) following oral administration to rats, cynomolgus monkeys, and dogs. Table 6-4. Page 11

In the mouse locomotor activity test (# R-7692) animals received a single dose of vehicle, 0.1 mg/kg, 1.0 mg/kg and 10 mg/kg of FTY720 or 15 mg/kg of diazepam. FTY720 treated animals did not show significant effects on locomotor activity; diazepam produced marked decreases in locomotor activity.

However, the data provided are inconsistent and difficult to interpret. The group mean activity at the start of the observation is higher for 1.0 mg/kg and 0.1 mg/kg FTY720 doses than for vehicle; over the 1 hour observation period, there is a decrease of activity in all FTY720 groups but also in the vehicle group. The decreases of activity do not seem to be dose related: vehicle ~30%, ~50% for 0.1 mg/kg and 1.0 mg/kg doses, but only ~30% for 10 mg/kg. In the 10 mg/kg group, there is an unexplained increase in activity after 10 and 20 min. The diazepam group shows from the beginning much lower activity ~30% of vehicle group, but after 10-30 min there is an unexplained increase in activity and then abrupt decrease to 50% of the initial point of observation and this pattern does not seem to be consistent with the pharmacodynamics of diazepam. The individual animal data are even less consistent.

FTY720 did not have effects on locomotor activity and theophylline-induced convulsions (study # R-76350), but did produce significant prolongation of narcotic sleep in both dose groups, which was interpreted as mild CNS depressant activity at doses tested (10 mg/kg to 30 mg/kg). These doses are approximately 86-fold higher than expected human exposure (R-7635).

The preclinical tests specifically designed to test abuse potential, and studies such as self-administration, drug discrimination or conditioned place preference were not performed.

C. Clinical pharmacology

The sponsor conducted a total of 56 human studies: 31 clinical pharmacology studies (12 pharmacokinetic studies, 14 pharmacodynamic studies and 5 biopharmaceutics studies) and 25 safety and efficacy studies. The safety profile of the drug was characterized in 2300 MS patients; more than 1700 were exposed to the drug at doses of 0.5 mg and 1.25 mg in two completed Phase 3 studies.

Fingolimod is slowly absorbed as indicated by its tmax of 8-36 h; extent of absorption is estimated to be ~85% of dose 6. Fingolimod undergoes biotransformation by 3 pathways: 1) reversible phosphorylation to FTY720-P, the main active metabolite; 2) hydroxylation->oxidation, which produces metabolites M1, M2, M3, and M4; and, 3) formation of nonpolar ceramide M27-M30. In blood, FTY720 accounts for 23.3%, FTY720-P for 10.3%, M3 for 8.3%, M29 for 8.9%, and M30 for 7.3% (Study FTY720A 2217) 5. M3 is pharmacologically inactive. FTY720 and FTY720-P are eliminated by oxidative metabolism and FTY720 and its metabolites are excreted slowly, predominately through the kidneys, as fecal excretion is minor.

Fingolimod and its main active metabolite FTY720-P have long terminal half-lives of 5.7 (137 h) and 6.9 days (166 h), respectively. The apparent volume of distribution of

[5] EDR. NDA 22-527. Study # FTY720A2217. A study to assess the disposition and biotransformation of [^{14}C]FTY720 and metabolites after a single oral dose to healthy male subjects ; page 18, 56, 65

FTY720 is large ~1509L. After the oral dose of 5 mg, the blood levels of FTY720 and FTY720-P at Cmax are 2.83 ng/mL and 3.26 ng/mL, respectively [6].

D. Clinical Studies

A human abuse potential study in recreational drug abusers was not conducted.

1. Adverse events profile through all phases of development

The sponsor performed the safety analysis of AEs and additionally an analysis of abuse related MedDRA terms using a CSS provided list.

In the analysis of all pooled Phase 1 clinical pharmacological studies (FTY720-treated N=843, non-FTY720, N=174 and placebo N=611), approximately 450 (53%) patients treated with FTY720 experienced AEs comparing to 132 (22%) treated with placebo and 81 (46%) treated with non-FTY720 (Table 3).

Table 3. Abuse-related and safety-related CNS adverse events in pooled Phase 1 studies

Risk Category Preferred term	Placebo (N=611) n (%)	Non-FTY720 (N=174) n (%)	FTY720 (N=843) n (%)
-Abuse Potential (overall)			
-Total	22 (3.6)	13 (7.5)	70 (8.3)
Euphoria-related terms			
-Total	19 (3.1)	7 (4.0)	63 (7.5)
Agitation	0	0	1 (0.1)
Dizziness	19 (3.1)	7 (4.0)	59 (7.0)
Feeling drunk	0	0	1 (0.1)
Insomnia	0	0	2 (0.2)
Nervousness	0	0	2 (0.2)
Subjective response terms indicative of impaired attention, cognition, mood, and psychomotor events which are often associated with drugs of abuse			
-Total	3 (0.5)	6 (3.4)	9 (1.1)
Depression	0	0	1 (0.1)
Mood swings	0	0	1 (0.1)
Psychomotor hyperactivity	1 (0.2)	0	0
Restlessness	0	6 (3.4)	1 (0.1)
Somnolence	2 (0.3)	0	6 (0.7)
Dissociative/psychotic (terms often associated pcp, and ketamine)			
-Total	0	0	1 (0.1)
Agitation	0	0	1 (0.1)

Modified from Table 4.7-1, from Amendment - Abuse potential

Abuse related AEs were more frequent for FTY720 group 70 (8.3%) comparing to placebo 22 (3.6%) and the comparator (labeled Non-FTY720 in the table above) 13 (7.5%). In the FTY720 treated group, the most frequent AEs were dizziness[7] 59 (7%),

[6] EDR. NDA 22-527. Study # FTY720A2217. A study to assess the disposition and biotransformation of [^{14}C]FTY720 and metabolites after a single oral dose to healthy male subjects ; page 18, 56, 65

[7] MedDRA term "dizziness" by itself may be associated with abuse potential only when described as "dizziness and giddiness".

somnolence 6 (0.7); there were also a few AEs indicating stimulatory activity of the drug such as insomnia (2), nervousness (2), restlessness (1), agitation (1).

For the analysis of the safety population of MS patients, the sponsor used a pre-defined grouping system group A, B, C, D, E, and F (ISS, page 30) varying by the time of exposure to the drug from 6 months to 24 months from 3 completed studies (D2301, D2302, D2201) and 2 long-term extension studies in MS patients. Group A includes all pooled clinical pharmacological studies (D2301 and D2302) with the drug exposure of 12 months and includes placebo and comparator interferon arms. The analysis encompassed FTY720-treated MS patients with 1.25 mg N=849, with 0.5mg N=854, interferon N=431 and placebo N=418).

In group A, 1521 (89.3%) patients treated with FTY720 had AEs, 396 (92%) patients treated with interferon and 369 (88%) patients treated with placebo. Additional analysis performed by the sponsor for abuse related MedDRA terms shows that FTY720 treatment resulted in 386 (23%) AEs in patients, whereas placebo caused 94 (25%) AEs in patients and interferon caused 96 (24%) AEs (Table 4). The most common AEs in the FTY720 treated group were: dizziness (125; 11.9%), depression 96 (5%), insomnia (64; 3.7%), and anxiety (44; 2.5%), somnolence 19 (1%), irritability 13 (0.8%), disturbance in attention 9 (0.5%) , memory impairment 9 (0.5%), and amnesia 6 (0.35%), much less frequent although present were mood altered (5), mood swings (5), confusional state (4), depersonalization (1), derealization (1), euphoric mood (1), agitation (2), agitated depression (1) and suicide attempt (1).

Table 4. Abuse-related and safety-related CNS adverse events profile in group A, safety population during 12 months of treatment.)

Risk Category Preferred term	FTY720 1.25 mg N=849/ Ny=746.8 n (PR)	FTY720 0.5 mg N=854/ Ny=793.2 n (PR)	Placebo N=418/ Ny=376.7 n (PR)	Interferon N=431/ Ny=401.9 n (PR)
Abuse Potential (overall)				
- Total	180(24.1)	206(26.0)	94(25.0)	96(23.9)
Euphoria-related terms				
- Total	102(13.7)	101(12.7)	45(11.9)	42(10.5)
Dizziness	64(8.6)	61(7.7)	26(6.9)	25(6.2)
Insomnia	33(4.4)	36(4.5)	18(4.8)	14(3.5)
Nervousness	2(0.3)	2(0.3)	1(0.3)	2(0.5)
Abnormal behaviour	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Euphoric mood	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Feeling drunk	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Agitation	0(0.0)	2(0.3)	0(0.0)	0(0.0)
Feeling abnormal	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Subjective response terms indicative of impaired attention, cognition, mood, and psychomotor events which are often associated with drugs of abuse				
- Total	74(9.9)	100(12.6)	46(12.2)	54(13.4)
Depression	37(5.0)	49(6.2)	19(5.0)	36(9.0)
Somnolence	9(1.2)	10(1.3)	10(2.7)	4(1.0)
Disturbance in attention	5(0.7)	4(0.5)	4(1.1)	3(0.7)
Irritability	4(0.5)	9(1.1)	2(0.5)	0(0.0)
Memory impairment	3(0.4)	6(0.8)	4(1.1)	5(1.2)
Amnesia	2(0.3)	4(0.5)	2(0.5)	0(0.0)
Emotional disorder	2(0.3)	0(0.0)	0(0.0)	0(0.0)
Abnormal behaviour	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Affect lability	1(0.1)	2(0.3)	1(0.3)	2(0.5)
Affective disorder	1(0.1)	0(0.0)	1(0.3)	0(0.0)
Attention deficit/hyperactivity disorder	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Confusional state	1(0.1)	3(0.4)	1(0.3)	2(0.5)
Depersonalisation	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Emotional distress	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Impatience	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Mental disorder	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Mood altered	1(0.1)	5(0.6)	0(0.0)	0(0.0)
Mood swings	1(0.1)	4(0.5)	0(0.0)	0(0.0)
Restlessness	1(0.1)	1(0.1)	0(0.0)	1(0.2)
Amnestic disorder	0(0.0)	0(0.0)	1(0.3)	0(0.0)
Cognitive disorder	0(0.0)	3(0.4)	1(0.3)	0(0.0)
Mental impairment	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Dissociative/psychotic (terms often associated pcp, and ketamine)				
- Total	8(1.1)	10(1.3)	5(1.3)	3(0.7)
Affective disorder	1(0.1)	0(0.0)	1(0.3)	0(0.0)
Aggression	1(0.1)	1(0.1)	0(0.0)	0(0.0)
Confusional state	1(0.1)	3(0.4)	1(0.3)	2(0.5)
Depersonalisation	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Derealisation	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Dysarthria	1(0.1)	0(0.0)	1(0.3)	0(0.0)
Muscle rigidity	1(0.1)	1(0.1)	0(0.0)	0(0.0)
Speech disorder	1(0.1)	3(0.4)	1(0.3)	0(0.0)
Agitation	0(0.0)	2(0.3)	0(0.0)	0(0.0)
Mental impairment	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Psychotic disorder	0(0.0)	0(0.0)	1(0.3)	0(0.0)

Modified from Table 4.5-1 from Amendment – Abuse potential

Summary of AEs for the Group E (includes data from studies D2301, D2302 as in Group A ,with the addition of studies D2201 and extension studies D2201E1 and D2302E1) with a time period of 24 months shows a similar profile of AEs, however, 4 hallucinations and 2 cases of paranoia were also noted.

After FTY720 treatment, the AEs related to abuse potential were not very common; however, their profile might indicate drug activity on dopaminergic, serotonergic receptors consistent with the results of the in vitro study # RD-2006-50119 and high predicted levels of FTY720 in the human brain of approximately ~ 1055 ng/ml following an oral dose of 0.5 mg of FTY720 [4].

It is possible that AEs such as depressions, paranoia, mood altered, mood swings, affect lability, depersonalization, derealization, and hallucinations reflect the activity of the drug in CNS in particular on the dopaminergic and serotonergic receptor systems.

2. Safety profile

Accidental overdose in the patient population and vulnerable populations

The sponsor states that no cases of overdose have been reported to date [8]. Fingolimod was administered to humans in doses up to 40 mg. There was dose dependent decrease in lymphocytes count up to 91% at 40 mg. Additionally, at this dose heart rate reduction was seen, reduced pulmonary function and chest tightness and discomfort.

Overdose associated with misuse and abuse

No data are provided for the evaluation of drug misuse, abuse and diversion during clinical development.

Withdrawal and dependency.

No study was performed to specifically evaluate drug withdrawal effects. However an analysis 9 from more than 400 patients who discontinued FTY720 treatment and more than 100 patients who discontinued placebo treatment in the FTY720 clinical trials was performed. The collected AEs during the time period 1-45 day after study drug discontinuation in patients from the safety studies D2301, and study D2302 show presence of some withdrawal AEs.

In the study D2301 for FTY720 treated patients: for 1.25 mg, N=114, for 0.5 mg, N=74, and for placebo, N=94, AEs total was 36 (31.6%) and 20 (27%), and 23 (24.5%), respectively. The most common AEs for FTY720 treated patients were infections - 15 (7.9%); AEs from the Nervous system -14 (7.4%) included headaches, MS relapse, CVA, epilepsy, neuralgia; GI system - 7 (3.7%) nausea, vomiting, abdominal pain; Musculoskeletal - 4 (2.1%), back pain; and Psychiatric AEs - 3 (1.5%), PTSD, anxiety, depression (Study D2301, below).

[8] EDR. NDA 22-527. Mod 2.5 Clinical Overview; page 71
[9] EDR. NDA 22-527. Mod 2.7.4 Summary of Clinical Safety; page 343

Table 5. Withdrawal symptoms in the study D2301

Table 14.3.1-1.12 (Page 1 of 8)
Adverse events, regardless of study drug relationship, after study drug discontinuation (day 1 to 45), by primary system organ class, preferred term and treatment
Follow-up population

Primary system organ class Preferred term	FTY720 1.25mg N=114 n (%)	FTY720 0.5mg N=74 n (%)	Placebo N=94 n (%)
-Any primary system organ class			
-Total	36(31.6)	20(27.0)	23(24.5)
Gastrointestinal disorders			
-Total	4(3.5)	1(1.4)	3(3.2)
Nausea	2(1.8)	0(0.0)	1(1.1)
Vomiting	2(1.8)	0(0.0)	0(0.0)
Abdominal pain	1(0.9)	0(0.0)	0(0.0)
Infections and infestations			
-Total	6(5.3)	9(12.2)	5(5.3)
Musculoskeletal and connective tissue disorders			
-Total	3(2.6)	1(1.4)	2(2.1)
Back pain	3(2.6)	1(1.4)	0(0.0)
Nervous system disorders			
-Total	11(9.6)	3(4.1)	1(1.1)
Headache	4(3.5)	1(1.4)	1(1.1)
Multiple sclerosis relapse	2(1.8)	0(0.0)	0(0.0)
Cerebrovascular accident	1(0.9)	0(0.0)	0(0.0)
Epilepsy	1(0.9)	0(0.0)	0(0.0)
Neuralgia	1(0.9)	0(0.0)	0(0.0)

Modified from Table 14.3.1, Summary of Clinical Safety

In the study D2302 for FTY720 treated patients: 1.25 mg N=91, 0.5 mg N=74, comparator N=89, the withdrawal AEs were less common and showed a total of 17 (18.7%), 10 (13.5%) and 12 (13.5%), respectively. The most common AEs were from the Nervous system 8 (4.8%) coma, brain edema, headache, cognitive disorder, paraesthesia; Psychiatric AEs 3, (1.8%), depression, agitated depression, suicide attempt; from GI tract 7 (4.2%) constipation, gastritis, nausea; General disorders: 5 (2.6%) fatigue, influenza like illness, irritability, Cardiac AEs 3 (1.8%) myocardial ischemia, tachycardia, palpitations, conduction disorder (Table 6).

Table 6. Withdrawal symptoms in the study D2302; Summary of Clinical Safety, modified Table 14.3.1- 1.8 Adverse events, regardless of study drug relationship, after study drug discontinuation (day 1 to 45), Follow-up population

Primary system organ class Preferred term	FTY720 1.25mg N=91 n (%)	FTY720 0.5mg N=74 n (%)	Interferon beta-1a i.m. N=89 n (%)
-Any primary system organ class			
-Total	17(18.7)	10(13.5)	12(13.5)
Nervous system disorders			
-Total	2(2.2)	1(1.4)	1(1.1)
Areflexia	1(1.1)	0(0.0)	0(0.0)
Brain oedema	1(1.1)	0(0.0)	0(0.0)
Coma	1(1.1)	0(0.0)	0(0.0)
Headache	1(1.1)	0(0.0)	1(1.1)
Cognitive disorder	0(0.0)	1(1.4)	0(0.0)
Hemiparesis	0(0.0)	1(1.4)	0(0.0)
Hypoaesthesia	0(0.0)	0(0.0)	1(1.1)
Paraesthesia	0(0.0)	1(1.4)	0(0.0)
Psychiatric disorders			
-Total	1(1.1)	1(1.4)	1(1.1)
Suicide attempt	1(1.1)	0(0.0)	0(0.0)
Agitated depression	0(0.0)	1(1.4)	0(0.0)
Depression	0(0.0)	0(0.0)	1(1.1)
Insomnia	0(0.0)	1(1.4)	0(0.0)
Gastrointestinal disorders			
-Total	2(2.2)	4(5.4)	1(1.1)
Constipation	2(2.2)	1(1.4)	0(0.0)
Gastritis	1(1.1)	1(1.4)	0(0.0)
Dental caries	0(0.0)	1(1.4)	1(1.1)
Nausea	0(0.0)	1(1.4)	0(0.0)
Cardiac disorders			
-Total	2(2.2)	1(1.4)	1(1.1)
Myocardial ischaemia	1(1.1)	0(0.0)	0(0.0)
Tachycardia	1(1.1)	0(0.0)	0(0.0)
Conduction disorder	0(0.0)	0(0.0)	1(1.1)
Palpitations	0(0.0)	1(1.4)	0(0.0)
General disorders and administration site conditions			
-Total	3(3.3)	2(2.7)	1(1.1)
Fatigue	1(1.1)	0(0.0)	0(0.0)
Influenza like illness	1(1.1)	1(1.4)	0(0.0)
Irritability	1(1.1)	1(1.4)	0(0.0)

The withdrawal AEs from the safety studies D2301 and D2302 show some AEs which could potentially indicate physical dependence however they can indicate also delayed toxicity of the drug and possibly symptoms related to MS itself.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

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/s/

ALICJA LERNER
09/10/2010

MICHAEL KLEIN on behalf of LORI A LOVE
09/10/2010

MICHAEL KLEIN
09/10/2010

Division of Drug Marketing, Advertisement, and Communications

Internal Consult

****Pre-decisional Agency Information****

To: Eric Basting, MD, Deputy Director, Division of Neurology Products DNP)
Hamet Toure, PharmD, MPH, Regulatory Project Manager, DNP

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Reviewer, Division of Drug Marketing, Advertising, and Communications, (DDMAC)

CC: Andy Haffer, Group Leader, DDMAC
Catherine Gray, Management Advisor, DDMAC

Date: September 7, 2010

Re: Comments on draft labeling (Package Insert) for Gilenya (fingolimod)
NDA 22-527

Thank you for the opportunity to review the proposed PI for Gilenya (FDA dated version 9/2/2010). Please see attached PI with our comments incorporated therein.

19 page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

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/s/

QUYNH-VAN TRAN
09/07/2010

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: July 27, 2010

TO: Hamet Toure, PharmD, MPH, Regulatory Health Project Manager
Heather Fitter, M. D., Medical Officer
Division of Neurology Products

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-527

APPLICANT: Novartis Pharmaceuticals Corporation

DRUG: Gilenia (fingolimod) 0.5mg capsules

NME: Yes.

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of patients with relapsing forms of multiple sclerosis

CONSULTATION REQUEST DATE: January 21, 2010

DIVISION ACTION GOAL DATE: June 21, 2010, extended to 9/21/10

PDUFA DATE: Extended to September 21, 2010

I. BACKGROUND:

The Sponsor, Novartis, submitted a New Drug Application (NDA) for the use of fingolimod (FTY720) in relapsing forms of multiple sclerosis (MS). Fingolimod is a novel, synthetic small molecule in clinical development for renal transplantation, in addition to MS.

The clinical experience with fingolimod with single or multiple doses (2.5 or 5mg/day) in combination with cyclosporine A and corticosteroids in the context of de novo renal transplantation has demonstrated evidence of acceptable tolerability according to the applicant. Based on the renal transplant experience, pharmacodynamic effects ascribed to fingolimod are:

- a rapid and persistent reduction of the peripheral lymphocyte count that is reversible after discontinuation,
- a predictable reduction in heart rate that is maximal upon treatment initiation and attenuates over time under control treatment,
- and a mild–to moderate increase in airway resistance early after continued treatment.

The applicant purports that the molecular basis of these effects is well understood and compatible with the known mode of action fingolimod via engagement of sphingosine-1 phosphate (SIP) receptors. According to the applicant "FTY720" acts as "super agonist" of the SIP1 receptor on thymocytes and lymphocytes, inducing internalization of that receptor. This renders cells unresponsive to SIP1 signaling, which results in a decrease in the number of B and T lymphocytes in the CNS. Diminishing the number of lymphocytes in the CNS results in less of an immunologic reaction against the myelin sheath, thus leading to the purported benefits in MS.
The results of two pivotal studies were submitted in support of the application:

- Protocol FTY720D-2301 entitled: **"**A 24 Month, Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel Group Study Comparing Efficacy and Safety of FTY720 1.25mg and 0.5 mg Administered Orally once Daily Versus Placebo in Patients with relapsing-Remitting Multiple Sclerosis"; and

- Protocol CFTY720D-2302 entitled: **"**A 12 Month, Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel Group Study Comparing Efficacy and Safety of FTY720 1.25mg Fingolimod (FTY720) Administered Orally once Daily Versus Interferon ß -1a (AvoneX) administered i.m. once Weekly in Patients with relapsing-Remitting Multiple Sclerosis". Both Protocols describe studies that are of 24 weeks in duration.

In Study FTY720D-2301, subjects with a clinically defined diagnosis of Multiple Sclerosis with a relapsing-remitting course with at least 1 documented relapse during the last year, or two documented relapses in the last 2 years, preceding their enrollment to the study were to be randomized, to receive in a1:1:1 ratio, to oral treatment with FTY720 1.25 mg, FTY 720 0.5 mg, or placebo once daily for up to 24 months.

In Study FTY720D-2302, subjects with a clinically defined diagnosis of MS were to be randomized to receive, in a 1:1:1 ratio, treatment with FTY 720 1.25mg/day, FTY720 0.5mg /day, or interferon ß-1a (30µg week i.m.) in a double dummy design (fingolimod capsules and matching placebo) were to be packed in identical bottles.

A brief description of the study objectives are presented below.

Study Protocol FTY720D-2301's primary objective was to evaluate the efficacy of two doses of FTY720 (1.25mg and 0.5mg) in reducing the frequency of relapses compared to placebo in subjects with relapse-remitting MS (RRMS) treated for up to 24 months. The treatment included male and female subjects between 18-55 years of age.

The key secondary objectives of the study were: 1) to evaluate the effect of FTY720 relative to placebo on disability progression as measured by the time to confirmed disability progression in subjects treated for up to 24 months, and 2) to demonstrate that FTY720 is effective in reducing the frequency of relapses compared to placebo in subjects treated for up to 12 months.

Study Protocol FTY720D-2302's primary objective was to compare fingolimod 1.25mg and 0.5 mg with interferon ß-1a and to demonstrate that at least fingolimod 1.25 mg was superior to interferon ß-1a in terms of annualized relapse rate for subjects with RRMS treated up to 12 months. The treatment included both male and female subjects between18 -55 years of age.

The key secondary objectives (considered key by review staff) of the study were: 1) to demonstrate superiority of fingolimod (1.25mg and 0.5 mg per day) over interferon ß 1a (30µg/week i.m.) in subjects with RRMS treated for up to 12 months in the proportion of relapse –free patients, and 2) to test for difference in efficacy of fingolimod (1.25mg and 0.5mg per day) vs. interferon ß-1a for the proportion of subjects with confirmed disability progression.

The review division requested inspection of three foreign clinical investigators in Protocols FTY720D-2301 and CFTY720D-2302 as data from the two studies are considered essential to the approval decision. One foreign clinical investigator was selected from Protocol CFTY720D-2301 and two foreign investigators were selected from Protocol FTY720D-2302. These sites were targeted for inspection due to enrollment of a relatively large number of subjects and significant primary efficacy results pertinent to decision- making.

II. RESULTS (by protocol/site):

Name of CI, site # and location	**Protocol and # of subjects**	**Inspection Dates**	**Final Classification**
Krzysztof Selmaj, M.D Oddzial kliniczny Neurologii Uniwesytecki Szpital Kliniczny nr 1im. Barlickkiego UI Kopcinskiego 22, 90-153 Lodz, Poland Site# 707	Protocol D-2301 Number of subjects listed 53	5/4-10/10	NAI
Ruggero Capra, M.D. Presidio Ospedaliero di Montichari Montichiari BS 25018 Italy Site # 211	Protocol D-2302 Number of subjects listed 22	4/26-30/10	Pending Preliminary: NAI
Karl Baum, M.D. Oberhavel Kliniken GmbH Heningsdorf 16761 Germany Site # 303	Protocol D-2302 Number of subjects listed 19	5/3-7/10	VAI

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Note: Observations noted below for Dr. Capra's site are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

Protocol CFY 720D-2301

1. **Krzysztof Selmaj, M.D.**
   Lodz, Poland

   a. What Was Inspected: At this site, a total of 65 subjects were screened, 12 subjects were reported as screen failures, 53 subjects randomized, 50 subjects completed the study, and 3 subjects withdrew their consent. There were no deaths reported at this site. Review of Informed Consent Documents, for all records reviewed, verified that subjects signed prior to enrollment.

   A review of the medical records/source documents was conducted. The medical records for 30 subjects were reviewed, including drug accountability records, vital signs, laboratory test results, sponsor correspondence, and inclusion/exclusion criteria; source documents were compared to case report forms and to data listings, including primary efficacy endpoints and adverse events.

   b. **General observations/commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Selmaj. Our investigation found minor insignificant discrepancies between the source documents and the case report forms for four study subjects regarding calculation of pulmonary function tests (based on previous hemoglobin instead of current hemoglobin) which appear to be an error that was detected and corrected. In addition, 2 subjects had discrepancies in drug accountability records. Subject 707-051, Visit 11 reported 20 capsules returned instead of 17; and Subject707-0062, Visit 11 there were 19 capsules returned and not 9. The clinical investigator acknowledged the inspectional findings and stated that corrective action plans will be instituted and promised to be vigilant in the oversight of his staff.

   c. **Assessment of Data Integrity:** Although very minor regulatory violations were noted, the findings are unlikely to affect data integrity as they appear to be isolated occurrences and not systemic in nature. The remaining data generated from Dr. Selmaj's site are considered reliable and appear acceptable in support of the application.

Protocol CFY720D-2302

2. **Ruggero Capra, M.D.**
   Montechiaro, Italy

   a. What Was Inspected: At this site, a total of 23 subjects were screened and 23 subjects were randomized into the study. Seventeen subjects completed the study and six subjects were discontinued and the reasons were documented. There were no deaths reported at this site and no evidence of under-reporting of adverse events. Review of Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for all subjects were reviewed, including drug accountability records, vital signs, laboratory results, IRB records, inclusion/exclusion criteria, adverse events, and laboratory results; source documents for 5 subjects were compared to case report forms and to data listings, to include primary efficacy endpoints. No Form FDA 483 was issued at the conclusion of the inspection.

b. General Observations/Commentary: Our investigation found no evidence of under reporting of adverse events.

The medical records/source document reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and verifiable. There were no known limitations to this inspection.

c. Assessment of Data Integrity

The data from Dr. Capra's site are considered reliable and appear acceptable in support of the pending application.

3. Karl Baum, M.D.
Heningsdorf, Germany

a. What Was Inspected: At this site, a total of 22 subjects were screened, 2 subjects were reported as screen failures, 20 subjects were randomized into the study, one subject withdrew from the study and 19 subjects completed the study. There were no deaths and no under-reporting of adverse events. Review of Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 22 subjects were reviewed, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, use of concomitant medications, and protocol deviations; source documents were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events.

b. General Observations/Commentary: At the conclusion of the inspection, a two item FDA 483 was issued to Dr. Baum. Our investigation found that the drug storage for the comparator drug AvoneX (interferon beta-1a) syringes exceeded the storage temperatures of 2-8º C (35.6-46.4 º F) set by the protocol. Our field investigator noted weekly temperature charts between 10/28/07- 9//15/08 in the range of 8.1- 16.9 º C. The storage temperatures of AvoneX (interferon beta-1a) syringes were discussed with the review team and all agreed that this finding should have no impact on study results since the AvoneX label allows storage temperatures as high as 25º C. Although this observation has not adversely impacted study results and represents a minor protocol violation, DSI has retained a final classification of VAI for this inspection, as a similar finding for another drug could potentially have impacted stability. In addition, 3 site

personnel (independent Physicians who assessed EDSS) failed to document their yearly re-certification.

With the exception of the items noted above, the records reviewed were found to be in order and the data verifiable and the data generated by this site appear acceptable in support of the respective indication. There were no known limitations to this inspection.

c. Assessment of Data Integrity: Although regulatory violations were noted, these are unlikely to impact data reliability. The data from Dr. Baum's site are considered reliable and appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three foreign clinical investigators were inspected in support of this application. The inspections of Drs. Salmej, Capra, and Baum revealed no significant problems that would adversely impact data acceptability. Overall the data submitted from these sites are acceptable in support of the pending application.

Note: Observations noted for Dr. Capra's site are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

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/s/

ANTOINE N EL HAGE
07/29/2010

TEJASHRI S PUROHIT-SHETH
07/29/2010

MEMORANDUM

To: **Hamet Toure, PharmD, MPH**
Division of Neurology Products

From: **Iris Masucci, PharmD, BCPS**
for Study Endpoints and Label Development (SEALD) Team, OND

Date: **May 27, 2010**

Re: **Comments on draft labeling for fingolimod capsules**
NDA 22-527

We have reviewed the proposed label for fingolimod capsules (sponsor's version dated 5/24/10) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes. Please note that this version of the label did not yet include changes from the review team. Further comments are likely to follow.

20 page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

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/s/

IRIS P MASUCCI
06/17/2010

LAURIE B BURKE
06/21/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 24, 2010
To:	Russell Katz, MD, Director Division of Neurology Products
Through:	Zachary Oleszczuk, PharmD, Acting Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Felicia Duffy, RN, BSN, MSEd, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name:	Gilenia (Fingolimod) Capsules 0.5 mg
Application Type/Number:	NDA 022527
Applicant:	Novartis
OSE RCM #:	2010-355

1 INTRODUCTION

This review responds to a request from the Division of Neurology Products for DMEPA's assessment of labels and labeling for Gilenia (Fingolimod) Capsules for their vulnerability to medication errors.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis[1] (FMEA) in our evaluation of the container label, carton labeling and insert labeling that were submitted by the Applicant on March 4, 2010 (see Appendix A through E; no image of insert labeling).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be clarified and improved upon to minimize the potential for medication errors. Section 3.1 *(Comments to the Division)* contains our recommendations for the insert labeling. Section 3.2 (*Comments to the Applicant)* contains our recommendations for the container label and carton labeling. We request these recommendations be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Laurie Kelley, OSE Regulatory Project manager, at 301-796-5068.

3.1 COMMENTS TO THE DIVISION

1. Revise the statement: (b) (4) in the Dosage and Administration section to read as: (b) (4).
2. Since the initiation of this product may not be well tolerated by patients susceptible to bradycardia and it is recommended that these patients be monitored for 6 hours after the first dose, repeat the following statement in the both the Highlights of the Dosage and Administration section and in the Full Prescribing Information of the Dosage and Administration section:

   (b) (4)

3. We note that the carton labeling and container labels contain (b) (4). This statement is confusing as it appears that Gilenia (b) (4). We defer to CMC on whether or not this (b) (4) statement is necessary. If the statement is not necessary, we recommend deleting it from all carton labeling and container labels.

[1] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

3.2 COMMENTS TO THE APPLICANT

A. Inner Sleeve Blister Label (7 count, Physician Sample)

1. Delete the [redacted] (b) (4) from the front and back of the sleeve as the same dose is administered each day. In its place, insert the dosage across the bottom of the sleeve: [redacted] (b) (4) The current presentation may be confusing and lead patients to believe they have to wait until Monday to start their medication. Additionally, the start day of the week will vary between patients depending upon which day patients start taking their medication.
2. On the front of the blister, delete the statement: [redacted] (b) (4)

B. Inner Sleeve Blister Label (28 count)

1. The current presentation of the days of the week and the weeks on the blister label is confusing. As currently presented patients may mistakenly administer two capsules as a single dose rather than one capsule (see Figure 1 below). [redacted] (b) (4) from the front of the sleeve as not all patients will have a Monday start and this may be confusing. Additionally, relocate the pink lines separating the days to appear beneath each capsule (see Figure 2 below).

[redacted] (b) (4)

2. Include a dosage statement on the inner sleeve: [redacted] (b) (4)

C. Carton Labeling (7 count- Sample and Trade, and 28 count)

1. The carton labeling for the 28 count carton does not contain a bar code. Revise the labels to include a bar code to comply with 21 CFR 201.25.
2. On the principle display panel of the trade carton, switch the location of the product strength and net quantity in order to improve the flow of readability from the proprietary name to the established name to the product strength. The product strength should maintain its prominence.

5 page(s) of Draft Carton and Container Labels have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

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/s/

FELICIA DUFFY
05/24/2010

ZACHARY A OLESZCZUK
05/24/2010

DENISE P TOYER
05/25/2010

CAROL A HOLQUIST
05/25/2010

DSI CONSULT: Request for Clinical Inspections

Date: January 21, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Eric Bastings, MD, Deputy Director/Cross-Discipline Team Leader, DNP
Russell Katz, MD, Director, DNP

From: Hamet Touré, PharmD MPH, Regulatory Health Project Manager, DNP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 022527
Applicant: Novartis Pharmaceuticals Corporation
Applicant contact information (to include phone/email):

Mara Stiles
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080, USA
Phone: +1 862 7783771
Fax: +1 973 7813310
Email : mara.stiles@novartis.com

Drug Proprietary Name: Gilenia (fingolimod) 0.5 mg capsules
NME or Original BLA (Yes/No): Yes
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication: For the treatment of treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

PDUFA: June 21, 2010
Inspection Summary Goal Date: May 28, 2010

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Center 707 Dr. Krzysztof Selmaj:PI Oddzial Kliniczny Neurologii Uniwersytecki Szpital Kliniczny nr 1 im. Barlickiego UI. Kopcinskiego 22, 90-153 Lodz Poland	D2301	53	As stated above
Center 211 Dr.ssa Ruggero Capra: PI Presidio Ospedaliero di Montichiari Montichiari BS 25018 Italy	D2302	22	As stated above
Center 303 PD Dr.med.Karl Baum:PI Oberhavel Kliniken GmbH Heningsdorf 16761 Germany	D2302	19	As stated above

III. Site Selection/Rationale

Most study centers in both studies enrolled very small number of patients. Center 707 is the largest site for protocol D2301, and is one of the only 4 sites that enrolled 30 or more patients. Center 707 is chosen for its size and its contribution to efficacy. No US sites participated in study D2301.

Center 211 is chosen because Italy enrolled the largest number of subjects in Protocol D2302, and center 211 is one of the two largest centers in Italy for Study D2302.

Center 303 is chosen because a relatively larger proportion (compared to other sites) of unconfirmed relapses were treated by rescue medication.
No specific concerns were raised from the preliminary analysis of the data for centers 707 and 211.

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

__X__ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Should you require any additional information, please contact LT Hamet Touré, PharmD MPH, at 301-796-7534 or Heather Fitter, MD, DNP Medical Officer at 301-796-3984.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HAMET M TOURE
02/22/2010

RUSSELL G KATZ
02/25/2010