CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-527

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Toure, Hamet (LT,USPHS)

From: mara.stiles@novartis.com
Sent: Tuesday, September 21, 2010 7:06 PM
To: Toure, Hamet (LT,USPHS)
Cc: Toure, Hamet (LT,USPHS)
Subject: Re: 022527_Approval Letter
Attachments: 022527_Fingolimod approval letter_092110.pdf; emfinfo.txt

Dear Hamet,
We acknowledge receipt of the attached approval letter for NDA 22527.

thank you very much

Mara Stiles

Mara Stiles
Novartis Pharmaceuticals Corporation
DRA-NSO
USEH, 404-416
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

"Toure, Hamet (LT,USPHS)" <Hamet.Toure@fda.hhs.gov>
09/21/2010 06:49 PM

Please respond to
Hamet.Toure@fda.hhs.gov

To
"'mara.stiles@novartis.com'" <mara.stiles@novartis.com>
cc
"Toure, Hamet (LT,USPHS)" <Hamet.Toure@fda.hhs.gov>
Subject
022527_Approval Letter

Dear Ms. Stiles,

We refer you to NDA 022527. Please find attached the approval letter for your NDA.
Please confirm in writing that you have received and can open the document.

Please let me know if you have any questions.

Respectfully,

Hamet Touré, PharmD MPH
LT, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation - Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
Email: hamet.toure@fda.hhs.gov

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/s/

HAMET M TOURE
09/22/2010

Toure, Hamet (LT,USPHS)

From: Toure, Hamet (LT,USPHS)
Sent: Tuesday, September 21, 2010 8:26 AM
To: 'mara.stiles@novartis.com'
Cc: Toure, Hamet (LT,USPHS)
Subject: RE: 022527_Revised PI

Dear Ms. Stiles,

Please note that the Group D analysis sent around 4:10 PM yesterday does not change the review team's conclusions that the statement should be deleted.

Sincerely,

Hamet Touré, PharmD MPH
LT, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
Email: hamet.toure@fda.hhs.gov

From: mara.stiles@novartis.com [mailto:mara.stiles@novartis.com]
Sent: Monday, September 20, 2010 6:53 PM
To: Toure, Hamet (LT,USPHS)
Cc: Toure, Hamet (LT,USPHS); Bastings, Eric
Subject: Re: 022527_Revised PI

Dear Hamet,

Regarding the deletion of the statement in section 7 Drug Interactions, we are wondering if this conclusion was reached before we sent the Group D analysis around 4:10 PM today. (archival submission of this data is also going through the gateway this evening if not already.)

Does the Group D analysis provided change the FDA outlook regarding this point?

thanks
Mara Stiles

Mara Stiles
Novartis Pharmaceuticals Corporation
DRA-NSO
USEH, 404-416
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

"Toure, Hamet (LT,USPHS)" <Hamet.Toure@fda.hhs.gov>
09/20/2010 05:40 PM

Please respond to
Hamet.Toure@fda.hhs.gov

To
"'mara.stiles@novartis.com'" <mara.stiles@novartis.com>
cc
"Toure, Hamet (LT,USPHS)" <Hamet.Toure@fda.hhs.gov>
Subject
022527_Revised PI

Dear Ms. Stiles,

We refer you to NDA 022527. Please find enclosed the revised labeling. We may have additional changes tomorrow.
Sincerely,

Hamet Touré, PharmD MPH
LT, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation - Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
Email: hamet.toure@fda.hhs.gov

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/s/

HAMET M TOURE
09/22/2010

Toure, Hamet (LT,USPHS)

From: Toure, Hamet (LT,USPHS)
Sent: Tuesday, September 21, 2010 12:15 PM
To: 'mara.stiles@novartis.com'
Cc: Toure, Hamet (LT,USPHS)
Subject: 022527_Updated document

Dear Ms. Stiles,

We refer you to NDA 022527. Please find enclosed the final version of the PMRs and PMC.

PMRs

1: Deferred pediatric study under PREA: a 24-month, randomized, active-controlled, parallel group study to evaluate the single and multiple dose pharmacokinetics of fingolimod, and the safety and efficacy of multiple doses of fingolimod compared to interferon beta 1-a-intramuscular (Avonex) for the treatment of relapsing-remitting multiple sclerosis. The efficacy portion of this trial should be designed to show superiority of fingolimod over active control.

Final Protocol Submission Date: December 1, 2011
Study Completion Date: August 6, 2015
Final Report Submission: January 1, 2016

Submit the protocol for the study to your IND as a special protocol assessment (SPA), with a cross-reference letter to this NDA. Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment**".

2: 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.

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission: January 31, 2011
Study Completion: May 15, 2020
Final Report Submission: December 15, 2020

3: 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.

In addition, for guidance on how to establish a pregnancy exposure registry, please review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071639.pdf.

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 21, 2010
Study Completion:	March 31, 2017
Final Report Submission:	October 31, 2017

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

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	February 1, 2011
Study Completion:	September 1, 2011
Final Report Submission:	December 1, 2011

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

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Study Completion:	July 15, 2010
Final Report Submission:	October 15, 2010

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

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	February 1, 2011
Study Completion:	September 1, 2011
Final Report Submission:	December 1, 2011

7: 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).

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 21, 2010
Study Completion:	June 30, 2011
Final Report Submission:	January 30, 2012

8: 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.

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	January 31, 2011
Study Completion Date:	October 29, 2011
Final Report Submission:	March 31, 2012

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

The timetable you submitted on September 17, 2010 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	February 1, 2011
Trial Completion:	April 1, 2012
Final Report Submission:	July 1, 2012

PMC

10: 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.

Final Protocol Submission:	September 30, 2011
Study Completion:	March 30, 2015
Final Report Submission:	July 30, 2015

You do not need to respond to this communication; it is for your information only.

Sincerely,

Hamet Touré, PharmD MPH
LT, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
Email: hamet.toure@fda.hhs.gov

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/s/

HAMET M TOURE
09/22/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Office of Compliance

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Eric Bastings, MD, Deputy Director, Division of Neurology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/16/2010		022527		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Fingolimod	Priority	Multiple sclerosis	9/20/2010

NAME OF FIRM: Novartis Pharmaceuticals Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

We request evaluation of the REMS and draft approval letter for fingolimod. The action date is Tuesday, September 21, 2010.

A word version of the document will be sent by email. Attached are PDF versions of the documents. The REMS supporting document will follow shortly.

Thank you

15 pages of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/

HAMET M TOURE
09/16/2010

ERIC P BASTINGS
09/16/2010

Toure, Hamet (LT,USPHS)

From: Toure, Hamet (LT,USPHS)
Sent: Wednesday, September 01, 2010 10:54 PM
To: 'mara.stiles@novartis.com'
Cc: Toure, Hamet (LT,USPHS)
Subject: 022527_1 September 2010_PMRs

Dear Ms. Stiles,

We refer you to NDA 022527. Below is the list of postmarketing requirements (PMRs) for fingolimod.

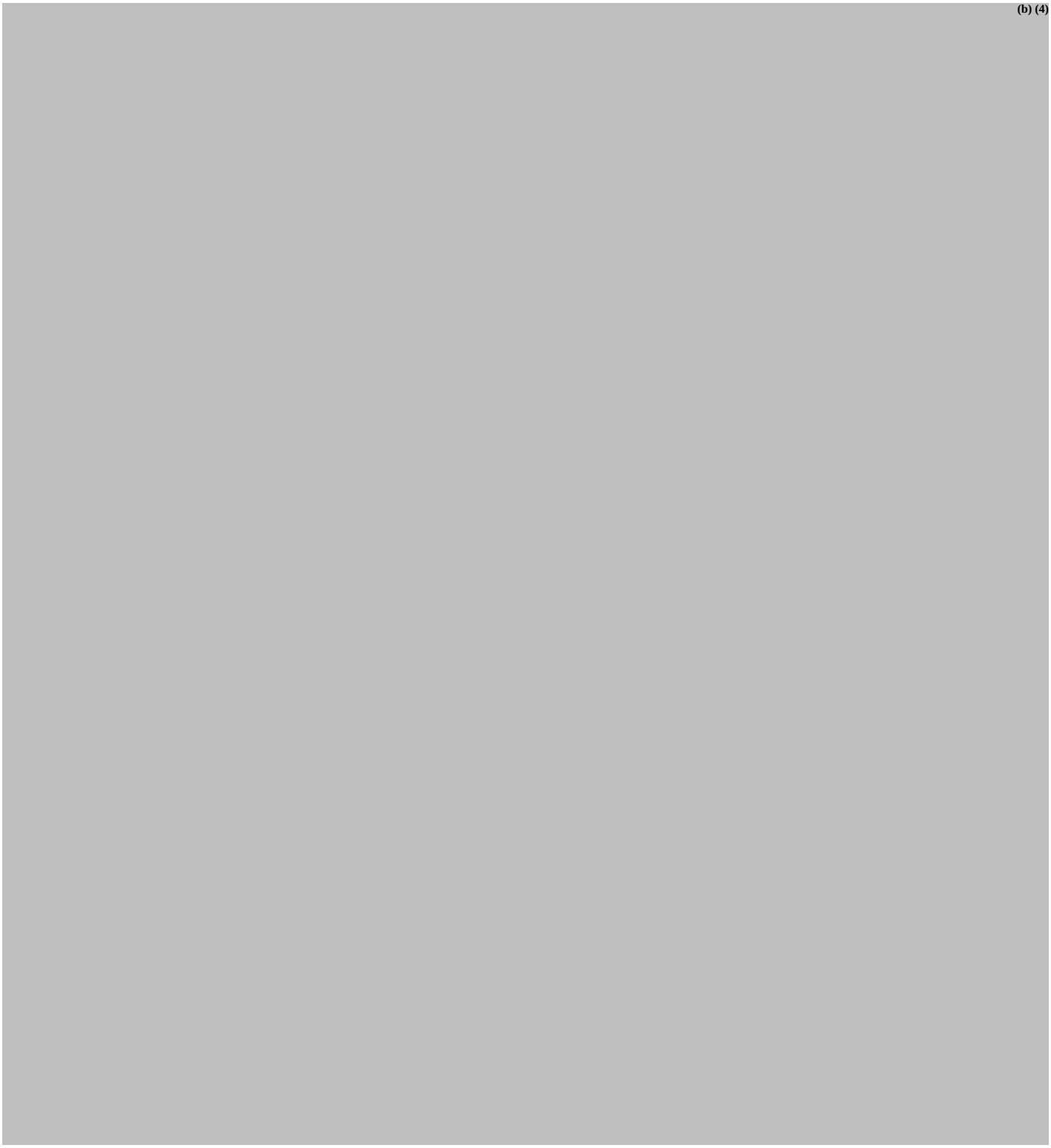
For each PMR (except #1), please provide a date for final protocol submission, study/trial completion, and final report submission.

1: Deferred pediatric study under PREA: a 24-month, randomized, active-controlled, parallel group study to evaluate the single and multiple dose pharmacokinetics, and the safety and efficacy of multiple doses of fingolimod compared to interferon beta 1-a-intramuscular (Avonex) for the treatment of relapsing-remitting multiple sclerosis. The efficacy portion of this trial must be designed to show superiority of fingolimod over active control.

Final Protocol Submission: December 1, 2011
Study/Trial Completion: August 6, 2015
Final Report Submission: January 1, 2016

(b) (4)

(b) (4)



Please provide your answer by email at your earliest convenience and follow with an archival submission to NDA 022527.

Best regards,

Hamet Touré, PharmD MPH
LT, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration

Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
Email: hamet.toure@fda.hhs.gov

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/

HAMET M TOURE
09/01/2010

Toure, Hamet (LT,USPHS)

From: Toure, Hamet (LT,USPHS)
Sent: Wednesday, August 25, 2010 12:35 PM
To: 'mara.stiles@novartis.com'
Subject: RE: copy of email

Dear Ms. Stiles,

The revised labels and labeling are fine from a DMEPA perspective. We recommend that you use version 2 (second presentation) of the inner front 28 count (last of the eight attachments above).

Please let me know if you have any questions.

Sincerely,

Hamet Touré, PharmD MPH
LT, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
Email: hamet.toure@fda.hhs.gov

From: mara.stiles@novartis.com [mailto:mara.stiles@novartis.com]
Sent: Thursday, August 19, 2010 4:54 PM
To: Chen, Lana Y; Toure, Hamet (LT,USPHS)
Subject: copy of email

Dear DNP and DMEPA reviewers,
Thank you for the teleconference today. The components have been revised as discussed and are provided below.

the following changes have been made.

- The statement [redacted] (b) (4) has been changed to Each capsule contains 0.5 mg fingolimod wherever it appeared
- Dosage statement has been changed to: Dosage: One capsule by mouth daily and point size has been increased
- [redacted] (b) (4), arrows and Novartis statement, [redacted] (b) (4) have been deleted

- Product strength has been moved beneath brandname on all panels where space allowed
- Capsule count has been moved
- Color of blisters has been changed to reflect the same color on all pieces

the requested second version of the 28 innerfront is sent with a separate email immediately to follow

We look forward to hearing from you on these revisions and the two versions of the innerfront 28 count

Mara Stiles

Mara Stiles
Novartis Pharmaceuticals Corporation
DRA-NSO
USEH, 404-416
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

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/

HAMET M TOURE
08/25/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Dr. Eric Bastings, Deputy Director, Division of Neurology Products

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
23 August 2010		022527	(PLEASE CHECK OFF BELOW) NDA

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Fingolimod	Priority	Multiple Sclerosis	(Generally 1 week before the wrap-up meeting) September 3, 2010

NAME OF FIRM:	
Novartis Pharmaceuticals	PDUFA Date: 21 September 2010

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☑ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☑ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☑ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☑ LABELING REVISION

EDR link to submission:
Cover Letter: \\CDSESUB1\EVSPROD\NDA022527\0111\m1\us\cover.pdf

EDR Location: \\CDSESUB1\EVSPROD\NDA022527\0111

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

The sponsor submitted revised labeling on July 9, 2010. Please provide your review for the substantially complete fingolimod labeling. The word version containing DNP comments will be forwarded to DDMAC..

Thank you

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/

HAMET M TOURE
08/24/2010

ERIC P BASTINGS
08/25/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022527

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

ATTENTION: Mara Stiles
Regional Brand Regulatory Manager

Dear Ms. Stiles:

Please refer to your New Drug Application (NDA) dated December 18, 2009, received December 21, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fingolimod Capsules, 0.5 mg.

We also refer to your May 24, 2010, correspondence, received May 25, 2010, requesting review of your proposed proprietary name, Gilenya. We have completed our review of the proposed proprietary name, Gilenya and have concluded that it is acceptable.

The proposed proprietary name, Gilenya, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 24, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Hamet Toure, at (301) 796-7534.

Sincerely,
{See appended electronic signature page}

Denise P. Toyer, PharmD
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/

LAURIE A KELLEY
08/23/2010

DENISE P TOYER
08/23/2010

Toure, Hamet (LT,USPHS)

From: Toure, Hamet (LT,USPHS)
Sent: Friday, August 06, 2010 1:35 PM
To: 'mara.stiles@novartis.com'
Cc: Toure, Hamet (LT,USPHS)
Subject: 022527_Comments

Attachments: 022527_Comments.pdf

Dear Ms. Stiles,

We refer you to NDA 022527. DMEPA had completed a review of the carton and container label on May 25, 2010. These comments were never sent. Please find them attached.

022527_Comments.
pdf (40 KB)

Please let me know if you have any questions.

Sincerely,

Hamet Touré, PharmD MPH
LT, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
Email: hamet.toure@fda.hhs.gov

1 page 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/

HAMET M TOURE
08/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Office of Surveillace and Epidemiology. (Epidemiology consult)	Russell Katz, MD, Division Director, DNP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
7/15/10		22-527	Postmarketing Registry	7/9/10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Fingolimod (Gilenya)	High	Multiple sclerosis	8/10/10

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☒ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☒ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Background: Fingolimod is a Sphingosine-1 phosphate (S1P) modulator under review for the tratment of multiple sclerosis. S1P is involved in multiple biological activities including lymphocyte trafficking, regulation of vascular permeability and tone, angiogenesis, atherogenesis and thrombogenesis. The drug is effective in reducing the rate of relapse at the doses of 1.25 and 0.5 mg daily, and shows a clear dose-related response in terms of safety. The drug was also studied in renal transplant patients at the doses of 2.5 and 5 mg/day but development was dropped because of toxicity. Main safety concerns raised with fingolimod in MS were bradycardia and atrioventricular block upon first dose, macular edema, increased risk of serious viral infections, potential for vascular toxicity, seizures, increased transaminases, decrease in pulmonary function (FEV1 and DLCO) and theoretical potential for increased risk of malignancies. Some of these events were observed only with the 1.25 mg dose, but there is uncertaintity as to the safety of the chronic use of the drug, particularly in patients with diabetes and other conditions that were specifically excluded from the clinical studies. The application was discussed at the Peripheral and Central Nervous System Advisory Committee on 6/10/10. The panel overwhelmingly voted in favor of approval of the lower dose (0.5 mg daily), with adequate monitoring, a Risk Evaluation and Mitigation Strategy, and provided that posmarketing data be collected to better characterize the long term safety of the 0.5 mg dose and a study be

conducted to evaluate the efficacy of a lower dose (0.25 mg/day). It is anticipated that fingolimod 0.5 mg will be approved. The PDUFA date is September 21, 2010.

Please provide comments to the protocol synopsis entitled "Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy" submitted by the applicant on 7/9/10 (attached). Specifically, please comment whether the size and duration of the registry is likely to provide useful information, and give any additional advice you may have. Please feel free to contact Dr. Villalba (maria.villalba@fda.hhs.gov) or Dr. Yasuda (sally.yasuda@fda.hhs.gov) if you have any questions.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) ☐ DFS ☐ EMAIL ☒ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

15 pages 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/

HAMET M TOURE
07/16/2010
On Behalf of Dr. Bastings

Email sent to sponsor 7.1.10 9 am

With regards to patient 0409/00008 in study FTY720D2301, please provide the full report of the CT scan obtained on 16-Nov-2007 as well as the full report of the initial and follow up CSF analyses (November 10 and November 16, 2007). Please include the RBC count for all CSF analyzed.

Please provide this information by COB July 7, 2010.

Thank you,

Cathy (for Hamet Toure)

Cathleen Michaloski, BSN / MPH
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov

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/

CATHLEEN B MICHALOSKI
07/01/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Maternal Health Team

FROM:
HFD-120/Division of Neurology Products

DATE	IND NO.	BLA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6/5/2010		022527	NDA	12/21/2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Fingolimod	Priority	Multiple sclerosis	7/12/2010

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Pregnancy Labeling review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Please comment on NDA 022527 (fingolimod) and its labeling section on pregnancy and nursing mothers. Please comment on the need for postmarketing requirements for a pregnancy registry and/or clinical lactation study.

Entire submission: \\CDSESUB1\EVSPROD\NDA022527\022527.enx

Link for submission on labeling: \\Cdsesub1\evsprod\NDA022527\0070\m1\us

The medical and safety reviewers are Dr. Heather Fitter and Dr. Lourdes Villalba respectively. Thank you

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/

HAMET M TOURE
06/05/2010

ERIC P BASTINGS
06/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22527

REVIEW EXTENSION – MAJOR AMENDMENT

Novartis Pharmaceutical Corporation
Attention: Mara Stiles
Regional Branch Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Stiles:

Please refer to your new drug application (NDA) dated December 18, 2009, received December 21, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Gilenia® (fingolimod) 0.5 mg capsules.

On April 5, 2010, we received your April 2, 2010 solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 21, 2010.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 31, 2010.

If you have any questions, call LT Hamet Touré, PharmD MPH, Regulatory Project Manager, at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Center of Drug Evaluation I
Center of Drug Evaluation and Research

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/

RUSSELL G KATZ
05/14/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-527 **INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation
Attention: Mara Stiles
RBRM, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Stiles:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fingolimod Hydrochloride.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. (b) (4) identify the target temperature set point or range for the (b) (4) process. Update the detailed process description to include the operating set points or ranges for (b) (4) speed, (b) (4) time, and temperature for the (b) (4) process.
2. Based on the recommendation of our pharmacology/toxicology review staff, include limits of NMT (b) (4) each for the starting materials (b) (4) as well as for the (b) (4) intermediate (b) (4) in either the final drug substance or at an appropriate intermediate stage to control the content of these impurities at the (b) (4) limit for potentially genotoxic impurities. Update all relevant sections of the submission to support these new specification criteria (i.e. analytical methods, method validation etc.).
3. Based on your justification, we will allow the limits for impurities (b) (4) to remain at NMT (b) (4) each in the final drug substance specification. Provide an updated drug substance regulatory specification incorporating all agreed upon changes.

Drug Product

4. You state in Section P.2.1.2.1 (b) (4) that experiments conducted with different grades of (b) (4) found that (b) (4) provided optimum content uniformity. Identify the (b) (4) characteristics evaluated in these experiments and provide justification, supported by data, for your selection of (b) (4) as the - (b) (4) for use in the drug product.

5. Provide any available data demonstrating that increased magnesium stearate levels do not negatively affect the dissolution of the 0.5 mg commercial drug product.
6. Confirm if, at a minimum, an identification test is conducted on the final drug product received at the packaging site prior to packaging to confirm that the correct drug product will be packaged.
7. Conduct (b) (4) uniformity testing on the first three commercial batches manufactured post-approval to confirm that the drug product manufacturing process provides compression (b) (4) with acceptable homogeneity.
8. Provide a revised regulatory specification for (b) (4) that includes the proposed limits for particle size.
9. Based on the batch and individual dissolution results provided, revise the drug product dissolution criterion to Q = (b) (4) at 15 minutes. Provide an updated drug product regulatory specification incorporating all agreed upon changes.
10. We note your intent to use both the manual sampling and automated sampling method as part of the regulatory dissolution method. However, your response did not address two points included in the original information request. Identify under what circumstances the automated dissolution sampling method would be used. Provide a comparison of the dissolution results obtained using both dissolution sampling methods for the 0.5 mg drug product.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/

RAMESH K SOOD
05/07/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022527

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

ATTENTION: Mara Stiles, Regional Brand Regulatory Manager
Drug Regulatory Affairs, Neuroscience and Ophthalmics

Dear Ms. Stiles:

Please refer to your New Drug Application (NDA) dated December 18, 2009, received December 21, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fingolimod Hydrochloride Capsules, 0.5 mg.

We also refer to your February 8, 2010, correspondence, received February 12, 2010, requesting review of your proposed proprietary name, Gilenia. We evaluated this proposed proprietary name and determined it was acceptable under your Investigational New Drug Application. At that time, [redacted] (b) (4) for the product, 0.5 mg [redacted] (b) (4) However, in your NDA submission you propose marketing [redacted] (b) (4) 0.5.mg, [redacted] (b) (4) [redacted] (b) (4). This represents a change in product characteristic. We have completed our review of this proposed proprietary name along with this change in product characteristic and conclude that this name is unacceptable for the following reasons.

[redacted] (b) (4)

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm121568.htm and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Hamet Toure at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/

CAROL A HOLQUIST
05/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **OSE**			FROM: Sally Yasuda, MS, PharmD Safety Team Leader, DNP	
DATE: 5/3/10	IND NO.	NDA NO.:22-527	TYPE OF DOCUMENT: Case narrative	DATE OF DOCUMENT: 4/30/10
NAME OF DRUG: Fingolimod (FTY720)	PRIORITY CONSIDERATION P		CLASSIFICATION OF DRUG Sphingosine-1 phosphate Modulator for MS	DESIRED COMPLETION DATE: 5/24/10

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- x SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The DNP requests the opinion of Dr. John Senior regarding hepatotoxicity that occurred in a patient (D2302E1-0303-00021) receiving fingolimod (FTY 720) for multiple sclerosis in clinical study FTY720D2302. The patient had 2 episodes of increased transaminases. The first occurred 14 days after starting the study drug. Study medication was interrupted. The event had not completely resolved by 4 months later, but had resolved completely approximately 7 months after discontinuation. Study medication was then restarted. Approximately 10 months after re-starting FTY720, the patient presented with jaundice. Transaminases became elevated > 20X ULN, and this time were associated with increased bilirubin, but also with increased alkaline phosphatase. The case report is attached.

NDA 22-527 for fingolimod is currently being evaluated by DNP. Fingolimod (also referred to as FTY720) is a sphingosine-1-phosphate receptor modulator. The key mechanism of action in MS is proposed to be the decrease in egress of lymphocytes from lymphoid tissue and the reduction of auto-aggressive T-lymphocytes in the peripheral circulation. Regarding the clinical pharmacology, the average apparent terminal half-life for both fingolimod and is 6-9 days and steady-state exposure is reached between 1 to 2 months during once-daily dosing. Fingolimod is believed to be metabolized mainly via the cytochrome P450 4F2 isoenzyme. In the ISS more than

2000 MS patients had exposure for over 1 year and approximately 1000 patients for over 2 years

According to Dr. Villalba's interim review of NDA 22-527, "a review of liver related SAE indicates a relationship between the use of fingolimod and liver enzyme elevation, mostly transaminase and GGT elevation, with normal BR and alkaline phosphatase. Patients were asymptomatic and the diagnosis was made during protocol scheduled laboratory examinations, as early as 2-3 weeks into the study (mean 162 days, range 19 to 301 days in the FTY group; the case on placebo was diagnosed on day 540). Several cases were confounded by the use of concomitant medications that may have caused hepatotoxicity, such as paracetamol or other analgesics. However, all cases improved and most fully resolved after fingolimod discontinuation (10 days to 3 months after dc). One patient who was on FTY received intravenous paracetamol and developed ALT> 4000. There was at least one clean case with FTY 0.5 mg where there was no use of concomitant medications (2302_0330_00004)."

In evaluation of the liver enzymes in the ISS, ALT ≥3xULN was shown by 9.7% and 8.5% of subjects in the FTY 1.25 and 0.5 mg groups, respectively, as compared to 1.6% of those in the placebo group, in the controlled studies. The percentage of patients with ALT ≥5xULN was also higher in the FTY groups (2.2% and 1.6%) as compared to placebo (0.8%). Therefore, there is a clear effect on increase in liver enzyme elevations. However, the great majority of these cases had normal BR and ALK Phosphatase.

There were five cases in the entire ISS in which there was increase in transaminases ≥3xULN and increase in BR ≥ 2x ULN. One of them was a case of hepatic necrosis in a patient who died of disseminated herpes zoster; one was a patient who received intravenous paracetamol for hip pain; 2 cases occurred in subjects suspected of having Gilbert's disease, and one occurred on placebo.

The Advisory Committee for fingolimod is planned for 6/10/10.

If you need further information, please contact Lourdes Villalba or Sally Yasuda.

SIGNATURE OF REQUESTER Sally Yasuda (6-1633)	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Patient [D2302E1-0303-00021] – Jaundice

Patient: 41 years old (DOB: (b) (6), Caucasian, male

Treatment group: Interferon beta 1a (Core phase), FTY720 1.25 mg (Extension phase)

Relationship to study treatment: Suspected

Prematurely discontinued: Yes

Event(s): Icteric syndrome

Case No: PHHO2010DE05968

A 41 year old, Caucasian male (0303_00021) with relapsing remitting multiple sclerosis was enrolled in the study FTY720D2302 (a 12-month randomized, double-blind, multicenter, active-controlled, parallel-group study comparing the efficacy and safety of 1.25mg and 0.5mg of oral FTY720 compared to interferon beta-1a i.m.). The patient entered the core phase on 30-Jul-2007 and received the first dose of study drug (interferon beta-1a) on 13-Sep-2007. The patient completed the core study, and entered the extension phase study and received the first dose of the study drug (FTY720 1.25 mg) on 12-Sep-2008.

The patient was diagnosed with multiple sclerosis in Apr-2007. The patient had 3 relapses in the 2 years prior to randomization and 2 relapses in the year prior to randomization and his last relapse prior to randomization was in Jun-2007. The patient was not treated with any MS disease modifying drugs prior to randomization. No additional immunomodulatory/immunosuppressive drugs for MS were administered. At baseline, the patient's EDSS score was 1.5.

The patient's medical history included ear operation in 1972, inguinal hernia in 1973, and amblyopia on 21-Aug-2007. The patient did not have a history of diabetes mellitus or evidence of retinopathy prior to study entry. At the time of screening the patient was an active smoker. The patient did not have a history of liver disease or risk factors for liver disease. The patient did not have drug or alcohol abuse history.

Other concomitant medications taken prior to randomization included ranitidine and prednisolone for MS relapse.

During the study the patient also received ibuprofen for flu like symptoms, mepivacaine hydrochloride as local anaesthetic, magnesium as health supplement, amantadine hydrochloride for fatigue, heparin fraction calcium salt for thrombosis prophylaxis, ranitidine for gastritis prophylaxis, homeopathic preparation as prophylaxis and influenza virus vaccine monovalent as vaccination swine influenza. During the study, the patient also underwent excision biopsy with histology of a histozytom (benign fibrous histiocytoma).

At baseline, the patient's SGOT, SGPT, alkaline phosphatase, total bilirubin and direct bilirubin were noted to be 15 U/L, 26 U/L, 66 U/L, 14 U/L and 4 U/L respectively. On 24-Sep-2008 (Day 378, extension Day 14, i.e. 14 days after switching from interferon beta-1a to FTY720 1.25 mg), the patient was noted with moderate increase in transaminases with SGOT at 43 U/L and SGPT at 113 U/L. On 14-Nov 2008 (Day 429, extension Day 65), the patient's SGOT and SGPT further increased to 83 U/L and 246 U/L respectively. The study medication was temporarily interrupted from 14-Nov-2008 (Day 429, extension Day 65) to 07-Jun-2009 (Day 634, extension Day 269) due to the event. The event resolved completely on 05-Jun-2009 (Day 632, extension Day 267), when his SGOT and SGPT were noted to be 24 U/L and

39 U/L respectively. The patient re-commenced FTY720 1.25 mg on 8-June-2009. In accordance with a protocol amendment requiring that all patients receiving FTY720 1.25 mg be switched to lower dose, he was switched to FTY720 0.5 mg on 25-Mar-2010.

On 14-Apr-2010 (Day 945, extension day 580), the patient informed investigator by telephone that his co-workers had drawn his attention to his markedly yellow appearance. The onset date of the symptoms was 12-Apr-2010 (Day 943, extension day 578). The study medication was immediately discontinued due to the event, and he recived the last dose of study medication (FTY720 0.5 mg) on 14-Apr-2010 (Day 945, extension day 580). On 15-Apr-2010 (Day 946, extension Day 581), the patient presented with jaundice with distinct scleral involvement, fatigue, exhaustion, feeling of pressure under the right costal arch, relatively light coloured stools and relatively dark urine, and was diagnosed with icteric syndrome. On 15-Apr-2010 (Day 946, extension Day 581), his SGOT was 1466 U/L, SGPT was 2787 U/L, GGT was 292 U/L, total bilirubin was 177 µmol/L, direct bilirubin was 139 µmol/L and alkaline phosphatase was 218 U/L.

On [redacted] (b) (6) his liver function tests were slightly decreased and were noted to be: SGOT 13.62 µkat/L (801 U/L), SGPT 38.11 µkat/L (2242 U/L), GGT 3.88 µkat/L (228 U/L), total bilirubin 194.23 µmol/L, direct bilirubin 168.92 µmol/L, and alkaline phosphatase 4.55 µkat/L (268 U/L). The patient was hospitalized due to the event (icteric syndrome) on [redacted] (b) (6) He also underwent an abdominal ultrasound which revealed a moderate splenomegaly. The liver was normally sized and smoothly delimited, of homgeneous and normal internal echo structure and with normal intrahepatic vessels. The gall bladder was normal.

On 22-Apr-2010 (Day 953, extension Day 588), his liver function tests further decreased and were noted to be: SGOT 2.79 µkat/L (164U/L), SGPT 13.64 µkat/L (802U/L), GGT 2.77 µkat/L (163U/L), total bilirubin 115.69 µmol/L, and direct bilirubin 100.78 µmol/L. He was also noted with slightly reduced serum albumin at 34 g/L (NR 35-50 g/L) and increased ferritin at 775 ng/mL (NR 22-322 ng/mL). The patient had negative findings for hepatitis A virus IgG and IgM, hepatitis B surface (HBs) antigen, anti-HBs, hepatitis B core (HBc) IgG and IgM. Serum creatinine was within the normal range on multiple measurements on 19 & 20-Apr-2010 (78-86 µmol/L; NR 74-110 µmol/L) as were serum electrolytes (sodium, potassium). Prothrombin ratio (INR) ranged between 1.01 and 1.08, Quick test was normal ranging between 82.1% and 95.1% (NR 70-130%) as was PTT which which ranged between 28-29 sec (NR 22-29 sec). C-reactive protein was elevated at 14.5 mg/L (NR 0.1-5 mg/L) on 19-Apr-2010. Serum amylase and lipase and blood glucose were all normal.

Further history revealed that the patient's female partner was discovered "by chance" to have a hepatitis C infection in 2005. This was reported to be a chronic form with liver damage. However, no treatment had been instituted because of low viral load. The viral load was determined again in 2009 and was again found to be low. Reportedly, she had not so far taken any virus inhibiting medications.

In response to questioning on 15-Apr-2010, the patient reported having taken Bullrich (sodium bicarbonate) salts (2/day) from 11 to 13-Apr-2010 and Riopan stomach gel (combination of magnesium and aluminium salts) from 14 to 15-Apr-2010 for heartburn. He stated that he had not taken paracetamol. Without a prior medical consultation, on 15-Apr-

2010 the patient visited a pharmacy and purchased the "household remedy" holy thistle and took a total of four capsules from 15 to 19-Apr-2010.

The patient was discharged from hospital on (b) (6). A repeat abdominal ultrasound was performed on the day of discharge and showed no change from that performed on (b) (6) The patient was reported to be improving clinically with decreasing jaundice. The patient returned to the out-patient department on 26-Apr-2010. His clinical condition had further improved and this was also reflected in further improvement in the liver biochemistry values (see table below). Serum albumin was also normal at 44 g/L (NR 32-55 g/L).

The patient was again seen by the investigator on 29-Apr-2010. The patient's clinical condition continued to improve following discharge. He had only slight scleral jaundice. Urine and feces were of normal color. On questioning the patient reported that in early April 2010, he developed pain in the lower legs after cutting down a big tree. To treat this he applied Chinese oil (contains herbs) to the lower limbs. Duplex ultrasonography performed on the same date showed no abnormalities of the liver blood vessels.

The investigator suspected a relationship between the event (icteric syndrome) and the study medication.

Selected Laboratory Values (Blood Chemistry)

Visit, Visit date (Study Day)	SGPT (NR 0-45 U/L)	SGOT (NR 0-41 U/L)	GGT (NR 2-65 U/L)	Total Bilirubin (NR 2-21 µmol/L)	Direct Bilirubin (NR 0-7 µmol/L)	Alkaline Phos (NR 30-125 U/L)
Screening, (30-Jul-2007) (Not applicable)	21	13	27	8	2	61
Baseline, 11-Sep-2007 (Not applicable)	26	15	33	14	4	66
Commenced interferon beta-1a i.m on 13-Sep-2007						
Visit 4, 28-Sep-2007 (Day 16)	17	16	22	13	3	64
Visit 5, 12-Oct-2007 (Day 30)	22	17	25	9	4	66
Visit 6, 09-Nov-2007 (Day 58)	21	17	24	16	4	65
Visit 7, 14-Dec-2007, (Day 93)	25	30	23	8	3	62
Visit 8, 14-Mar-2008, (Day 184)	35	22	26	7	3	60
Visit 9, 06-Jun-2008, (Day 268)	22	17	24	10	3	64

Visit, Visit date (Study Day)	SGPT (NR 0-45 U/L)	SGOT (NR 0-41 U/L)	GGT (NR 2-65 U/L)	Total Bilirubin (NR 2-21 µmol/L)	Direct Bilirubin (NR 0-7 µmol/L)	Alkaline Phos (NR 30-125 U/L)
Visit 777, 08-Sep-2008, (Day 362)	39	22	27	7	2	60
Commenced FTY720 1.25 mg on 12-Sep-2008						
Visit 12, 24-Sep-2008 (Day 378)	113	43	46	7	2	71
Visit 13, 06-Oct-2008 (Day 390)	79	34	58	16	4	65
Visit 14, 07-Nov-2008, (Day 422)	250	74	100	10	3	66
Discontinued FTY720 1.25 mg on 13-Nov-2008						
Unscheduled, 14-Nov-2008, (Day 429)	246	83	105	12	3	70
Unscheduled, 27-Nov-2008, (Day 442)	119	48	91	15	4	68
Visit 15, 12-Dec-2008, (Day 457)	85	40	65	10	2	64
Unscheduled, 30-Dec-2008, (Day 475)	81	48	91	10	3	70
Unscheduled, 05-Feb-2009, (Day 512)	66	32	70	13	3	63
Visit 16, 13-Mar-2009 (Day 548)	51	26	45	12	3	63
Visit 17, 05-Jun-2009 (Day 632)	39	24	33	9	2	64
FTY720 1.25 mg re-started on 08-June- 2009						
Unscheduled, 22-Jun-2009, (Day 649)	55	28	48	15	4	71
Unscheduled, 06-Jul-2009, (Day 663)	91	39	68	7	2	75
Visit 18, 31-Aug-2009 (Day 719)	62	32	66	10	3	67

Visit, Visit date (Study Day)	SGPT (NR 0-45 U/L)	SGOT (NR 0-41 U/L)	GGT (NR 2-65 U/L)	Total Bilirubin (NR 2-21 µmol/L)	Direct Bilirubin (NR 0-7 µmol/L)	Alkaline Phos (NR 30-125 U/L)
Visit 19, 10-Dec-2009 (Day 820)	91	33	90	7	2	67
Switched to FTY720 0.5 mg on 25-Mar-2010 (study-wide, not patient-specific switch)						
Visit 20, 25-Mar-2010 (Day 925)	90	41	110	12	4	71
FTY720 0.5 mg discontinued on 14-April-2010 (last day of drug intake)						
15-Apr-2010 (Day 946)	2787	1466	292	177	139	218
Following laboratory examinations performed at local laboratory						
Visit, Visit date (Study Day)	**SGPT (0.5-1.08** µkat/L**)**	**SGOT (0.25-0.62** µkat/L**)**	**GGT (0.25-1.42** µkat/L**)**	**Total Bilirubin (NR 2-21 µmol/L)**	**Direct Bilirubin (NR 0.1-3.4 µmol/L)**	**Alkaline Phos (0.5-2** µkat/L**)**
(b) (6)	38.11 µkat/L	13.62 µkat/L	3.88 µkat/L	194.23	168.92	4.55 µkat/L
20-Apr-2010 (Day 951)	27.07 µkat/L	8.21 µkat/L	3.25 µkat/L	163.60	141.16	3.74 µkat/L
21-Apr-2010 (Day 952)	19.85 µkat/L	4.81 µkat/L	3.05 µkat/L	144.19	122.37	-
22-Apr-2010 (Day 953)	13.64 µkat/L	2.79 µkat/L	2.77 µkat/L	115.69	100.78	-
Following laboratory examinations performed at central laboratory						
Visit, Visit date (Study Day)	**SGPT (NR 0-45 U/L)**	**SGOT (NR 0-41 U/L)**	**GGT (NR 2-65 U/L)**	**Total Bilirubin (NR 2-21 µmol/L)**	**Direct Bilirubin (NR 0-7 µmol/L)**	**Alkaline Phos (NR 30-125 U/L)**
26-Apr-2010 (Day 957)	318	103	97	60	40	122

Other Laboratory tests in Serum (April 2010)

Test	Result	Reference range
ANA (anti-nuclear antibody)	Negative	Negative
dsDNA	0.8 IU/mL	< 10
AMA (anti-mitochondrial antibody)	<1:50	<1:50

ASMA (anti-smooth muscle antibody)		
LKM-ab (liver kidney microsome)		
Anti-neutrophil cytoplasmic antibodies (c-ANCA & p-ANCA)	<1:10	<1:10
Cardiolipin IgG auto-antibodies	1.1 GPL U/mL	<10
Cardiolipin IgM auto-antibodies	3.6 MPL U/mL	<10
Carbohydrate-deficient Transferrin	1.50%	<2.15

Virology (April 2010)

Test	Result	Reference range
HBs antigen	negative	negative
Anti-HBs	<8 mIE/mL	<8
Anti-HBc	negative	negative
Hepatitis C virus RNA in blood (RT-PCR)	negative	negative
Hepatitis D antibodies		
Hepatitis E virus IgG		
Hepatitis E virus IgM		
EBV-VCA-gp125 IgG	Positive	negative
EBV-VCA-p18 IgG	negative	negative
EBV-VCA IgM antibodies	<4 U/mL	<9
EBV-EBNA1 IgG	Positive	negative
EBV-EA1 IgG	negative	negative
CMV IgG antibodies	0.8 AE/mL	<15
CMV IgM antibodies	negative	negative
HSV 1/2 IgG in serum	514 U/mL	<20
HSV 1/2 IgM in serum	18 U/mL	<20
HIV		
Echinococcus		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES
IND-70139	SAFETYRPT-1	NOVARTIS PHARMACEUTICALS CORP	FTY 720D CAPSULES

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/s/

HAMET M TOURE
05/03/2010

SALLY U YASUDA
05/04/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Drug Oncology Products	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Eric Bastings, MD, Deputy Director, Division of Neurology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/15/2010		022527		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Fingolimod	Priority	Multiple sclerosis	3/31/2010

NAME OF FIRM: Novartis Pharmaceuticals Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☒ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

We request evaluation of one potential case of disseminated lymphoma in a patient receiving fingolimod, an oral immunosuppressor for the treatment of multiple sclerosis (MS) (NDA 22-527).

Fingolimod is a sphingosine- 1- phosphate (S1P) modulator that reduces circulating lymphocytes. The drug was initially developed in the renal transplant population at doses up to 5 mg/day but that indication is no longer pursued. The dose proposed for approval in MS is 0.5 mg/day.

The narrative of the case we request evaluation for (ID# D1201E1-0005-00001) is presented in the following page (verbatim sponsor's narrative). A follow up IND safety report is attached to this consult.

This is a rolling NDA. The clinical data in the MS population was submitted on December 18, 2009 (SN 003). The link to the ISS can be found at:
\\Cdsesub1\evsprod\NDA022527\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relapsing-remitting-ms\5353-rep-analys-data-more-one-stud\fty720diss

For your information, one T cell lymphoma, one B cell lymphoma and one lymphoproliferative disorder were identified in renal transplant patients treated with fingolimod at doses of 2.5 mg/day.

Please complete your evaluation by 3/31/10.

Please contact Dr. Lourdes Villalba if you have any questions.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Patient [D1201E1-0005-00001] - 1) Multiple sclerosis relapse 2) Possible malignant kidney, lung and brain tumor, Aspiration bronchopneumonia
Patient: 42 year old, Japanese male
Treatment group: FTY720 0.5 mg (Code was broken by the investigator)
Relationship to study treatment: 1) Suspected, 2) Suspected
Prematurely discontinued: Yes (due to Event 1)
Event(s): 1) Multiple sclerosis relapse, Abasia, 2) Renal neoplasm, Lung neoplasm, Brain neoplasm, Pneumonia aspiration, Staphylococcal infection, Pleural effusion, Atelectasis

A 42 year old Japanese male (0005/00001) with relapsing multiple sclerosis was randomized in the core study FTY720D1201 on 26-Feb-2008. He completed the core study on 25-Aug-2008 and entered in the extension study FTY720D1201E1 on 26-Aug-2008.
The patient was diagnosed with multiple sclerosis on 19-Jan-2003. The patient had a total of 6 relapses since diagnosis with 5 relapses treated with steroids. The patient had 3 relapses in the 2 years prior to randomization, no relapse in the year prior to randomization and his last relapse prior to randomization was on 10-Jan-2007. The patient was not treated with any MS disease modifying drugs prior to randomization. At baseline, the patient's EDSS score was 4.0.

His medical history included infantile asthma, atopic dermatitis (current condition), thyroid tumor (benign), low back pain and osteoporosis. Relevant concomitant medications included magnesium oxide and Sennoside for constipation, Onealfa for osteoporosis, and Loxonin for low back pain.

Event 1 Multiple sclerosis relapse
On 22-Aug-2008, before entering the extension study, a MRI scan showed that new T2 weighted lesions had appeared in the deep white matter of the anterior horn of the right lateral (ventricle?) and the left centrum semiovale. These lesions showed clear ring shaped enhancement on Gd-enhanced T1 weighted scan, suggesting the destruction of the blood brain barrier (BBB). These lesions were considered to be new MS lesions. The patient did not have any symptoms.
On (b) (6) the patient was admitted for a course of steroid pulse therapy for 3 days (1,000 mg methylprednisolone/day). The patient was discharged on (b) (6) However, the patient's MS symptoms deteriorated and he became unable to walk on 10-Oct-2009.
On (b) (6), the patient was emergently admitted to the hospital. Paralysis of the upper and lower right limbs was clearly confirmed. A second course of steroid pulse therapy was administered for 3 days. On (b) (6) the patient was discharged with walking ability at the level of a wheelchair user, as because the patient was unable to follow hospital rules because of a decline in his cognitive function and steroid psychosis.
On (b) (6) the patient was again admitted emergently to the hospital, because paralysis of the upper right limb had progressed. On (b) (6) the demyelinating lesion in the deep white matter of the left parietal lobe spread from the center to the left side of the posterior half of the corpus callosum. There was an enlargement of the area of strong inflammation, causing BBB destruction in the central area.
On (b) (6) the study medication was discontinued (the last date of study medication was on (b) (6)) and the patient was withdrawn from the trial. A third course of steroid pulse therapy was administered for 3 days.
On (b) (6), a fourth course of steroid pulse therapy was administered for 3 days.
On (b) (6), a MRI scan was performed and the enlarged lesions were not changed, compared with the previous MRI scan of (b) (6)

On [redacted], a fifth course of steroid pulse therapy was administered for 3 days.
On [redacted], the possibility of the complication of malignant lymphoma in addition to multiple sclerosis was considered based on the MRI scan. On [redacted], a cell diagnosis report from a spinal fluid test showed the presence of an extremely small quantity of lymphocytes. No malignant cells were identified. No findings actively suggesting malignant lymphoma were found.
On [redacted], a sixth course of steroid pulse therapy was administered for 3 days.
On [redacted], an isotope brain flow scintigraphy with 123I-IMP was performed. On the early image, areas of decreased blood flow were identified in the left basal ganglion, left parietal lobe and left frontal lobe. On the late image, the above areas of decreased blood flow were reduced in size and in particular the intake to the left basal ganglion had increased in comparison with the early image.
On [redacted], a seventh course of steroid pulse therapy was administered for 3 days. The dosage of steroids was gradually reduced from Prednisolone 60 mg/day, ending on 07-Mar-2009.
On [redacted], magnetic resonance spectroscopy (MRS) performed on the lesions in the left parietal lobe showed no clear increase in choline. A mild increase in lactate was found, but no significant decrease in N-acetyl aspartate (NAA) was identified. Since no notable increase in choline was found, it was not possible to say that the finding was tumerous.
On [redacted], from the facts that the lesions were disappearing to some extent, and that a MRS showed no increase in choline, and the results of brain flow scintigraphy, the probability of malignant lymphoma was low, although it could not be ruled out. A biopsy was not performed.
On [redacted], the patient was transferred from an investigating hospital to a different hospital; since the patient's general condition was stable.
The investigator indicated that the causality between the event and study medication could not be ruled out, because the MS symptoms had progressed and the lesion in the brain had spread further after study medication was started.

Event 2 Possible malignant kidney, lung and brain tumor
On [redacted] the patient was transferred back to the investigating hospital due to suspected malignant findings on a chest x-ray which revealed multiple irregularly shaped tumor lesions. The patient was concurrently suffering from aspiration pneumonia. A chest and an abdominal CT (computerized tomography) scan on [redacted] at the investigator's hospital revealed multiple low absorption regions and nodules in both lungs and both kidneys, pleural effusion on both sides and atelectasis with displacement in the periphery of the lower lobes. There was no changes in size regarding the pre-existed thyroid tumor. Small scattered lymph nodes were found in the region of the pulmonary hilum, mediastinum, the neck and axilla on both sides and the abdominal para-aorta. The above findings from the images suggested the possibility of atypical malignant lymphoma or metastases of malignant tumors. The patient had generalized pyrexia of 39 degrees Celsius which was treated with unspecified antibiotics. The patient's lab test was also showed pancytopenia and abnormal coagulation.
A single frontal chest x-ray examination was performed on [redacted]. In the upper right lung field borderline mass lesions, somewhat unclear and irregular in shape were noted. In addition in the lower lung field on both sides, around the bronchus, invasion was present with the complication of aspiration bronchopneumonia. No abnormal findings had been seen on the chest x-ray from 22-Aug-2008 (at Month 6) or 28-Nov-2008 (at the study drug discontinuation visit).
The initial diagnosis was suspected malignant kidney, lung and brain tumor.
A kidney biopsy was performed for diagnosis. Based on the results of the biopsy, an Epstein-Barr (EB) virus related lymphoproliferative disorder was possible, but since only a small

amount of biopsy tissue was available and additional staining was not possible, a determination could not be made.
On (b) (6), sputum tested positive for methicillin-resistant staphylococcus aureus (MRSA). Based on an abdominal CT scan performed, malignant lymphoma was suspected. The CT scan revealed mass-shaped-structures in both kidneys. A kidney biopsy was performed. The result of the cytodiagnosis of the kidney was classified as class III, which means a possible malignancy. On a single chest x-ray, the invasive shadow in the upper right lung field was noted to be tending to fade and no new invasion was noted.
On (b) (6), a MRI scan was performed. The demyelinating lesion was in remission after steroid therapy, although gliosis and hemosiderin deposit remained. A history of multiple micro-hemorrhage was noted; however, the MRI revealed no edematous changes nor clear abnormal strengthening effects nor activity. As in the previous examination, multiple nodular lesions presenting multiple ring enhancements were identified, which were centered around the borderline of the cortex and medulla. The examination also revealed that a similar lesion had appeared in the subcortical left insular gyrus with edematous activity in the surrounding area.
MR spectroscopy then revealed that the lesion showed an increase in choline and a decrease in N-acetyl aspartate (NAA). The ring enhancement and the fact that many lesions were in the cortical white matter was typical of metastases to the brain. So, the radiologist noted that it was possible that the lesions in either the chest or abdomen were the primary site.
On (b) (6), a single frontal chest x-ray revealed that the pleural effusion in both lungs appeared to be fading: there was no change in the mass shadows in the upper right lung field and the area of increasing density
On (b) (6) an enhanced CT scan of the chest and abdomen and a chest x-ray were performed. The following findings were reported:
• An improvement in the patient's pneumonia was noted, the pleural effusions were still present in both lungs (and noted to have increased in size) and passive atelectasis was seen in the lower lobes.
• There were no findings clearly indicating active pneumonia. However, the patient still had pyrexia of at least of 38 degrees Celsius.
• Multiple large and small nodules and masses indicating the known metastasized lung tumors were seen and a trend towards an increase in the number and size of tumors was noted when compared to the CT scan performed on (b) (6)
• No change in the size of the thyroid tumor was noted, as was hepatosplenomegaly.
• The investigator noted that the low density nodule indicated in the liver at S5 was more pronounced than in the previous CT examinations and that the possibility of metastasis could not be ruled out.
• No notable change was seen in the multiple low density nodule masses in both kidneys nor in the mild swelling in the abdominal lymph nodes.
• A very small amount of ascites was present. No additional clear infection lesions were identified in the abdominal region.
The patient was diagnosed with multiple metastases and pleural effusion in both lungs. The investigator noted that multiple liver tumors, possibly metastases or malignant lymphoma were present, as was hepatosplenomegaly. The investigator noted that within the scope of the scan no other clear specific abnormalities which could have caused the pyrexia were identified.
On (b) (6), an upper endoscopy identified either tumor or lipoma in the esophageal mucosa in the lower esophagus and multiple polyps in the stomach. A stomach biopsy revealed no findings of malignancy. The multiple stomach polyps were tested for Helicobacter pylori with a positive result.
On (b) (6), the patient body temperature had fallen to between 36 and 37 degrees

Celsius. Thereafter, the antibiotics were no longer administered. The patient's MRSA was in a carriage state. The outcome of the MRSA pneumonia was reported as resolving as of (b) (6) .

On (b) (6), gallium scintigraphy was performed. The results of the gallium scintigraphy showed an increase in uptake to the upper left abdomen (probably the stomach) and to both kidneys. Suspected illnesses included interstitial pneumonia, malignant lymphoma of the kidneys and leukemia invasion of the kidneys. Possible determinations for the uptake to the stomach included gastritis and malignant lymphoma.

The investigator did suspect a relationship between the event (MRSA pneumonia, brain lesions and generalized tumorous lesions) and the study medication.

On 14-Sep-2009, the investigator provided the following update at a meeting with the Novartis Japan clinical team.

The patient's general condition is not so good, therefore an additional biopsy of the tumors in the kidney can not be conducted. The patient is still using an insertion of a gastric tube because of aspiration pneumonia. In addition, the blood platelet counts of this patient are too low to conduct a bone-marrow puncture.

Another skin biopsy was conducted because invasive erythematous eruptions have been increasing in number. A pathologist diagnosed this case as "highly suspicious of T cell lymphoma of the skin" based on both immunostaining results and gene rearrangement using skin tissues.

According to the latest CT report on (b) (6), the nodules in the lung or kidney have increased in size or number again without any triggers, although at an earlier time point the nodules in the lung or kidney have been reported as decreasing in size or number. Steroid treatment has not been administered since 07-Mar-2009, although steroid treatment can affect the malignant tumors in size or number.

The investigator stated that she could diagnose this case as T cell lymphoma based on the latest pathological report from the new biopsy of the skin lesion, however, T cell lymphoma could not explain the fluctuation of nodules in the lung or kidney in size or number. So this diagnosis could not be definitely confirmed until she gets the second opinion from an expert of lymphoma at a special hospital for cancer and infectious diseases.

The investigator has been consulting closely with the expert of lymphoma to get an accurate diagnosis and save the patient and his caregiver. The latest CT imaging and the new specimen slide of skin tissue have been sent to the expert of lymphoma as requested by the expert. If the expert of lymphoma cannot diagnose this case in 2 weeks using these additional data, the investigator will consult with another expert of lymphoma at another special hospital for cancer as requested by the Novartis global clinical team.

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/

HAMET M TOURE
03/15/2010
Consult requested by safety team

ERIC P BASTINGS
03/19/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22527

FILING COMMUNICATION

Novartis Pharmaceutical Corporation
Attention: Mara Stiles
Regional Branch Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Stiles:

Please refer to your new drug application (NDA) dated December 18, 2009, received December 21, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Gilenia® (fingolimod) 0.5 mg capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is June 21, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 1, 2010.

During our filing review of your application, we have identified the following potential review issues:

1. We note the absence of preclinical and clinical studies evaluating abuse potential of the drug and the absence of a discussion of abuse potential of the drug.

   Although we are not recommending at this time that any new studies be conducted, we request that you submit a section on abuse potential that includes summaries and evaluations of all preclinical and clinical data related to the drug's abuse potential. This may include animal studies that demonstrate the drug’s activity in the central nervous system and descriptions from the clinical trials of all or any reports related to drug

misuse, diversion (drug accountability issues), overuse/overdose, abuse and drug withdrawal.

We also request that you submit an integrated table of all abuse-related adverse events; please refer to the attachment for the list of MEDRA terms to include in the search.

2. The statistical analysis plans (SAPs) for the two pivotal studies, submitted to the NDA on January 28, 2010 in response to the Agency's request, have release dates after the unblinding of the data. Please submit versions of the respective SAPs that were finalized before the unblinding of the data. The SAPs should be filed under Section 16.1.9 in the Appendix of the appropriate protocol in Module 5 of the NDA.

   Specifically, submit the following:
   - The SAP for each pivotal study, finalized before the unblinding of the data, with the signature page for all studies. In addition, a copy of the SAP for each study with marked changes from the latest version reviewed by the Agency should also be submitted.
   - A list of SAP changes made after the final version of the SAP, rationale for the changes, and the marked copy of changes for all studies.
   - Reports of deviations from planned analyses and results that are obtained from changed analysis methodologies in the study reports and other documents, with details of the sections of the documents.
   - Corrections of reported study results for any analysis performed using changed methodologies.

   Please provide this statistical information as soon as possible, as it is critical for our review of this application. We remind you that it is not always possible for the Agency to review in the same cycle information submitted after the review clock has started.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following additional information:

1. The final protocols and the protocol amendments for the pivotal efficacy trials were located in your NDA submission, but we were not able to locate the original protocols for these trials. Please direct us to where the original protocols are located in the submission, or provide them if they are not already included.

2. The principal database provided to support efficacy in this NDA is derived from the clinical trials D2301 and D2302. Within this database only 144 patients were enrolled from United States centers (all from study D2302). Please submit a rationale for

assuming the applicability of predominantly foreign data to the U.S. population/practice of medicine.

3. We acknowledge that you have submitted a revised statistical analysis for D2302 for certain secondary outcomes, including the key secondary outcome, new or newly enlarged T2 lesions. Please provide the following information concerning this analysis:
    - Describe whether the new or newly enlarged T2 lesions were analyzed and counted in the same way for studies D2301 and D2302;
    - Provide the documents (or direct us to the section of the current application) that pre-specifies how these MRI inflammatory lesions were to be counted;
    - If the method was different for studies D2301 and D2302, please provide a detailed description and comparison of the two methods;
    - Please also provide documentation of how these lesions were counted and reported in trial D2201.

4. In this submission, you present tables that summarize MRI data in terms of new or newly enlarged lesions up to month 24 (D2301) or month 12 (D2302). Please describe how you counted these lesions. Please compare this to how T2 lesions were counted when summarized as "number at month 12 or 24". Two examples of these tables using the term "up to" are in the clinical efficacy module 2.7.3 p. 40-41, Table 3-14 and 3-15.

In addition, we remind you that the following information has been previously requested via electronic communication and is pending at this time:

1) Post Table 4.4-1 of the MS ISS (AEs in Group D) shows several cases of seizure-related events (epilepsy, convulsion, grand mal convulsion, partial seizures and petit mal) on FTY, one case of convulsion in the placebo group and no such cases in the INF group. It is unclear if some of these events occurred in the same patient. Please provide the rate (n/patient years of exposure) of all seizure-related terms in Safety Pool D. Also provide full narratives for these patients, as well as of any additional case of convulsions/grand mal convulsions/seizures in Safety Pool E.

2) Review of Post-text Table 4.4-2 of the Transplant ISS (SN 002) (Serious adverse events in the Key Safety population) shows the following SAEs:
    - Convulsions: 5 (1.1%) in the FTY 5 mg group, 6 (1.3%) in the FTY 2.5 mg group, 1 (0.2%) in the MMF group
    - Grand mal convulsion: 2 (0.4%) in the FTY 5 mg group
    - Partial seizures in 1 (0.2%) in the FTY 2.5mg group

    It is unclear whether the numbers refer to events or patients. Please provide brief narratives of these cases.

3) Study FTY720AB102 evaluated effects of multiple dose (28-day) fingolimod on lymphocyte subpopulations in humans. At the time of last evaluation (Day 56 [28 days post last dose]), the lymphocyte count had not fully recovered. Please clarify if

you have any other multiple dose study that follows lymphocyte levels until full recovery.

4) Your tabulations of adverse events include events that occurred up to 45 days after drug discontinuation in the multiple sclerosis studies and up to 7 days after drug discontinuation in the renal transplant studies. However, it is our understanding that serious adverse event data were collected up to 90 days, per protocol, and beyond that time, at the investigator discretion.

   Please submit rates (n/patient years) of serious AEs a) up to 3 months after drug discontinuation and b) during the complete observation period for both, the MS (all populations) and the transplant population (key safety population). We acknowledge that these data will require careful interpretation.

5) Please clarify whether there is available information on WBC, lymphocyte counts and immunoglogulin levels at the time of serious infections. If that information is available please provide a table that shows WBC, lymphocyte counts and immunoglobulin levels at baseline and the time of the event for patients who had serious infections in pools D and E (sample table was provided)

6) If data are available, provide similar information to request #5, for patients who had an AE of MS/MS relapse.

7) The following patients had negative CSF PCR for JC virus:

   D2301-0307-00015
   D2301-0409-00008
   D2201E1-0029-00008
   D1201E1-0112-00004
   Please send remaining CSF samples from these patients for JC virus PCR testing at the National Institutes of Health.

8) The safety reviewer was not able to find the following narratives:

   D2201_0004_00009 – MS relapse in AE dataset
   D2201_0051_00001 – MS relapse in AE dataset
   D2302_0202_00010 – Unusually severe MS relapse in AE dataset
   Please submit these narratives or direct the reviewer to the exact location in the NDA submission.

9) The MS ISS includes narratives of AEs of MS relapse that are not included in the AE dataset (SCSAEV) submitted with SN 003 (12/18/09). Please clarify why these events are not in the AE dataset.

   D2301-0453-00003

D2301-0307-00015
D2302-0328-00003
D2302-0822-00003
D2201E1-0018-00002
D1201E1-0005-00001

10) Regarding patient ID 2302-821-00007 who died of Herpes simplex encephalitis, please confirm date of diagnosis of MS and date of randomization. Please provide the final results from the CSF testing at NIH.

11) Please provide the following tables from Safety Pool D and Safety Pool E in the Fingolimod NDA: Incidence rate of Adverse events leading to Discontinuation per 100 patient-years (total number of events and number of events per 100 PYRs) by primary SOC and preferred term (all events).

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your requests for a partial waiver and partial deferral of pediatric studies for this application. However, one of the requirements of a deferral request is that you submit a timeline for the completion of pediatric studies. Your submission does not contain such a timeline. Within 30 days of the date of this letter, submit a timeline that includes the following dates (month, day, year): (1) protocol submission; (2) study completion; and (3) submission of study reports. We also recommend that you comment on any intention to extrapolate pediatric effectiveness from adult studies. In addition, we understand that the European Medicines Agency (EMA) has approved a Paediatric Investigation Plan (PIP) for fingolimod. Therefore, we request that you submit the EMA Pediatric Committee (PDCO) Summary Report on the PIP for fingolimod. Once we have received this information and reviewed the partial waiver and partial deferral request, we will notify you if the waiver and/or deferral requests are denied.

If you have any questions, call LT Hamet Touré, PharmD MPH, Regulatory Project Manager, at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Center of Drug Evaluation I
Center of Drug Evaluation and Research

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/

RUSSELL G KATZ
02/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-527 **INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation
Attention: Mara Stiles
RBRM, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Stiles:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fingolimod Hydrochloride.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. Provide data on the appearance, solubility, [(b) (4)], and stability for [(b) (4)] fingolimod HCl.
2. Identify the critical process parameters, and their respective operating ranges, for the fingolimod HCl manufacturing process. Provide justification for the proposed operating ranges.
3. You state that the manufacturing process may be adjusted based on batch size or equipment. Identify the process parameters that would be adjusted, the associated ranges for these parameter adjustments, and under what circumstances these parameters may be adjusted. Provide justification for the proposed adjustment ranges.
4. For each process step, identify what parts of that process step, if any, may be repeated if a batch fails. Any proposed extensive reprocessing should be supported by appropriate data.
5. Specify the method of [(b) (4)] used for fingolimod HCl.
6. Provide information on the criteria used to determine which batches of [(b) (4)] drug substance may be [(b) (4)] to form one single production lot as well as the method used to [(b) (4)] these batches. Clarify if this [(b) (4)] is done before or after [(b) (4)].
7. Provide the control testing specifications for those [(b) (4)] that may be recovered during processing via [(b) (4)]. Identify the process steps where these [(b) (4)] may be used.

8. Based on the [(b) (4)] pathways provided for the starting material [(b) (4)] revise the specification for this starting material to include limits for [(b) (4)]. Provide data on the amounts of [(b) (4)] observed in all of the available [(b) (4)] batches used to manufacture the drug substance during development. You may justify your proposed limits based on the data demonstrating the fate of these impurities during downstream processing.
9. Based on the [(b) (4)] pathways provided for the starting material [(b) (4)], revise the specification for this starting material to include limits for [(b) (4)] Provide data on the amounts of [(b) (4)] observed in all of the available [(b) (4)] batches used to manufacture the drug substance during development.
10. Provide all available data on the residual amounts of [(b) (4)] detected in the final drug substance.
11. Revise your proposed limits for the specified impurities [(b) (4)] in the drug substance specification based on levels observed at release and during stability.
12. The data provided for residual solvents in prototype batches of intermediate [(b) (4)] do not support your lack of testing of the final drug substance for the ICH Class 2 solvents [(b) (4)] Revise the drug substance specification to include limits for these solvents or provide justification, supported by relevant data, to support the exclusion of limits for these solvents.
13. Provide the system suitability criteria for the [(b) (4)] diffraction and particle size methods. Identify the contents and known particle size distribution of the test dispersion sample used for the particle size method.
14. As the USP/NF compendia is the official compendia in the US, provide justification for the use of European Pharmacopeia standards for the color of solution and heavy metals analytical procedures. Provide copies of the standards referenced in the European Pharmacopeia. Provide a statement acknowledging that the corresponding USP/NF monograph is the official standard or that the corresponding analytical procedure is the regulatory analytical procedure.
15. Revise the post-approval stability protocol and commitment to include the addition of at least one drug substance batch to the stability program annually.
16. Provide any available particle size distribution data that demonstrates the drug substance does not agglomerate when stored at the recommended storage conditions in the intended commercial packaging.

Drug Product

17. Provide data to demonstrate that the proposed regulatory dissolution method is discriminating between acceptable and unacceptable batches.
18. Provide data to demonstrate that the vibrations from the encapsulator do not promote [(b) (4)] over the encapsulation run time.

19. Provide justification, supported by data at commercial scale, for the exclusion of an in-process control for (b) (4) uniformity in the drug product manufacturing process.
20. As changes in (b) (4) particle size distribution may impact (b) (4) homogeneity, provide justification, supported by data, for the exclusion of a control for (b) (4) particle size.
21. As the USP/NF compendia is the official compendia in the US, provide justification for the use of European Pharmacopeia monograph for Gelatin and the Japanese Pharmacopeia monograph for Capsules. Provide copies of the standards referenced in the European Pharmacopeia. Provide a statement acknowledging that the corresponding USP/NF monograph is the official standard or that the corresponding analytical procedure is the regulatory analytical procedure.
22. Provide system suitability criteria for the dissolution apparatus. Identify which dissolution sampling method is intended for use with the regulatory dissolution method during commercial manufacturing. Identify under what circumstances the alternate dissolution sampling method would be used. Provide a comparison of the dissolution results obtained using both dissolution sampling methods.
23. Provide justification as to why the validation of the dissolution method is valid for the 0.5 mg strength capsule when it was not tested or provide validation data for the 0.5 mg strength capsule.
24. Provide the individual dissolution results for the drug product registration batches (Batches H375BD, H376BD, and H377BD). Provide any available individual dissolution data at time points earlier than 30 minutes.
25. Identify the reference standards for the other specified degradation products.
26. In accordance with the USP requirement for agreement between the established name and the strength of the drug product, revise the proposed labels to remove “hydrochloride” from the drug product as the capsule strength is based on the content of the fingolimod free base. Replace statements indicating that the capsule contains 0.5 mg of fingolimod with “equivalent to XX mg of fingolimod hydrochloride.” Include the expression of capsule strength in the block of text containing the trade name, established name, and dosage form.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

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/s/

RAMESH K SOOD
02/17/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Dr. Renata Albrecht, Director of Division of Special Pathogen and Transplant Products (DSPTP)	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Dr. Eric Bastings, Deputy Director, Division of Neurology. Ext. 6-1039.

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2-14-2010		022527		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gilenia (fingolimod)	6-month review	Multiple sclerosis drug	March 12, 2010

NAME OF FIRM: Novartis Pharmaceutical Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☒ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Please evaluate the risk of infections with fingolimod, an oral agent for the treatment of multiple sclerosis (MS) (NDA 22-527). We request advice on to how to adequately identify, monitor, treat early and/or prevent opportunistic infections in this population.

Fingolimod is a sphingosine- 1- phosphate (S1P) modulator that induces immuno- suppresion by reduction of circulating lymphocytes. The drug was initially developed in the renal transplant population at doses of 2.5 and 5 mg/day but that indication is no longer pursued. The dose proposed for approval in MS is 0.5 mg/day. This is a rolling NDA (**\\CDSESUB1\EVSPROD\NDA022527**). The clinical data in the MS population was submitted in December, 2009 (SN 003 and 004). Clinical data in the transplant population was submitted in October 2009 (SN 002). This application has a priority review (PDUFA goal date June 21, 2010) and will go to an advisory committee meeting on June 10, 2010).

The applicant states that single doses of fingolimod from 0.5 to 5.0 mg result in a dose dependent decrease in

lymphocyte count (all, B and T [helper, suppressor, memory and naïve T]). This decrease occurs rapidly, within 3-4 hours of the first oral dose. With single doses from 5 to 40 mg, there is minimal additional effect on the lymphocyte count. With multiple dosing of fingolimod from 0.125 mg to 5 mg there is a dose-dependent decrease in lymphocyte count, resulting in counts reduced to 60% of baseline count to 10- 15% of baseline count, respectively. In a multiple dose study (FTY720AB102) all lymphocyte subsets (CD20 [B cell], CD3 [T cell], CD4 [T helper], CD8 [T suppressor], CD16 [Natural killer], CD45RO [T memory], CD45RA [T naïve] were found to decrease in a dose dependent manner in the setting of multiple doses of fingolimod. The monocyte count was not affected by multiple dose fingolimod treatment.

Two young patients (ID# D2302-0212-00021 and D2302-0821-00007) died of disseminated herpes infections (one herpes simplex encephalitis and one disseminated herpes zoster) among approximately 3000 subjects with MS exposed to fingolimod. Both deaths occurred in the 1.25mg/day dose group. Narratives of these cases can be found in the attached document below.

Please evaluate the risk for opportunistic infections with fingolimod treatment and provide advice on how to adequately identify, monitor, treat early and/or prevent opportunistic infections in this population. A finalized review is desired by March 12, 2010.

It is anticipated that the risk of opportunistic infections and how to minimize this risk will be discussed at the AC meeting. Please assign a reviewer to represent your division at the AC. We also request that you suggest three outside experts to participate in the AC panel. Please provide these names at your earlier convenience.

Please feel free to contact Dr. Villalba (maria.villalba@fda.hhs.gov) if you have any questions.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Electronic	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Attachment 1.

Table 1. Duration of exposure to study drug after randomization in Group E (all FTY720-treated patients open label and controlled studies, safety population)

	FTY720 5 mg–1.25 mg (N=137)	**FTY720 1.25 mg (N=1157)**	**FTY720 0.5 mg (N=1021)**	**Total (N=2315)**
Exposure (days)	n (%)	n (%)	n (%)	n (%)
≥ 1 day	137 (100)	1157 (100)	1021 (100)	2315 (100)
≥ 90 days	126 (92.0)	1074 (92.8)	986 (96.6)	2186 (94.4)
≥ 180 days	118 (86.1)	1027 (88.8)	958 (93.8)	2103 (90.8)
≥ 270 days	111 (81.0)	969 (83.8)	907 (88.8)	1987 (85.8)
≥ 360 days	108 (78.8)	831 (71.8)	781 (76.5)	1720 (74.3)
≥ 540 days	101 (73.7)	715 (61.8)	691 (67.7)	1507 (65.1)
≥ 720 days	96 (70.1)	354 (30.6)	289 (28.3)	739 (31.9)
≥ 1080 days	85 (62.0)	85 (7.3)	0 (0.0)	170 (7.3)
≥ 1440 days	70 (51.1)	79 (6.8)	0 (0.0)	149 (6.4)
≥ 1620 days	58 (42.3)	70 (6.1)	0 (0.0)	128 (5.5)
≥ 1710 days	42 (30.7)	48 (4.1)	0 (0.0)	90 (3.9)
≥ 1800 days	33 (24.1)	36 (3.1)	0 (0.0)	69 (3.0)
Patient-years	439.5	1919.9	1583.3	3942.7

The duration of exposure is the total actual days patients took the study medication until cut-off date. Patients are cumulatively counted by each level of the duration of exposure intervals. The FTY720 5 mg–1.25 mg group includes patients who received either FTY720 5 mg alone or FTY720 5 mg switched to 1.25 mg. Source: Table 5-3 Applicant's Clinical Overview.

In addition to the MS studies, there are approximately 800 subjects in clinical pharmacology studies, and 1000 subjects exposed in the transplant population.

Narratives of deaths:

Patient [D2302-0212-00021] – Herpes zoster disseminated
Treatment Group: FTY720 1.25mg
Treatment Period: Active Treatment Phase
ARGUS Case No: PHHO2008IT06575
Event(s): Immunosuppression, multiple sclerosis relapse, abdominal pain upper, viremia, asthenia, transaminases increased, hepatic necrosis, hepatitis, renal haemorrhage, disseminated intravascular coagulation, blister, fatigue, disseminated intravascular coagulation, hepatic function abnormal, endotracheal intubation, hematuria, bradycardia, acute hepatic failure, muscular weakness, hypoaesthesia, paraesthesia, gait disturbance, tension headache, alopecia, depression, presyncope

Demography/Baseline Status

Birth date	Age	Sex	Race	Country
(b) (6)	29	Female	Caucasian	ITA

Study Treatment

Randomized	Last date of study drug	Completed the study?	Reason discontinued	Death (Date)	Cause of death
12-Jul-2007 (Day 1)	23-May-2008 (Day 317)	No	Adverse Event(s)	(b) (6)	Herpes Zoster Disseminated

Narrative Text

The first symptoms probably related to MS occurred in August 2004. The patient was diagnosed with multiple sclerosis in August-2006. No previous MS disease-modifying therapies were given and last corticosteroid use was in August-2006. Prior to study entry the patient also experienced two MS relapses in 2007; in January 2007 a mild event for which no treatment was administered and in May 2007 for which only diazepam was administered. During the study, the patient had a relapse in February 2008, which was treated with 5 mg iv methylprednisolone.

Based on information which the patient provided to a Gastroenterologist in Siena in May 2008, she did not have a history of Varicella as a child and also was not vaccinated against varicella. Serology tests for neurotropic viruses were believed to have been performed at the time of diagnosis of MS in August 2006. It was later determined that the patient was negative for VZV IgG from the August 2006 serology and stored sera collected during study visits in Jan/April 2008.

On 12-July-2007 patient commenced FTY720 1.25 mg daily.

On 8-Feb-2008 (Friday) patient was seen by the investigator complaining of a 6 day history of progressive weakness in the right lower limb. Clinical examination confirmed right lower limb weakness. No other investigations were performed – MRI was not performed. She had been able to continue to work as a teacher in a local Nursery (for children aged 0 – 3 years) up to 7-Feb. There was no mention of specific infections in the Nursery at this time.

On (b) (4) (Monday) commenced methylprednisolone 1g i.v. daily for MS relapse. Treatment administered as an out-patient at the (b) (4) (investigational site). Continued for 5 days up to Friday, (b) (4). Patient was off work during this time period. Routine hematology and biochemistry was performed at the (b) (4) [In the week of 26-May-2008, investigator learned that the lymphocyte count was 434/mm3 at this time; LFTs were normal.]

On 27-Feb-2008 complete recovery from the MS relapse documented.

On 8-Apr-2008 the patient was seen by the neurologist for their month 9 visit and reported no symptoms.

On 6-May-2008, approximately 10 months after receiving study medication the patient was seen for a suspected MS relapse. Symptoms consisted of intermittent paresthesia in both lower limbs. On physical examination, plantar hypoesthesia was noted in both feet. There was no muscle weakness noted in the lower limbs but her gait was affected by the paresthesia and hypothesia. Despite the relapse, the patient continued to work because she did not wish her work colleagues to think that MS was affecting her working ability. It was decided to wait before starting corticosteroid treatment.

On 12-May-2008, the patient reported deterioration in symptoms and it was decided to start corticosteroid treatment. Apart from the neurological symptomatology the patient was feeling well. [The patient subsequently reported that there was a Varicella outbreak in the Nursery at this time.]

On (b) (4) patient commenced methylprednisolone 1g i.v. daily for MS relapse. Treatment administered as an out-patient by an Ambulatory service where she lived. Continued for 5 days up to (b) (4). She also received omeprazole therapy. Despite being advised by the investigator to rest, she continued to work at the Nursery during the course of

this therapy.
On 20-May-2008 without the knowledge of the investigator, the patient continued on oral steroid therapy with medication which she had at home. From 20-May to 22-May she took Medrol 48 mg daily (16 mg t.i.d.). She planned to reduce this to 32 mg daily (16 mg b.i.d.) on 23-May.
On (b) (6) in the early morning (i.e. during the night), the patient called the local physician on-call because of epigastric pain. He recommended to double the omeprazole dosage. At 8:30 AM, she called the investigator because of continuing epigastric pain. The investigator instructed her to stop the Medrol therapy – she may have taken 16 mg that morning although this is not certain. In the late afternoon, she went to the Emergency dept. at a hospital in (b) (4). The investigator was contacted by the ED physician at 7:30 PM. He informed her that the liver transaminases were approx. 300. Abdominal ultrasound was normal and drug-induced liver toxicity was suspected. The investigator recommended to stop the study medication. The investigator also spoke with the patient on the phone who complained only of epigastric pain and general weakness. The patient was admitted to the hospital and then sent to the gastroenterology department.
On (b) (6) the investigator was contacted by the Gastroenterologist at approx. 5:30 PM. Liver transaminases had increased to 1200. [Lymphocytes were 2.5% of approx. 10,000 leucocytes] He also noted vesicles in the throat, compatible with herpes (did not look like candida). At 6:30 PM the investigator was contacted again. The Gastroenterologist now also noted a vesicular eruption on the trunk. Consultations with an Infectious Disease specialist and a hematologist were organized. Acyclovir therapy i.v. was now commenced. At 8:00 PM, the investigator spoke with the patient on the phone. Although speaking with a weak voice, she was fully orientated. She complained of epigastric pain and was extremely tired. Later that evening, coagulation tests were reported to have worsened, DIC was suspected and the patient was transferred to the ICU. A request was made to the Transplantation center in Pisa concerning a possible hepatic transplantation, which was felt to be contraindicated due to the suspicion of viremia. The patient was conscious and breathing well. [On this date, the patient informed the Gastroenterologist, on direct questioning, about a Varicella outbreak at the Nursery where she worked, approx. 14 days earlier.]
Serology tests for hepatitis viruses A, B, C were all negative. Herpes virus serology and aspiration of skin lesions for microbiological tests also performed (Reported by gastroenterologist to investigator later that skin vesicles positive for VZV). Blood cultures and throat swabs were probably not performed.
On (b) (6) the patient was in the ICU. The investigator was called by the Anesthesiologist in the evening. The patient was conscious and able to speak but, because of the rules of the ICU, was not permitted to speak with the investigator on the phone. The Anesthesiologist stated that hepatic function was “extremely poor” [no LFT figures mentioned]. Other organs were functioning, the patient was not intubated and was passing urine. The patient received platelet transfusions and coagulation factors.
On (b) (6) a dramatic deterioration in the patient’s condition during the early morning hours was noted. She was intubated, had massive hematuria and renal dialysis considered which didn't occur due to bradycardia..The patient died at 10:00 AM.
On (b) (6) an autopsy was performed. Cause of death stated to be acute hepatic failure. Initial autopsy report to be provided on (b) (4)
During the study the patient had the following adverse events suspected to be related to study drug:.tension headache (Jul-Oct-2007) and alopecia (Aug-2007 to Jan-2008) and the following adverse events not suspected to be related to study drug.presyncope (3-Sep-2007), depression (Aug-Sep-2007. Concomitant medications taken during the study included: fluribiprofen (Jan-2008), clarithromycin (Jan-2008), ibuprophen (Aug-2007-current), paracetamol (Oct-08), sertraline hydrochloride (Aug-Sep-2007). The patient had one confirmed relapse (EDSS value increased from score of 1.0 to 3.5) from 2-Feb-2008 to 27-Feb-2008..The patient was treated with steroids.and completely recovered..The patient did not have any notable vital sign values and all PFT values were within expected ranges..The patients laboratory values were generally within normal ranges without any pattern of change

observed. The investigator suspected a relationship between the event (herpes zoster disseminated) and the study medication.

Patient [D2302-0821-00007] – Death, herpes simplex encephalitis, grandmal convulsion, coma, pyrexia,
Treatment Group: FTY720 1.25mg
Treatment Period: Active Treatment Phase
ARGUS Case No: PHHO2008KR06307
Event(s): Encephalitis herpes, pyrexia, grandmal convulsion, partial seizures, partial seizures with secondary generalization, depressed level of consciousness, brain edema, CSF protein increased, CSF pressure increased, unresponsive to stimuli, intracranial pressure increased, electroencephalogram abnormal, coma, hyperventilation, mechanical
ventilation, areflexia, headache, dizziness

Demography/Baseline Status

Birth date	Age	Sex	Race	Country
(b) (6)	23	Male	Asian	KOR

Study Treatment

Randomized	Last date of study drug	Completed the study?	Reason discontinued	Death (Date)	Cause of death
11-Jun-2007 (Day 1)	14-May-2008 (Day 339)	No	Adverse Event(s)	(b) (6)	Herpes Simplex Encephalitis

Medical History / Current Medical Conditions

History / condition Verbatim Term (Preferred Term)	Diagnosis / surgery (Date)	Active problem at start of study drug
Right Leg Spasticity (Muscle Spasticity)	29-May-2007	No

Previous MS Treatment

Trade (Generic) name/Non-drug therapy	Start Date	End Date
Betaferon (Interferon Beta-1b)	29-Mar-2007	19-May-2007

Narrative Text
The patient was diagnosed with multiple sclerosis in Mar-2007. Previous therapy includes interferon-beta-1b from Mar-2007 to May-2007 and the last corticosteroid use was in Apr-2007.
The patient's past medical history included: muscle spasticity (Mar-2007), which was not continuing at start of study. There was no past medical history of seizures.
On 13-May-2008, approximately 11 months after receiving the first dose of study medication, the patient experienced fever, headache and URI symptoms. Most of the symptoms subsided with a common cold medicine. Study drug was permanently discontinued on 13-May-2008.
On (b) (6) the patient developed sudden generalized tonic-clonic seizures and was hospitalized at an outside university hospital close to his place of residence. Initial routine blood testing was unremarkable. CSF tests did not reveal any significant findings (specific details pending), except for an increased opening pressure of 22 cmH20. In the CSF, microbiological analysis was negative for cryptococcal antigen, HSV IgG/IgM and tuberculosis PCR. HSV PCR from this first CSF sample was not performed. A brain MRI scan performed on the same day revealed diffuse low intensity lesion at the left temporal and parietal cortex and subcortical WM on ADC mapping image. No Gd-enhancing lesions were found and there was no significant change in the previously seen multifocal white matter lesions involving both fronto-temporal-parietal PVWM, thalamus, brainstem and cerebellum. No specific diagnosis was made and the patient was treated with the antiepileptic drug,

oxcarbazepine. See medication list for medications administered during the hospitalization (update on dosages and timing of administration is pending).
During his hospital course, the patient continued to have intermittent high fevers and partial seizures, but his level of consciousness was not seriously altered until he developed of series of seizures (partial seizures with secondary generalization) on [redacted] Phenytoin and Phenobarbital were administered (unclear start date and duration of treatment), but the seizures did not completely abate. An EEG showed periodic sharp waves on both hemispheres (left > right). The patient's level of consciousness rapidly deteriorated.
On [redacted], a follow-up MRI revealed a markedly progressed confluent cortex and subcortical white matter lesion with extensive gyral swelling at both cerebral hemispheres mainly in the insula, and temporal and frontal lobes. The patient received antibiotics for aspiration pneumonia, cerol and high dose methylprednisolone (unclear dosage and treatment duration) empirically.
On [redacted] the patient was transferred to the affiliated hospital of the PI (FTY720 study center hospital). After reviewing the medical records and MRI scans, the patient was tentatively diagnosed with viral encephalitis (most likely herpes simplex). The patient was immediately treated with acyclovir and therapies for cerebral edema were administered. After admission, the patient had a brief partial seizure on two occasions. Intravenous loading of valproate was done and the dosage of oxcarbazepine was increased..A second CSF sample from [redacted] supported the diagnosis of a viral encephalitis, showing 22 WBCs (84% of other cells, 16% of mononuclear cells and no granulocytes), 2 RBCs, normal glucose and markedly elevated protein (250 mg/dL), and an elevated opening pressure of 39 cmH2O. HSV PCR from this second CSF sample was positive (qualitative result only, unclear if HSV-1 or HSV-2). Additional CSF from this second sample was sent on [redacted] to the NIH (National Institute of Health) for further analysis (i.e., JC virus PCR, HSV-1 and HSV-2 PCR encephalitis panel).
On [redacted], the follow-up EEG demonstrated periodic sharp waves in both hemispheres. There was no further seizure activity. However, the patient's condition continuously deteriorated and mechanical ventilation was started.
On [redacted], the pupillary light response disappeared. In spite of antiviral therapy and massive therapies for increased intracranial pressure, including mannitol, dexamethasone and hyperventilation, his condition continued to deteriorate.
On [redacted], he only showed only minimal response on endotracheal suction and started having limitation of extraocular movements on Doll's eye maneuver. On EEG, there was no epileptiform discharges, but electrical potentials were markedly decreased (less than 5μV).
On [redacted], the patient did not show any response to external stimuli and brainstem reflexes had disappeared.
On [redacted] the patient's vital signs were stable, but his clinical condition had further deteriorated and he was reported as being fully comatose. The apnea test was negative (i.e., the patient showed minimal spontaneous respiratory movements).
The patient had been comatose, with mechanical ventilation, for about 2 months and died on [redacted]. An autopsy was not performed.
The investigator did suspect a relationship between this event and the study drug and considered the event to be life-threatening.

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
02/14/2010
At the request of Dr. Villalba

ERIC P BASTINGS
02/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Antivirals			FROM (*Name, Office/Division, and Phone Number of Requestor*): Dr. Eric Bastings, Deputy Director, Division of Neurology. Ext. 6-1039.	
DATE 2-05-2010	IND NO.	NDA NO. 022527	TYPE OF DOCUMENT	DATE OF DOCUMENT
NAME OF DRUG Gilenia (fingolimod)	PRIORITY CONSIDERATION 6-month review		CLASSIFICATION OF DRUG Multiple sclerosis drug	DESIRED COMPLETION DATE March 12, 2010
NAME OF FIRM: Novartis Pharmaceutical Corporation				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☒ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Please evaluate the risk of infections with fingolimod, an oral agent for the treatment of multiple sclerosis (MS) (NDA 22-527). We request advice on to how to adequately identify, monitor, treat early and/or prevent opportunistic infections in this population.

Fingolimod is a sphingosine- 1- phosphate (S1P) modulator that induces immuno- suppresion by reduction of circulating lymphocytes. The drug was initially developed in the renal transplant population at doses of 2.5 and 5 mg/day but that indication is no longer pursued. The dose proposed for approval in MS is 0.5 mg/day. This is a rolling NDA (**\\CDSESUB1\EVSPROD\NDA022527**). The clinical data in the MS population was submitted in December, 2009 (SN 003 and 004). Clinical data in the transplant population was submitted in October 2009 (SN 002). This application has a priority review (PDUFA goal date June 21, 2010) and will go to an advisory committee meeting on June 10, 2010).

The applicant states that single doses of fingolimod from 0.5 to 5.0 mg result in a dose dependent decrease in

lymphocyte count (all, B and T [helper, suppressor, memory and naïve T]). This decrease occurs rapidly, within 3-4 hours of the first oral dose. With single doses from 5 to 40 mg, there is minimal additional effect on the lymphocyte count. With multiple dosing of fingolimod from 0.125 mg to 5 mg there is a dose-dependent decrease in lymphocyte count, resulting in counts reduced to 60% of baseline count to 10- 15% of baseline count, respectively. In a multiple dose study (FTY720AB102) all lymphocyte subsets (CD20 [B cell], CD3 [T cell], CD4 [T helper], CD8 [T suppressor], CD16 [Natural killer], CD45RO [T memory], CD45RA [T naïve] were found to decrease in a dose dependent manner in the setting of multiple doses of fingolimod. The monocyte count was not affected by multiple dose fingolimod treatment.

Two young patients (ID# D2302-0212-00021 and D2302-0821-00007) died of disseminated herpes infections (one herpes simplex encephalitis and one disseminated herpes zoster) among approximately 3000 subjects with MS exposed to fingolimod. Both deaths occurred in the 1.25mg/day dose group. Narratives of these cases can be found in the attached document below.

Please evaluate the risk for opportunistic infections with fingolimod treatment and provide advice on how to adequately identify, monitor, treat early and/or prevent opportunistic infections in this population. A finalized review is desired by March 12, 2010.

It is anticipated that the risk of opportunistic infections and how to minimize this risk will be discussed at the AC meeting. Please assign a reviewer to represent your division at the AC. We also request that you suggest three outside experts to participate in the AC panel. Please provide these names at your earlier convenience.

Please feel free to contact Dr. Villalba (maria.villalba@fda.hhs.gov) if you have any questions.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Electronic	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Attachment 1.

Table 1. Duration of exposure to study drug after randomization in Group E (all FTY720-treated patients open label and controlled studies, safety population)

	FTY720 5 mg–1.25 mg (N=137)	**FTY720 1.25 mg (N=1157)**	**FTY720 0.5 mg (N=1021)**	**Total (N=2315)**
Exposure (days)	n (%)	n (%)	n (%)	n (%)
≥ 1 day	137 (100)	1157 (100)	1021 (100)	2315 (100)
≥ 90 days	126 (92.0)	1074 (92.8)	986 (96.6)	2186 (94.4)
≥ 180 days	118 (86.1)	1027 (88.8)	958 (93.8)	2103 (90.8)
≥ 270 days	111 (81.0)	969 (83.8)	907 (88.8)	1987 (85.8)
≥ 360 days	108 (78.8)	831 (71.8)	781 (76.5)	1720 (74.3)
≥ 540 days	101 (73.7)	715 (61.8)	691 (67.7)	1507 (65.1)
≥ 720 days	96 (70.1)	354 (30.6)	289 (28.3)	739 (31.9)
≥ 1080 days	85 (62.0)	85 (7.3)	0 (0.0)	170 (7.3)
≥ 1440 days	70 (51.1)	79 (6.8)	0 (0.0)	149 (6.4)
≥ 1620 days	58 (42.3)	70 (6.1)	0 (0.0)	128 (5.5)
≥ 1710 days	42 (30.7)	48 (4.1)	0 (0.0)	90 (3.9)
≥ 1800 days	33 (24.1)	36 (3.1)	0 (0.0)	69 (3.0)
Patient-years	439.5	1919.9	1583.3	3942.7

The duration of exposure is the total actual days patients took the study medication until cut-off date. Patients are cumulatively counted by each level of the duration of exposure intervals. The FTY720 5 mg–1.25 mg group includes patients who received either FTY720 5 mg alone or FTY720 5 mg switched to 1.25 mg. Source: Table 5-3 Applicant's Clinical Overview.

In addition to the MS studies, there are approximately 800 subjects in clinical pharmacology studies, and 1000 subjects exposed in the transplant population.

Narratives of deaths:

Patient [D2302-0212-00021] – Herpes zoster disseminated
Treatment Group: FTY720 1.25mg
Treatment Period: Active Treatment Phase
ARGUS Case No: PHHO2008IT06575
Event(s): Immunosuppression, multiple sclerosis relapse, abdominal pain upper, viremia, asthenia, transaminases increased, hepatic necrosis, hepatitis, renal haemorrhage, disseminated intravascular coagulation, blister, fatigue, disseminated intravascular coagulation, hepatic function abnormal, endotracheal intubation, hematuria, bradycardia, acute hepatic failure, muscular weakness, hypoaesthesia, paraesthesia, gait disturbance, tension headache, alopecia, depression, presyncope

Demography/Baseline Status

Birth date	Age	Sex	Race	Country
[redacted] (b) (6)	29	Female	Caucasian	ITA

Study Treatment

Randomized	Last date of study drug	Completed the study?	Reason discontinued	Death (Date)	Cause of death
12-Jul-2007 (Day 1)	23-May-2008 (Day 317)	No	Adverse Event(s)	[redacted] (b) (6)	Herpes Zoster Disseminated

Narrative Text

The first symptoms probably related to MS occurred in August 2004. The patient was diagnosed with multiple sclerosis in August-2006. No previous MS disease-modifying therapies were given and last corticosteroid use was in August-2006. Prior to study entry the patient also experienced two MS relapses in 2007; in January 2007 a mild event for which no treatment was administered and in May 2007 for which only diazepam was administered. During the study, the patient had a relapse in February 2008, which was treated with 5 mg iv methylprednisolone.

Based on information which the patient provided to a Gastroenterologist in Siena in May 2008, she did not have a history of Varicella as a child and also was not vaccinated against varicella. Serology tests for neurotropic viruses were believed to have been performed at the time of diagnosis of MS in August 2006. It was later determined that the patient was negative for VZV IgG from the August 2006 serology and stored sera collected during study visits in Jan/April 2008.

On 12-July-2007 patient commenced FTY720 1.25 mg daily.

On 8-Feb-2008 (Friday) patient was seen by the investigator complaining of a 6 day history of progressive weakness in the right lower limb. Clinical examination confirmed right lower limb weakness. No other investigations were performed – MRI was not performed. She had been able to continue to work as a teacher in a local Nursery (for children aged 0 – 3 years) up to 7-Feb. There was no mention of specific infections in the Nursery at this time.

On [redacted] (b) (6) (Monday) commenced methylprednisolone 1g i.v. daily for MS relapse. Treatment administered as an out-patient at the [redacted] (b) (6) (investigational site). Continued for 5 days up to Friday [redacted] (b) (6). Patient was off work during this time period. Routine hematology and biochemistry was performed at the [redacted] (b) (6). [In the week of 26-May-2008, investigator learned that the lymphocyte count was 434/mm3 at this time; LFTs were normal.]

On 27-Feb-2008 complete recovery from the MS relapse documented.

On 8-Apr-2008 the patient was seen by the neurologist for their month 9 visit and reported no symptoms.

On 6-May-2008, approximately 10 months after receiving study medication the patient was seen for a suspected MS relapse. Symptoms consisted of intermittent paresthesia in both lower limbs. On physical examination, plantar hypoesthesia was noted in both feet. There was no muscle weakness noted in the lower limbs but her gait was affected by the paresthesia and hypothesia. Despite the relapse, the patient continued to work because she did not wish her work colleagues to think that MS was affecting her working ability. It was decided to wait before starting corticosteroid treatment.

On 12-May-2008, the patient reported deterioration in symptoms and it was decided to start corticosteroid treatment. Apart from the neurological symptomatology the patient was feeling well. [The patient subsequently reported that there was a Varicella outbreak in the Nursery at this time.]

On [redacted] (b) (6) patient commenced methylprednisolone 1g i.v. daily for MS relapse. Treatment administered as an out-patient by an Ambulatory service where she lived. Continued for 5 days up to [redacted] (b) (6). She also received omeprazole therapy. Despite being advised by the investigator to rest, she continued to work at the Nursery during the course of

this therapy.
On 20-May-2008 without the knowledge of the investigator, the patient continued on oral steroid therapy with medication which she had at home. From 20-May to 22-May she took Medrol 48 mg daily (16 mg t.i.d.). She planned to reduce this to 32 mg daily (16 mg b.i.d.) on 23-May.
On (b) (6) in the early morning (i.e. during the night), the patient called the local physician on-call because of epigastric pain. He recommended to double the omeprazole dosage. At 8:30 AM, she called the investigator because of continuing epigastric pain. The investigator instructed her to stop the Medrol therapy – she may have taken 16 mg that morning although this is not certain. In the late afternoon, she went to the Emergency dept. at a hospital in (b) (6) The investigator was contacted by the ED physician at 7:30 PM. He informed her that the liver transaminases were approx. 300. Abdominal ultrasound was normal and drug-induced liver toxicity was suspected. The investigator recommended to stop the study medication. The investigator also spoke with the patient on the phone who complained only of epigastric pain and general weakness. The patient was admitted to the hospital and then sent to the gastroenterology department.
On (b) (6) the investigator was contacted by the Gastroenterologist at approx. 5:30 PM. Liver transaminases had increased to 1200. [Lymphocytes were 2.5% of approx. 10,000 leucocytes] He also noted vesicles in the throat, compatible with herpes (did not look like candida). At 6:30 PM the investigator was contacted again. The Gastroenterologist now also noted a vesicular eruption on the trunk. Consultations with an Infectious Disease specialist and a hematologist were organized. Acyclovir therapy i.v. was now commenced. At 8:00 PM, the investigator spoke with the patient on the phone. Although speaking with a weak voice, she was fully orientated. She complained of epigastric pain and was extremely tired. Later that evening, coagulation tests were reported to have worsened, DIC was suspected and the patient was transferred to the ICU. A request was made to the Transplantation center in Pisa concerning a possible hepatic transplantation, which was felt to be contraindicated due to the suspicion of viremia. The patient was conscious and breathing well. [On this date, the patient informed the Gastroenterologist, on direct questioning, about a Varicella outbreak at the Nursery where she worked, approx. 14 days earlier.]
Serology tests for hepatitis viruses A, B, C were all negative. Herpes virus serology and aspiration of skin lesions for microbiological tests also performed (Reported by gastroenterologist to investigator later that skin vesicles positive for VZV). Blood cultures and throat swabs were probably not performed.
On (b) (6) the patient was in the ICU. The investigator was called by the Anesthesiologist in the evening. The patient was conscious and able to speak but, because of the rules of the ICU, was not permitted to speak with the investigator on the phone. The Anesthesiologist stated that hepatic function was “extremely poor” [no LFT figures mentioned]. Other organs were functioning, the patient was not intubated and was passing urine. The patient received platelet transfusions and coagulation factors.
On (b) (6) a dramatic deterioration in the patient’s condition during the early morning hours was noted. She was intubated, had massive hematuria and renal dialysis considered which didn't occur due to bradycardia..The patient died at 10:00 AM.
On (b) (6) an autopsy was performed. Cause of death stated to be acute hepatic failure. Initial autopsy report to be provided on (b) (6)
During the study the patient had the following adverse events suspected to be related to study drug:.tension headache (Jul-Oct-2007) and alopecia (Aug-2007 to Jan-2008) and the following adverse events not suspected to be related to study drug.presyncope (3-Sep-2007), depression (Aug-Sep-2007. Concomitant medications taken during the study included: fluribiprofen (Jan-2008), clarithromycin (Jan-2008), ibuprophen (Aug-2007-current), paracetamol (Oct-08), sertraline hydrochloride (Aug-Sep-2007). The patient had one confirmed relapse (EDSS value increased from score of 1.0 to 3.5) from 2-Feb-2008 to 27-Feb-2008..The patient was treated with steroids.and completely recovered..The patient did not have any notable vital sign values and all PFT values were within expected ranges..The patients laboratory values were generally within normal ranges without any pattern of change

observed. The investigator suspected a relationship between the event (herpes zoster disseminated) and the study medication.

Patient [D2302-0821-00007] – Death, herpes simplex encephalitis, grandmal convulsion, coma, pyrexia,
Treatment Group: FTY720 1.25mg
Treatment Period: Active Treatment Phase
ARGUS Case No: PHHO2008KR06307
Event(s): Encephalitis herpes, pyrexia, grandmal convulsion, partial seizures, partial seizures with secondary generalization, depressed level of consciousness, brain edema, CSF protein increased, CSF pressure increased, unresponsive to stimuli, intracranial pressure increased, electroencephalogram abnormal, coma, hyperventilation, mechanical
ventilation, areflexia, headache, dizziness

Demography/Baseline Status

Birth date	Age	Sex	Race	Country
(b) (6)	23	Male	Asian	KOR

Study Treatment

Randomized	Last date of study drug	Completed the study?	Reason discontinued	Death (Date)	Cause of death
11-Jun-2007 (Day 1)	14-May-2008 (Day 339)	No	Adverse Event (s)	(b) (6)	Herpes Simplex Encephalitis

Medical History / Current Medical Conditions

History / condition Verbatim Term (Preferred Term)	Diagnosis / surgery (Date)	Active problem at start of study drug
Right Leg Spasticity (Muscle Spasticity)	29-May-2007	No

Previous MS Treatment

Trade (Generic) name/Non-drug therapy	Start Date	End Date
Betaferon (Interferon Beta-1b)	29-Mar-2007	19-May-2007

Narrative Text
The patient was diagnosed with multiple sclerosis in Mar-2007. Previous therapy includes interferon-beta-1b from Mar-2007 to May-2007 and the last corticosteroid use was in Apr-2007.
The patient's past medical history included: muscle spasticity (Mar-2007), which was not continuing at start of study. There was no past medical history of seizures.
On 13-May-2008, approximately 11 months after receiving the first dose of study medication, the patient experienced fever, headache and URI symptoms. Most of the symptoms subsided with a common cold medicine. Study drug was permanently discontinued on 13-May-2008.
On (b) (6) the patient developed sudden generalized tonic-clonic seizures and was hospitalized at an outside university hospital close to his place of residence. Initial routine blood testing was unremarkable. CSF tests did not reveal any significant findings (specific details pending), except for an increased opening pressure of 22 cmH20. In the CSF, microbiological analysis was negative for cryptococcal antigen, HSV IgG/IgM and tuberculosis PCR. HSV PCR from this first CSF sample was not performed. A brain MRI scan performed on the same day revealed diffuse low intensity lesion at the left temporal and parietal cortex and subcortical WM on ADC mapping image. No Gd-enhancing lesions were found and there was no significant change in the previously seen multifocal white matter lesions involving both fronto-temporal-parietal PVWM, thalamus, brainstem and cerebellum. No specific diagnosis was made and the patient was treated with the antiepileptic drug,

oxcarbazepine. See medication list for medications administered during the hospitalization (update on dosages and timing of administration is pending).
During his hospital course, the patient continued to have intermittent high fevers and partial seizures, but his level of consciousness was not seriously altered until he developed of series of seizures (partial seizures with secondary generalization) on (b) (6). Phenytoin and Phenobarbital were administered (unclear start date and duration of treatment), but the seizures did not completely abate. An EEG showed periodic sharp waves on both hemispheres (left > right). The patient's level of consciousness rapidly deteriorated.
On (b) (6), a follow-up MRI revealed a markedly progressed confluent cortex and subcortical white matter lesion with extensive gyral swelling at both cerebral hemispheres mainly in the insula, and temporal and frontal lobes. The patient received antibiotics for aspiration pneumonia, cerol and high dose methylprednisolone (unclear dosage and treatment duration) empirically.
On (b) (6), the patient was transferred to the affiliated hospital of the PI (FTY720 study center hospital). After reviewing the medical records and MRI scans, the patient was tentatively diagnosed with viral encephalitis (most likely herpes simplex). The patient was immediately treated with acyclovir and therapies for cerebral edema were administered. After admission, the patient had a brief partial seizure on two occasions. Intravenous loading of valproate was done and the dosage of oxcarbazepine was increased..A second CSF sample from (b) (6) supported the diagnosis of a viral encephalitis, showing 22 WBCs (84% of other cells, 16% of mononuclear cells and no granulocytes), 2 RBCs, normal glucose and markedly elevated protein (250 mg/dL), and an elevated opening pressure of 39 cmH2O. HSV PCR from this second CSF sample was positive (qualitative result only, unclear if HSV-1 or HSV-2). Additional CSF from this second sample was sent on (b) (6) to the NIH (National Institute of Health) for further analysis (i.e., JC virus PCR, HSV-1 and HSV-2 PCR encephalitis panel).
On (b) (6) the follow-up EEG demonstrated periodic sharp waves in both hemispheres. There was no further seizure activity. However, the patient's condition continuously deteriorated and mechanical ventilation was started.
On (b) (6), the pupillary light response disappeared. In spite of antiviral therapy and massive therapies for increased intracranial pressure, including mannitol, dexamethasone and hyperventilation, his condition continued to deteriorate.
On (b) (6), he only showed only minimal response on endotracheal suction and started having limitation of extraocular movements on Doll's eye maneuver. On EEG, there was no epileptiform discharges, but electrical potentials were markedly decreased (less than 5μV).
On (b) (6), the patient did not show any response to external stimuli and brainstem reflexes had disappeared.
On (b) (6), the patient's vital signs were stable, but his clinical condition had further deteriorated and he was reported as being fully comatose. The apnea test was negative (i.e., the patient showed minimal spontaneous respiratory movements).
The patient had been comatose, with mechanical ventilation, for about 2 months and died on (b) (6). An autopsy was not performed.
The investigator did suspect a relationship between this event and the study drug and considered the event to be life-threatening.

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/

HAMET M TOURE
02/05/2010

ERIC P BASTINGS
02/08/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Division of Biostatistic VI Attention: Karl Lin

FROM:
Russell Katz, MD, Division Director, DNP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 28, 2010		NDA 22-509	NDA	December 22, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gilenia (fingolimod) Capsules	Priority	1 - NME	April 15, 2010 (PDUFA due date: 6/21/10)

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☑ ELECTRONIC NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☑ OTHER *(SPECIFY BELOW)*: CAC Stat Consult Request

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☑ PHARMACOLOGY: CAC statistical data ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Please review and comment on the acceptability of the carcinogenicity statistical information for Gilenia (fingolimod)/NDA (b) (4) . The action date for this application is June 21, 2010. Here is the link to the EDR submission: \\CDSESUB1\EVSPROD\NDA022527\022527.enx. The items you will need are sequence 005 (dated 1/20/10) in folder m4/datasets (\\Cdsesub1\evsprod\nda022527\0005\m4\datasets)
Thanks.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Jackie Ware, PharmD, Supervisory Regulatory Project Manager, DNP Food and Drug Administration Phone: 301-796-1160 Email: jacqueline.ware@fda.hhs.gov	☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/

JACQUELINE H H WARE
01/28/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Pulmonary and Allergy Products	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Dr. Eric Bastings, Division of Neurology Deputy Director; Ext 6-1039

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/28/2010		022527		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gilenia (fingolimod)	6-month review	Multiple sclerosis	3/12/2010

NAME OF FIRM: Novartis Pharmaceuticals Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Pulmonary**

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

We request evaluation of the pulmonary safety of fingolimod, an oral agent for the treatment of multiple sclerosis (MS) (NDA 22-527).

Fingolimod is a sphingosine- 1- phosphate (S1P) modulator that induces immunosuppression by reduction of circulating lymphocytes. The drug was initially developed in the renal transplant population at doses up to 5 mg/day but that indication is no longer pursued. The dose proposed for approval in MS is 0.5 mg/day.

This is a rolling NDA (**\\CDSESUB1\EVSPROD\NDA022527**). The clinical data in the MS population was submitted on December 18, 2009 (SN 003 and 004). Clinical data in the transplant population was submitted on October 5, 2009 (SN 002). This application has a priority review (PDUFA goal date June 21, 2010) and will go to an advisory committee (AC) meeting on June 10, 2010.

In non-clinical studies in mice, rat, dog and monkey, there was evidence of lung toxicity in single and multiple-dose, intravenous and oral studies. In these studies, lung weights were increased; there was hypertrophy/hyperplasia of

smooth muscle in the broncho- alveolar junction, alveolar macrophage infiltration and inflammatory lesions, pneumonia and subpleural fibrosis.

In a study of patients with relapsing MS treated with placebo, 1.25 or 5.0 mg fingolimod for 6 months (study D2201), dyspnea was reported in 1.1%, 4.3% and 12.8% of patients in the placebo, 1.25 and 5 mg groups, respectively. The pulmonary function tests showed a significant and substantial detriment in function over the 6-month treatment period. For this and other reasons, the IND was on a Clinical hold. The Clinical hold was lifted on 5/19/06.

The DNP obtained input from the Division of Pulmonary and Allergy Drug Products at the IND stage regarding monitoring of lung toxicity (See reviews by Dr. Carol Bosken, dated 8/30/05, 11/30/05, 2/28/06 and 8/1/06). The reviewer concluded that the phase 2 studies suggested decreased pulmonary function with both restrictive and obstructive components. However, the monitoring was incomplete and the precise nature of the pulmonary toxicity was unclear. The reviewer provided specific recommendations as to how to best monitor the pulmonary toxicity of this drug.

The applicant has submitted clinical and PFT information from the completed renal transplant and MS clinical programs, and HRCT information from 360 subjects from study D2301 (a completed MS study) and 266 subjects enrolled in study 2309, an ongoing, 2-year study of approximately 1080 patients with MS receiving fingolimod 1.25 mg/day, 0.5 mg/day or placebo. Only special safety data (such as HRCT) were unblinded from study 2309 and submitted as part of a Special Safety Interim Report (SN 004). Attachment 1 provides some additional relevant background information from the clinical program in MS.

DNP is requesting evaluation of the risk of pulmonary toxicity associated with fingolimod in the MS population. Date of desired completion: by March 12, 2010 (before mid-cycle)

It is anticipated that pulmonary toxicity will be discussed at the AC meeting. Please assign a reviewer to represent your division at the AC. We also request that you suggest three outside experts to participate in the AC panel at your earliest convenience.

For all questions, please refer to Dr. Lourdes Villalba (maria.villalba@fda.hhs.gov). Thank you

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Electronic	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/

HAMET M TOURE
01/28/2010
Requested by Drs. Villalba and Bastings

ERIC P BASTINGS
02/01/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Anti-Infective and Ophthalmology Products	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Dr. Eric Bastings, Division of Neurology Deputy Director; Ext 6-1039

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/28/2010		022527		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gilenia (fingolimod)	6-month review	Multiple sclerosis	3/12/2010

NAME OF FIRM: Novartis Pharmaceuticals Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
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- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Ophthalmology**

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: NDA 22-527, Ophthalmology consult request

We request evaluation of the ophthalmologic toxicity of fingolimod, an oral agent for the treatment of multiple sclerosis (MS) (NDA 22-527). Please also refer to attachment 1 below.

Fingolimod is a sphingosine- 1- phosphate (S1P) modulator that induces immuno- suppression by reduction of circulating lymphocytes. The drug was initially developed in the renal transplant population at doses of 2.5 and 5 mg/day but that indication is no longer pursued. The dose proposed for approval in MS is 0.5 mg/day.

This is a rolling NDA (\\CDSESUB1\EVSPROD\NDA022527). The clinical data in the MS population was submitted in 18 December, 2009 (SN 003 and 004). Clinical data in the transplant population was submitted in October 5, 2009 (SN 002). This application has a priority review (PDUFA goal date June 21, 2010) and will go to an advisory committee meeting (estimated date June 10, 2010).

Several cases of macular edema were reported during the development of fingolimod for the renal transplant indication. Subsequently, ophthalmic screenings for macular edema were implemented in all MS studies.

Ophthalmic evaluations in MS studies D2301, D2302, D2302E1 and D2201Extension included assessment of visual acuity and dilated fundoscopy. Additionally, study D2309 (an ongoing study of approximately 1080 subjects) included OCT in all patients to determine retinal (including central foveal) thickness. OCT analyses were submitted as part of a Special Safety Interim Report (SN 004), however, clinical safety data from this study is still blinded. (Attachment 1 provides some additional relevant background information from the clinical program in MS.)

DNP is requesting evaluation of the risk of ophthalmologic toxicity associated with fingolimod in the MS population. We request that the review be completed by March 12, 2010 (before the midcycle meeting).

It is anticipated that ophthalmologic toxicity will be discussed at the AC meeting. Please assign a reviewer to represent your division at the AC. We also request that you suggest three outside experts to participate in the AC panel. Please provide these names at your earliest convenience.

For all questions, please refer to Dr. Lourdes Villalba (maria.villalba@fda.hhs.gov). Thank you

SIGNATURE OF REQUESTOR Electronic	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Attachment 1.

Table 1. Duration of exposure to study drug after randomization (Safety population, all double blind controlled studies – Group D)

	FTY720 5 mg N=94	FTY720 1.25 mg N=943	FTY720 0.5 mg N=854	Placebo N=511	IFN β-1a i.m. N=431
Exposure (days)	n (%)	n (%)	n (%)	n (%)	n (%)
≥ 1 day	94 (100)	943 (100)	854 (100)	511 (100)	431 (100)
≥ 90 days	86 (91.5)	874 (92.7)	827 (96.8)	487 (95.3)	413 (95.8)
≥ 180 days	52 (55.3)	800 (84.8)	803 (94.0)	433 (84.7)	399 (92.6)
≥ 270 days	0	726 (77.0)	784 (91.8)	372 (72.8)	386 (89.6)
≥ 360 days	0	623 (66.1)	671 (78.6)	356 (69.7)	300 (69.6)
≥ 540 days	0	316 (33.5)	363 (42.5)	324 (63.4)	0
≥ 720 days	0	183 (19.4)	196 (23.0)	199 (38.9)	0
Mean duration	167.7	430.4	493.2	533.9	340.6
Patient-years total	43.2	1111.2	1153.2	746.9	401.9

The duration of exposure is the total number of actual days patients took the study medication.
Patients are cumulatively counted by each level of the duration of exposure intervals. Includes studies 2301, 2302 and 2201.

Table 2. AE in the Eye disorders SOC, all DB, controlled studies (Group D).

Table 4.4-1 (Page 7 of 91)
Adverse events by primary system organ class and preferred term
Safety population
(Group D: All double-blind, randomized and controlled studies)

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Eye disorders					
-Total	5 (5.3)	136 (14.4)	135 (15.8)	74 (14.5)	52 (12.1)
Vision blurred	0 (0.0)	21 (2.2)	25 (2.9)	6 (1.2)	13 (3.0)
Eye pain	1 (1.1)	16 (1.7)	15 (1.8)	6 (1.2)	7 (1.6)
Conjunctivitis	1 (1.1)	12 (1.3)	21 (2.5)	11 (2.2)	6 (1.4)
Macular oedema	0 (0.0)	12 (1.3)	2 (0.2)	0 (0.0)	1 (0.2)
Visual acuity reduced	1 (1.1)	11 (1.2)	8 (0.9)	9 (1.8)	3 (0.7)
Dry eye	0 (0.0)	9 (1.0)	7 (0.8)	4 (0.8)	4 (0.9)
Diplopia	0 (0.0)	8 (0.8)	3 (0.4)	5 (1.0)	2 (0.5)
Myodesopsia	0 (0.0)	5 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Conjunctivitis allergic	1 (1.1)	3 (0.3)	3 (0.4)	3 (0.6)	0 (0.0)
Photopsia	0 (0.0)	3 (0.3)	1 (0.1)	1 (0.2)	0 (0.0)
Presbyopia	0 (0.0)	3 (0.3)	4 (0.5)	1 (0.2)	0 (0.0)
Retinal detachment	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)
Retinal haemorrhage	0 (0.0)	3 (0.3)	3 (0.4)	0 (0.0)	0 (0.0)
Asthenopia	0 (0.0)	2 (0.2)	1 (0.1)	1 (0.2)	0 (0.0)
Blepharitis	0 (0.0)	2 (0.2)	2 (0.2)	1 (0.2)	1 (0.2)
Cataract	0 (0.0)	2 (0.2)	2 (0.2)	1 (0.2)	1 (0.2)
Eyelid oedema	0 (0.0)	2 (0.2)	2 (0.2)	0 (0.0)	1 (0.2)
Lacrimation increased	0 (0.0)	2 (0.2)	3 (0.4)	1 (0.2)	2 (0.5)
Myopia	0 (0.0)	2 (0.2)	2 (0.2)	3 (0.6)	0 (0.0)
Optic atrophy	0 (0.0)	2 (0.2)	4 (0.5)	2 (0.4)	1 (0.2)
Retinal aneurysm	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal disorder	0 (0.0)	2 (0.2)	2 (0.2)	3 (0.6)	0 (0.0)

Uveitis	0 (0.0)	2 (0.2)	3 (0.4)	0 (0.0)	1 (0.2)
Visual impairment	0 (0.0)	2 (0.2)	4 (0.5)	5 (1.0)	3 (0.7)
Abnormal sensation in eye	0 (0.0)	1 (0.1)	4 (0.5)	2 (0.4)	1 (0.2)
Arteriosclerotic retinopathy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Blepharospasm	0 (0.0)	1 (0.1)	4 (0.5)	1 (0.2)	0 (0.0)
Blindness unilateral	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Chorioretinal atrophy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Ciliary muscle spasm	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)
Conjunctival haemorrhage	0 (0.0)	1 (0.1)	3 (0.4)	0 (0.0)	0 (0.0)
Dacryostenosis acquired	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)
Eye allergy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorder	1 (1.1)	1 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)
Eye irritation	1 (1.1)	1 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)
Eye pruritus	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)
Glare	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hypermetropia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Iritis	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.4)	0 (0.0)
Keratoconjunctivitis sicca	0 (0.0)	1 (0.1)	3 (0.4)	0 (0.0)	0 (0.0)
Lacrimal disorder	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Lens disorder	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Miosis	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Ophthalmoplegia	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)
Papilloedema	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Refraction disorder	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal exudates	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal pigment epitheliopathy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal pigmentation	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Retinitis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Retinopathy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vitritis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Xanthopsia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Accommodation disorder	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)
Amaurosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Amblyopia	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Blindness transient	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Cataract cortical	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Chalazion	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Chorioretinopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Corneal disorder	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Corneal oedema	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Detachment of retinal pigment epithelium	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Eczema eyelids	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Eye discharge	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Eye haemorrhage	0 (0.0)	0 (0.0)	4 (0.5)	2 (0.4)	0 (0.0)
Eye movement disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Eye swelling	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.2)	0 (0.0)
Eyelid ptosis	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)
Glaucoma	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Halo vision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Iridocyclitis	1 (1.1)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)
Keratitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Macular degeneration	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Maculopathy	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)
Ocular discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Ocular hyperaemia	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Ocular vascular disorder	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Optic disc haemorrhage	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Optic disc vascular disorder	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Oscillopsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Panophthalmitis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)
Photophobia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Retinal tear	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Scintillating scotoma	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Scleral discolouration	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Scotoma	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.6)	3 (0.7)
Sicca syndrome	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Strabismus	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)
Uhthoff's phenomenon	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the FTY720 1.25 mg column.- Source: MS ISS.

Table 3. Special safety evaluations in study 2309.

Table 1-2 Analysis populations and analysis sets, by treatment

	FTY720 1.25 mg n (%)	FTY720 0.5 mg n (%)	Placebo n (%)	Interferon beta-1a i.m. n	Total n (%)
Study D2309					
Randomized population	370 (100.0)	358 (100.0)	355 (100.0)	0	1083 (100.0)
Safety population	370 (100.0)	358 (100.0)	355 (100.0)	0	1083 (100.0)
Holter ECG analysis set	366 (98.9)	356 (99.4)	353 (99.4)	0	1075 (99.3)
Chest HRCT analysis set	88 (23.8)	88 (24.6)	90 (25.4)	0	266 (24.6)
OPH analysis set for OCT	357 (96.5)	348 (97.2)	348 (98.0)	0	1053 (97.2)
Study D2309 and study D2302					
Pooled echo analysis set	64	60	48	11	183

ECG = electrocardiogram, HRCT = high resolution computed tomography, OPH = ophthalmology, OCT = optical coherence tomography, echo = echocardiography

Source: PT-Table 14.3-1.2

Source: Special Safety Interim Report (**\\CDSESUB1\EVSPROD\NDA022527, SN 004)**

Table 4. Exposure in study 2309

Table 1-3 Duration of exposure to study drug (Safety population in study D2309)

	FTY720 1.25 mg N=370	FTY720 0.5 mg N=358	Placebo N=355	Total N=1083
Descriptive statistics (days)				
Mean (SD)	371.9 (242.54)	377.1 (245.10)	371.2 (237.23)	373.4 (241.46)
Median	356.0	344.0	335.0	343.0
Range	1 - 778	2 - 776	3 - 772	1 - 778
Duration of exposure in days - n (%)				
≥1	370 (100.0)	358 (100.0)	355 (100.0)	1083 (100.0)
≥7	363 (98.1)	357 (99.7)	354 (99.7)	1074 (99.2)
≥14	361 (97.6)	353 (98.6)	351 (98.9)	1065 (98.3)
≥30	358 (96.8)	345 (96.4)	349 (98.3)	1052 (97.1)
≥60	339 (91.6)	332 (92.7)	344 (96.9)	1015 (93.7)
≥90	309 (83.5)	300 (83.8)	309 (87.0)	918 (84.8)
≥180	261 (70.5)	248 (69.3)	252 (71.0)	761 (70.3)
≥270	218 (58.9)	211 (58.9)	204 (57.5)	633 (58.4)
≥360	183 (49.5)	173 (48.3)	165 (46.5)	521 (48.1)
≥450	146 (39.5)	149 (41.6)	137 (38.6)	432 (39.9)
≥540	119 (32.2)	120 (33.5)	111 (31.3)	350 (32.3)
≥630	80 (21.6)	91 (25.4)	81 (22.8)	252 (23.3)
≥720	39 (10.5)	34 (9.5)	33 (9.3)	106 (9.8)
Patient-years	377	370	362	1108

Source: Special Safety Interim Report (**\\CDSESUB1\EVSPROD\NDA022527, SN 004)**

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/

HAMET M TOURE
01/28/2010
Requested by Drs. Villalba and Bastings

ERIC P BASTINGS
02/01/2010

From: Ware, Jacqueline H
To: "mara.stiles@novartis.com"; Toure, Hamet;
cc: Ware, Jacqueline H;
Subject: RE: pop PK tables NDA 22-527
Date: Wednesday, January 27, 2010 4:13:53 PM

Dear Mara,

DNP has received the following request from the Clinical Pharmacology review team regarding the population PK data sets. It seems that I misunderstood the issue; OCP has clarified and the issue is related to locating the population PK datasets in the application, and is not an issue with opening files as I had originally stated during our conversation last week.

"Please provide all datasets and programs with outputs for population PK and exposure response analyses as described below:

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

If all datasets/programs already have been submitted with valid format, please provide an exact location."

Would you please ask your team to investigate and respond? If new datasets need to submitted, please submit them officially to the NDA.

Many thanks,
Jackie Ware

****
Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Supervisory Regulatory Project Manager

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
Silver Spring, MD 20993-0002

phone: 301-796-1160
fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

From: mara.stiles@novartis.com [mailto:mara.stiles@novartis.com]
Sent: Wednesday, January 27, 2010 1:31 PM
To: Ware, Jacqueline H; Toure, Hamet
Subject: pop PK tables NDA 22-527

Hi Jackie,
When we spoke on January 21 about the results of the filing meeting , you mentioned there were some population pk datasets that would not open and that subsequently we would hear which ones they were that gave that problem.

I just wanted to followup to see if the table numbers have been identified by the Clinical Pharmacology reviewer.

thank you

Mara Stiles

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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/

JACQUELINE H H WARE
01/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Cardio-Renal Division			FROM (*Name, Office/Division, and Phone Number of Requestor)*: Dr. Eric Bastings, Deputy Director, Division of Neurology. Ext. 6-1039.	
DATE 1-27-2010	IND NO.	NDA NO. 022527	TYPE OF DOCUMENT	DATE OF DOCUMENT
NAME OF DRUG Gilenia (fingolimod)	PRIORITY CONSIDERATION 6-month review		CLASSIFICATION OF DRUG Multiple sclerosis drug	DESIRED COMPLETION DATE March 12, 2010

NAME OF FIRM: Novartis Pharmaceutical Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☒ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

We request evaluation of the cardiovascular safety of fingolimod, an oral agent for the treatment of multiple sclerosis (MS) (NDA 22-527). Please see specific question below and refer to attachment 1 (tables) below.

Fingolimod is a sphingosine- 1- phosphate (S1P) modulator that induces immunosuppression by reduction of circulating lymphocytes. The drug was initially developed in the renal transplant population at doses up to 5 mg/day but that indication is no longer pursued. The dose proposed for approval in MS is 0.5 mg/day.

This is a rolling NDA (\\CDSESUB1\EVSPROD\NDA022527). The clinical data in the MS population was submitted on December 18, 2009 (SN 003 and 004). Clinical data in the transplant population was submitted on October 5, 2009 (SN 002). This application has a priority review (PDUFA goal date June 21, 2010) and will go to an advisory committee (AC) meeting on June 10, 2010.

In non-clinical oral toxicity studies in the dog, microscopic examination showed vascular wall thickening and perivascular and focal perimysial fibrosis of the left ventricular papilla in the heart. Additionally, several cases of

heart failure, pulmonary edema, pulmonary congestion and fluid overload were observed in the transplant trials, at doses above the dose currently recommended for approval. Subsequently, the DNP requested HRCT and echocardiographic monitoring in phase 3 studies in MS (Hold letter # 3, dated 3/19/06). The Clinical hold was lifted on 5/19/06.

The applicant has submitted echocardiogram information from a total of 183 subjects with MS involved in studies 2302 and 2309, receiving fingolimond 1.25 mg/day, 0.5 mg/day, placebo and interferon. Study 2302 is a 1300-patient one-year study for which full safety information is available. Study 2309 is an ongoing, 2-year study of approximately 1000 patients, for which special safety data (such as echocardiogram) has been unblinded but the remaining of clinical safety information is still blinded.
Attachment 1 provides some additional relevant background information.

Additionally, among other effects, fingolimod is associated with a transient reduction in heart rate and atrio-ventricular conduction on treatment initiation and a mild increase in blood pressure. The DNP has obtained input from the Division of Cardiorenal Products and the QT-IRT team, regarding Holter and ECG monitoring at the IND stage (Dr. Mehul Desai, December 9, 2005; IRT-QT team, 9/20/06, 10/20/08 and 11/7/08).

DNP is requesting evaluation of echocardiography data submitted in this application. We may have additional questions regarding heart conduction problems upon review of the current submission.

It is anticipated that cardiovascular issues will be discussed at the AC meeting. Please assign a reviewer to represent your division at the AC. We also request that you suggest three outside experts to participate in the AC panel.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Electronic	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Attachment 1

Table 1. Duration of exposure to study drug after randomization (Safety population, all double blind controlled studies – Group D)

	FTY720 5 mg N=94	FTY720 1.25 mg N=943	FTY720 0.5 mg N=854	Placebo N=511	IFN β-1a i.m. N=431
Exposure (days)	n (%)	n (%)	n (%)	n (%)	n (%)
≥ 1 day	94 (100)	943 (100)	854 (100)	511 (100)	431 (100)
≥ 90 days	86 (91.5)	874 (92.7)	827 (96.8)	487 (95.3)	413 (95.8)
≥ 180 days	52 (55.3)	800 (84.8)	803 (94.0)	433 (84.7)	399 (92.6)
≥ 270 days	0	726 (77.0)	784 (91.8)	372 (72.8)	386 (89.6)
≥ 360 days	0	623 (66.1)	671 (78.6)	356 (69.7)	300 (69.6)
≥ 540 days	0	316 (33.5)	363 (42.5)	324 (63.4)	0
≥ 720 days	0	183 (19.4)	196 (23.0)	199 (38.9)	0
Mean duration	167.7	430.4	493.2	533.9	340.6
Patient-years total	43.2	1111.2	1153.2	746.9	401.9

The duration of exposure is the total number of actual days patients took the study medication.
Patients are cumulatively counted by each level of the duration of exposure intervals. Includes studies 2301, 2302 and 2201.

Table 2. Exposure in study 2309

Table 1-3 Duration of exposure to study drug (Safety population in study D2309)

	FTY720 1.25 mg N=370	FTY720 0.5 mg N=358	Placebo N=355	Total N=1083
Descriptive statistics (days)				
Mean (SD)	371.9 (242.54)	377.1 (245.10)	371.2 (237.23)	373.4 (241.46)
Median	356.0	344.0	335.0	343.0
Range	1 - 778	2 - 776	3 - 772	1 - 778
Duration of exposure in days - n (%)				
≥1	370 (100.0)	358 (100.0)	355 (100.0)	1083 (100.0)
≥7	363 (98.1)	357 (99.7)	354 (99.7)	1074 (99.2)
≥14	361 (97.6)	353 (98.6)	351 (98.9)	1065 (98.3)
≥30	358 (96.8)	345 (96.4)	349 (98.3)	1052 (97.1)
≥60	339 (91.6)	332 (92.7)	344 (96.9)	1015 (93.7)
≥90	309 (83.5)	300 (83.8)	309 (87.0)	918 (84.8)
≥180	261 (70.5)	248 (69.3)	252 (71.0)	761 (70.3)
≥270	218 (58.9)	211 (58.9)	204 (57.5)	633 (58.4)
≥360	183 (49.5)	173 (48.3)	165 (46.5)	521 (48.1)
≥450	146 (39.5)	149 (41.6)	137 (38.6)	432 (39.9)
≥540	119 (32.2)	120 (33.5)	111 (31.3)	350 (32.3)
≥630	80 (21.6)	91 (25.4)	81 (22.8)	252 (23.3)
≥720	39 (10.5)	34 (9.5)	33 (9.3)	106 (9.8)
Patient-years	377	370	362	1108

Source: Special Safety Interim Report (**\\CDSESUB1\EVSPROD\NDA022527, SN 004)**

Table 3. Duration of exposure to study drug in pooled echo analysis set

Table 1-4 Duration of exposure to study drug (Pooled echo analysis set)

	FTY720 1.25 mg N=64	FTY720 0.5 mg N=60	Placebo N=48	Interferon beta-1a i.m. N=11	Total N=183
Descriptive statistics (days)					
Mean (SD)	385.6 (216.11)	391.2 (215.18)	408.3 (227.47)	364.3 (16.16)	392.1 (211.38)
Median	361.5	361.5	356.0	364.0	360.0
Range	10 - 733	15 - 753	66 - 751	346 - 392	10 - 753
Duration of exposure in days - n (%)					
≥1	64 (100.0)	60 (100.0)	48 (100.0)	11 (100.0)	183 (100.0)
≥7	64 (100.0)	60 (100.0)	48 (100.0)	11 (100.0)	183 (100.0)
≥14	62 (96.9)	60 (100.0)	48 (100.0)	11 (100.0)	181 (98.9)
≥30	62 (96.9)	59 (98.3)	48 (100.0)	11 (100.0)	180 (98.4)
≥60	59 (92.2)	58 (96.7)	48 (100.0)	11 (100.0)	176 (96.2)
≥90	58 (90.6)	58 (96.7)	47 (97.9)	11 (100.0)	174 (95.1)
≥180	54 (84.4)	48 (80.0)	39 (81.3)	11 (100.0)	152 (83.1)
≥270	43 (67.2)	42 (70.0)	29 (60.4)	11 (100.0)	125 (68.3)
≥360	32 (50.0)	31 (51.7)	24 (50.0)	6 (54.5)	93 (50.8)
≥450	21 (32.8)	21 (35.0)	19 (39.6)	0	61 (33.3)
≥540	18 (28.1)	18 (30.0)	17 (35.4)	0	53 (29.0)
≥630	13 (20.3)	15 (25.0)	13 (27.1)	0	41 (22.4)
≥720	6 (9.4)	6 (10.0)	7 (14.6)	0	19 (10.4)

Source: Special Safety Interim Report.
Please note that only 19 patients had echo available at 2 years.

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/

HAMET M TOURE
01/27/2010
At the request of Dr. Eric Bastings

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: HFD-710 Division of Biometrics Attn: Kun Jin, PhD			FROM (*Name, Office/Division, and Phone Number of Requestor)*: Russell Katz, MD, Division of Neurology Products	
DATE January 12, 2010	IND NO.	NDA NO. 22-527	TYPE OF DOCUMENT New original NME NDAs	DATE OF DOCUMENT December 18, 2009 (Note: this is a rolling NDA with earlier submissions)
NAME OF DRUG Gilenia (fingolimod) Capsules	PRIORITY CONSIDERATION Priority		CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE May 24, 2010; PDUFA goal date: June 21, 2010

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☒ OTHER (SPECIFY BELOW): New NDA

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The final part of NDA 22-527/Gilenia (fingolimod HCl) Capsules was received on December 21, 2009 and provides the results of the extensive development program supporting the registration of Gilenia (fingolimod HCl) capsules 0.5 mg for oral administration for an indication as 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. This product is a NME. The application has a PDUFA goal date of 6/21/10. The entire application may be accessed at : \\CDSESUB1\EVSPROD\NDA022527\022527.ENX Please review and comment on the acceptability of the efficacy data. The filing meeting for NDA 22-527 is scheduled for 1/20 at 4p (WO 22 Rm. 4270).

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)
☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/

JACQUELINE H H WARE
01/13/2010
Sent at request of Dr. Katz

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
HFD-009/Controlled Substances Staff
Attention: Corinne Moody/ Michael Klein

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Russell Katz, MD, Division of Neurology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 7, 2010		22-527	New original NME NDAs	December 18, 2009 (Note: this is a rolling NDA with earlier submissions)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gilenia (fingolimod) Capsules	Priority	1	May 24, 2010; PDUFA goal date: June 21, 2010

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Abuse Liability

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: NDA 22-527 was received on December 21, 2009 and provides for adjunctive therapy in refractory epilepsy patients with partial-onset seizures.This is a NME. The application has a PDUFA goal date of 6/12/10. The entire submission may be accessed at : \\CDSESUB1\EVSPROD\NDA022527\022527.ENX. Please review and comment on the abuse potential for this product, although the firm has not submitted any formal abuse liability information. The filing meeting for NDA 22-527 is scheduled for 1/20 at 4p (WO 22 Rm. 4270) if you or someone from your group would like to attend.

SIGNATURE OF REQUESTOR
Hamet Toure, Regulatory Project Manager, DNP
Food and Drug Administration

METHOD OF DELIVERY (Check one)
☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND

Phone: 301-796-7534 Email: hamet.toure@fda.hhs.gov	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/

JACQUELINE H H WARE
01/07/2010
Sent at request of Dr. Katz