CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-527

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 22-527, Gilenya (fingolimod) Capsules, 0.5 mg
Date: September 17, 2010

Introduction

Gilenya (fingolimod) Capsules, 0.5 mg are indicated as a disease modifying treatment for relapsing multiple sclerosis. Gilenya (fingolimod) Capsules, 0.5 mg are given once daily, with or without food.

Adminstrative

This was a rolling NDA submission submitted by Novartis Pharmaceutical Corp. The submission was complete on 21-DEC-2009 (original date of submission of record) and was accepted as a 505(b)(1) priority NDA application. An overall acceptable recommendation was received from The Office of Compliance on 03-FEB-2010. This NDA is supported by IND 70,139.
ONDQA recommends approval from the CMC perspective.

Drug Substance: Fingolimod hydrochloride

The drug substance is a white to practically white powder. Of the salts studied, the hydrochloride salt exhibited the best solubility characteristics in both water and 0.1 N HCl and the best stability characteristics.

Fingolimod hydrochloride has (b) (4) used throughout the toxicity and clinical program. (b) (4)

The sponsor manufactures fingolimod hydrochloride in an (b) (4) The structural elucidation data support the proposed structure of fingolimod hydrochloride.

The purity and quality of the drug substance are maintained through appropriate in-process controls and adequate final drug substance specification. The drug substance specification includes tests and acceptance criteria for description, particle size distribution, color and clarity of solution, identity (IR and XRPD), chromatographic purity (HPLC), residual solvents, heavy metals, (b) (4) assay (HPLC), chloride assay, and microbiological purity. All analytical methods are validated for their intended use. Novartis proposes a (b) (4) retest period for the drug substance.

Drug Product: Fingolimod Capsules 0.5 mg

Fingolimod 0.5 mg hard gelatin capsules are an immediate release dosage form for oral administration. The drug product manufacturing process is straightforward and consists of (b) (4) encapsulation (size 3, hard gelatin capsule), and packaging.

The capsule has a white, opaque body and a bright yellow, opaque cap that contains white to practically white powder. The capsule has a "FTY 0.5 mg" radial imprint with (b) (4) on the cap and two radial bands imprinted on the body with yellow ink. All of the formulation excipients as well as the capsule and ink components comply with compendial or regulatory standards. The drug product does not contain any novel excipients.

Drug product quality is controlled through appropriate in-process controls and final product specifications. These include tests and acceptance criteria for appearance, (b) (4), identification (TLC, HPLC), single-point dissolution, degradation products (HPLC), assay (HPLC), uniformity of dosage forms by content uniformity, and microbial purity. All analytical procedures are appropriately validated for their intended use.

The commercial packaging is blister packs. Novartis proposes a 24 month expiry for the drug product when stored in the commercial packaging at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF), protected from moisture.

Rik Lostritto, Ph.D., Director, ONDQA Division I.

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/s/

RICHARD T LOSTRITTO
09/17/2010

NDA 22-527
Quality Review #1
Addendum #2

GILENYA™ (fingolimod) Capsules
0.5 mg

Novartis Pharmaceuticals Corporation

Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Quality Assessment
For
Division of Neurology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22-257

2. REVIEW: 01 Addendum 02

3. REVIEW DATE: 26-AUG-2010

4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Addendum	30-JUN-2010
Review	30-APR-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	25-AUG-2010
Amendment	12-AUG-2010
Amendment	30-JUL-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, NJ 07936-1080
Representative:	Mara Stiles, RBRM, Drug Regulatory Affairs
Telephone:	862-778-3771

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: GILENYA™
b) Non-Proprietary Name (USAN): Fingolimod Hydrochloride
c) Code Name/# (ONDQA only): FTY720
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Treatment of Relapsing-Remitting Multiple Sclerosis

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 0.5 mg

13. ROUTE OF ADMINISTRATION: Oral

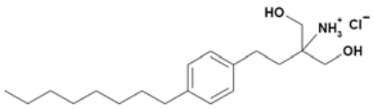
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2-amino-2-[2-(4-octylphenyl)ethyl]propan-1,3-diol hydrochloride
Mol. Formula: $C_{19}H_{33}NO_2 \bullet HCl$
Mol. Weight: 343.93 (HCl salt); 307.48 (free base)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		7	N/A	-	Bottle packaging dropped by sponsor
	III	(b) (4)		7	N/A	-	Bottle packaging dropped by sponsor
	III	(b) (4)		7	N/A	-	Bottle packaging dropped by sponsor
	III	(b) (4)		7	N/A	-	Bottle packaging dropped by sponsor
	III	(b) (4)		4	N/A	-	-
	III	(b) (4)		1	Adequate	23-FEB-2010	-
	III	(b) (4)		4	N/A	-	-
	III	(b) (4)		1	Adequate	19-FEB-2010	-
	III		(b) (4)	7	N/A	-	Bottle packaging dropped by sponsor

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,139	FTY720D Capsules for the Treatment of Multiple Sclerosis
IND	57,293	FTY720A for the Treatment of Prophylaxis of Organ Rejection
IND	70,407	FTY720 for the Treatment of Hepatitis C

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable	01-JUL-2010	X. Yan
EES	Acceptable.	03-FEB-2010	M. Stock
Pharm/Tox	Pending.	-	R. Siarey
Biopharm	Acceptable.	04-AUG-2010	J. Lai
LNC	N/A	-	-
Methods Validation	Method validation by FDA laboratory not needed.	20-JAN-2010	W. Wilson-Lee
DMEPA	GILENYA™ tradename granted. Labeling acceptable, with edits.	23-AUG-2010 25-MAY-2010	D. Baugh F. Duffy
EA	Categorical exclusion granted.	31-AUG-2009	W. Wilson-Lee
Microbiology	N/A	N/A	N/A

List of Tables

List of Figures

Chemistry Review for NDA 22-527

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, we recommend approval of 0.5 mg GILENYA™ (fingolimod) Capsules, pending labeling.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

We have no CMC Phase 4 commitments at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Fingolimod hydrochloride, a novel synthetic sphingosine analogue, is an S1P-receptor modulator that reversibly traps a proportion of lymphocytes in the lymph nodes, thereby reducing their recirculation in the bloodstream and the central nervous system. The drug substance is a white to practically white powder. During development of the drug substance, the base and (b) (4) salts of fingolimod were manufactured and tested for stability, solubility and polymorphic properties. Based on this testing, the hydrochloride salt was chosen for further development. It exhibited the best solubility characteristics in both water and 0.1 N HCl and the best stability characteristics with a standard excipient mixture.

Fingolimod hydrochloride has (b) (4) used throughout the toxicity and clinical program. (b) (4)

The sponsor manufactures fingolimod in (b) (4) .

The structural elucidation data support the proposed structure of fingolimod hydrochloride. The identity and quality of the drug substance is assured through appropriate in-process controls and adequate final drug substance specification. The drug substance specification includes tests and acceptance criteria for description, particle size distribution, color and clarity of solution, identity (IR and XRPD), chromatographic purity (HPLC), residual solvents, heavy metals, (b) (4) assay (HPLC), chloride assay, and microbiological purity. All analytical methods are validated for their intended use. Novartis proposes a (b) (4) (b) (4) retest period for the drug substance.

Fingolimod 0.5 mg hard gelatin capsules are an immediate release dosage form for oral administration. The 0.5 mg strength drug product is a size 3 capsule with a white, opaque body and a bright yellow, opaque cap that contains white to practically white powder. The capsule has a "FTY 0.5 mg" radial imprint (b) (4) on the cap and two radial bands imprinted on the body with yellow ink. All of the formulation excipients as well as the capsule and ink components comply with compendial or regulatory standards. The drug product does not contain any novel excipients.

The manufacturing process is straightforward and consists of (b) (4) encapsulation, and packaging. The drug product quality is controlled through appropriate in-process controls and final product specification. The drug product specification includes tests and acceptance criteria for appearance, (b) (4) identification (TLC, HPLC), single-point dissolution, degradation products (HPLC), assay (HPLC), uniformity of dosage forms by content uniformity, and microbial purity. All analytical procedures are appropriately validated for their intended use. The commercial packaging is blister packs. Novartis proposes a 24 month expiry for this product when stored in the commercial packaging at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF), protected from moisture.

B. Description of How the Drug Product is Intended to be Used

Fingolimod capsules are indicated 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 physical disability. The recommended daily dose 0.5 mg fingolimod. Fingolimod 0.5 mg capsules are for oral administration once daily, with or without food. Fingolimod capsules are supplied in blister packs as a carton of 28 capsules (b) (4)) or as a physician sample (one blister strip of 7 capsules in a carton).

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, we recommend approval of 0.5 mg GILENYA™ (fingolimod) capsules, pending labeling. The sponsor adequately responded to our request to revise the drug product regulatory specification to limit the shelf-life limit of the (b) (4) to NMT (b) (4). The updated carton and container labels are adequate.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson-Lee

B. Endorsement Block

WWilson-Lee:	26-AUG-2010
MHeimann:	26-AUG-2010
RSood:	26-AUG-2010

C. CC Block

TBouie
DHenry
HToumet

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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/

WENDY I WILSON
09/01/2010

RAMESH K SOOD
09/01/2010

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division:	Division of Neurology Products
NDA:	22-527
Applicant:	Novartis Pharmaceuticals Corporation
Stamp Date:	16-Jun-2009
PDUFA Date:	N/A (rolling NDA submission)
Trademark:	TBD
Established Name:	fingolimod hydrochloride
Dosage Form:	Capsules
Route of Administration:	Oral
Indication:	Relapsing-remitting multiple sclerosis
PAL:	Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

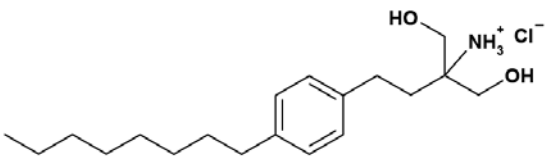
Summary and Critical Issues:

Summary

Fingolimod hydrochloride (FTY720) is a new molecular entity developed by Novartis. It is a novel sphingosine analogue that acts as a sphingosine 1-phosphate (S1P)-receptor modulator that reversibly traps a proportion of lymphocytes in the lymph nodes, thereby reducing their recirculation in the bloodstream and the central nervous system. FTY720 was initially studied (in combination with cyclosporine) as prophylaxis for organ rejection in renal transplantation but failed to show any benefit in Phase 3 trials. Novartis subsequently developed FTY720 for treatment of relapsing-remitting multiple sclerosis (RRMS). The firm was granted fast-track status for the RRMS indication and seeks to market FTY720 (b) (4) The initial submission to the rolling NDA consists of the CMC and nonclinical sections of the application.

Drug Substance

The active ingredient, fingolimod hydrochloride, is a small molecule with molecular formula $C_{19}H_{33}NO_2$•HCl. The molecular weight of the salt form and free base are 343.93 and 307.48, respectively. The chemical name is 2-amino-2-[2-(4-octylphenyl)ethyl]-1,3-propandiol, hydrochloride. There are no chiral centers. The structural formula of fingolimod hydrochloride is:



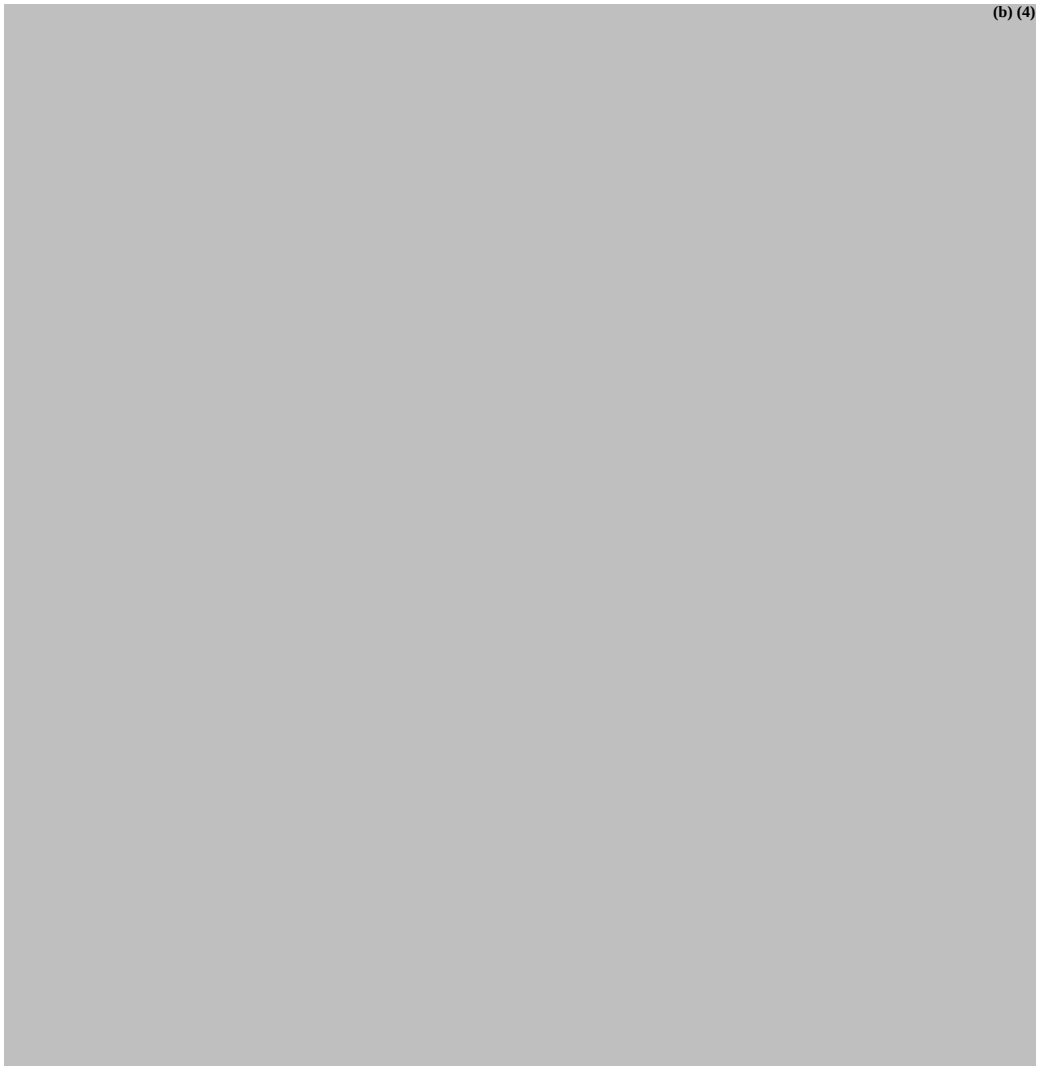
The drug substance is a white to practically white powder. It is soluble (>10%) in water, 0.9% saline and aqueous buffers at or below pH 2.0. It is very slightly soluble or practically insoluble in aqueous buffers at or above pH 3.0. The applicant states that fingolimod hydrochloride shows at (b) (4)

Fingolimod hydrochloride is manufactured by Novartis at the firm's facilities in Switzerland. The manufacturing process (b) (4) is outlined in Figures 2-1 and 2-2. The bulk drug substance is manufactured in (b) (4)

Figure 2-1 Synthesis scheme Fingolimod Hydrochloride (FTY720)

(b) (4)

Figure 2-2 Synthesis scheme Fingolimod Hydrochloride (FTY720, continued)



The proposed drug substance specification is reproduced below (Table 4-1). The proposed analytical procedures for fingolimod hydrochloride are straight-forward. Assay and related substances are determined using a (b) (4) HPLC method (b) (4) Analytical procedures and method validation data are included in the NDA.

Table 4-1 Fingolimod HCl specifications

	Test	Requirement
Description	Appearance (visual examination)	White to practically white powder
Physico-chemical properties	Particle size (b) (4)	
	(b) (4)	(b) (4)

	Test	Requirement
	Clarity of the solution	(b) (4)
	Colour of the solution	
Identity	Identity (IR)	
	Identity (X-ray diffraction pattern)	
Impurities	Impurities (HPLC)	
	(b) (4)	
Assay	Assay (HPLC)	
	(b) (4)	

The applicant has submitted long-term stability data through 60 months, plus 12 months intermediate stability data and 6 months accelerated data on three pilot scale drug substance batches. A retest date of (b) (4) is proposed. A standard stability commitment for full-scale post approval batches is provided.

Drug Product

The proposed dosage form is an immediate release capsule containing 0.5 mg (b) (4) fingolimod as the hydrochloride salt. The 0.5 mg presentation is a size 3 capsule with white opaque body and bright yellow opaque cap, radial imprint with (b) (4), "FTY 0.5 mg" on cap and two radial bands imprinted on the body with yellow ink. (b) (4) The capsule fill formulation is the same as that used in

clinical studies under the RRMS IND. The only differences between the clinical and commercial images are capsule shell color and imprinting.

Table 1-1 Composition of FTY720 hard capsules

Ingredient	Amount per 0.5 mg capsule (mg)	(b) (4)	Reference to standards	Function
FTY720 HCl [1]	0.56		Novartis monograph	Drug substance
Mannitol	(b) (4)		USP, Ph. Eur.	(b) (4)
Magnesium stearate [2]			NF, Ph. Eur.	
Capsule fill weight				
Empty capsule shell, pre-printed				
Capsule shell (theoretical weight)[3]			Novartis monograph	
(b) (4)				
Printing ink, yellow [4]				
(b) (4)				
Total capsule weight				

[1] 2-Amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride. The molecular weight ratio of FTY720 HCl to FTY720 base is approximately 1.12 to 1.0

[2] (b) (4)

[3] The composition of the capsule shells are provided in Table 1-2 and Table 1-3

[4] The qualitative composition of the inks is provided in Table 1-4.

The inactive ingredients, mannitol and magnesium stearate, comply with compendial requirements. The choice of capsule presentation and excipients is based on the functionality of the active ingredient, which is incompatible with most common diluents other than mannitol. Formulations containing mannitol exhibited (b) (4)

The commercial product will be manufactured by Novartis at the firm's Stein, Switzerland facility. The manufacturing process involves (b) (4) and encapsulation processes. Limited information regarding process development is provided in the Pharmaceutical Development section.

(b) (4) Acceptance criteria for the 0.5 mg strength are the same.

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Assay and related substances are determined using [redacted] HPLC method [redacted] A similar [redacted] method is used for determination of content uniformity. Dissolution results are quantitated using a separate [redacted] method [redacted]

The applicant proposes marketing of Fingolimod Capsules in [redacted] blister packs. The [redacted] blister packs use [redacted] film backed with [redacted] aluminum foil.

The NDA stability package includes long-term stability data through 18 months, intermediate data through 12 months, and accelerated data through 6 months for three production-scale batches per strength. All batches were manufactured at the Stein Switzerland facility and packaged in the proposed commercial packaging presentations. It is noted that some batches failed assay/related substances testing at the accelerated stability condition but all batches remained within specification through 12 months at the intermediate storage condition. A 24-month shelf life is proposed based on statistical analysis of the long-term assay results.

Critical issues for review

Drug Substance

The drug substance is manufactured in [redacted] using well precedented synthetic methodology. No critical issues related to manufacture and control of the drug substance were identified during the initial assessment.

Drug Product

The drug product is an immediate release capsule manufactured using [redacted] and encapsulation processes. Two critical issues were identified during the initial assessment. The first is blend uniformity/content uniformity [redacted] within the capsules. The second issue is the reactivity of the active ingredient. The applicant has tried to minimize degradation through [redacted] however, some degradation is still observed under long-term storage conditions. The reviewer should consult with the pharmacology review team to verify that all degradation products have been adequately qualified in nonclinical toxicology studies.

Additional issues

Administrative: A claim for categorical exclusion is included in Module 1 of the application.

Establishment Evaluation: PENDING

Labeling/Established Name: The USAN name for the drug substance is fingolimod hydrochloride. The potency claim, however, is based on content of the free base. Labeling is

not provided in the current submission. When labeling is submitted, the reviewer should verify that the correct established name, i.e., "fingolimod capsules" is used in product labeling.

Comments for 74-Day Letter

There are no comments for the 74 day letter

Review, Comments and Recommendation:

The CMC portion of the NDA is complete and reviewable. A recommendation regarding fileability is deferred pending submission of the complete application. The drug substance is a new molecular entity. The dosage form, however, is a very simple formulation containing only two excipients, mannitol and magnesium stearate and there are no QbD aspects to the application. Assignment of the NDA to a single reviewer is recommended.

Martha R. Heimann, Ph.D.

Pharmaceutical Assessment Lead, DPA 1, ONDQA Date

Ramesh Sood, Ph.D.

Branch Chief, DPA 1, ONDQA Date

CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA/BLA

NDA Numbers: 22-527 **Applicant: Novartis** **Stamp Date: 16-Jun-2009**

Drug Name: Fingolimod Capsules **NDA Type: Priority**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		A claim for categorical exclusion was submitted.
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	NA		
8	Have draft container labels and package insert been provided?		X	Labeling is not part of the CMC reviewable unit.
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	NA		

IS THE CMC SECTION OF THE APPLICATION FILEABLE? _____

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Martha R. Heimann, Ph.D.
Pharmaceutical Assessment Lead, DPA 1, ONDQA Date

Ramesh Sood, Ph.D.
Branch Chief, DPA 1, ONDQA Date

Manufacturing Facilities for Fingolimod Capsules

Drug Substance

Establishment	Contact Information	Establishment Registration #	Responsibility
Novartis Pharma AG Lichtstrasse 35 CH-4056 Basel Switzerland	Michael Bruckheimer Director Global Compliance and Auditing Tel.: (862) 778-7913 michael.bruckheimer@novartis.com	9611204	Manufacture of intermediate [redacted (b) (4)] quality control
Novartis Pharma Schweizerhalle AG Rothausweg CH-4133 Pratteln Switzerland	Michael Bruckheimer Director Global Compliance and Auditing Tel.: (862) 778-7913 michael.bruckheimer@novartis.com	9692042	Manufacture of [redacted (b) (4)] Fingolimod Hydrochloride [redacted (b) (4)] quality control
Novartis Pharma Stein AG Schaffhauserstrasse CH-4332 Stein Switzerland	Michael Bruckheimer Director Global Compliance and Auditing Tel.: (862) 778-7913 michael.bruckheimer@novartis.com	9692043	[redacted (b) (4)]
Novartis International Pharmaceutical Ltd. Branch Ireland Ringaskiddy Co. Cork Ireland	Michael Bruckheimer Director Global Compliance and Auditing Tel.: (862) 778-7913 michael.bruckheimer@novartis.com	9612715	Quality control, stability testing
[redacted (b) (4)]			Quality control

Drug Product

Establishment	Contact Information	Establishment Registration No.	Responsibility
Novartis Pharma Stein AG Schaffhauserstrasse CH-4332 Stein Switzerland	Michael Bruckheimer Director Global Compliance and Auditing Tel.: (862) 778-7913 michael.bruckheimer@novartis.com	9692043	Manufacture, quality control, packaging
Novartis Pharmaceuticals Corporation (Suffern) 25 Old Mill Road Suffern, New York 10901 USA	Ernesto Alfonso Executive Director, QA Tel.: (862) 368-6462 Ernestor.alfonso@novartis.com	2416082	Quality control, stability testing, packaging

Manufacturing Facilities for Fingolimod Capsules

Drug Product

Establishment	Contact Information	Establishment Registration No.	Responsibility
Novartis Pharmanalytica S.A. Via Serafino Balestra 31 CH-6601 Locarno Switzerland	Michael Bruckheimer Director Global Compliance and Auditing Tel.: (862) 778-7913 michael.bruckheimber@novartis.com	9614433	Stability testing
(b) (4)			

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/s/

Martha Heimann
6/29/2009 02:44:00 PM
CHEMIST

Ramesh Sood
6/29/2009 03:48:39 PM
CHEMIST

NDA 22-527
Quality Review #1
Addendum #1

Fingolimod Capsules
0.5 mg

Novartis Pharmaceuticals Corporation

Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Quality Assessment
For
Division of Neurology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22-257

2. REVIEW: 01 Addendum 01

3. REVIEW DATE: 22-JUN-2010

4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Review	30-APR-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	16-JUN-2010
Amendment	24-MAY-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, NJ 07936-1080
Representative:	Mara Stiles, RBRM, Drug Regulatory Affairs
Telephone:	862-778-3771

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Gilenya™ (proposed)
[alternate – Gylenia™]

b) Non-Proprietary Name (USAN): Fingolimod Hydrochloride

c) Code Name/# (ONDQA only): FTY720

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Treatment of Relapsing-Remitting Multiple Sclerosis

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 0.5 mg

13. ROUTE OF ADMINISTRATION: Oral

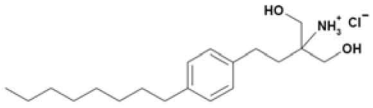
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed
X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2-amino-2-[2-(4-octylphenyl)ethyl]propan-1,3-diol hydrochloride
Mol. Formula: $C_{19}H_{33}NO_2 \bullet HCl$
Mol. Weight: 343.93 (HCl salt); 307.48 (free base)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		7	N/A	-	Bottle packaging dropped by sponsor
	III	(b) (4)		7	N/A	-	Bottle packaging dropped by sponsor
	III	(b) (4)		7	N/A	-	Bottle packaging dropped by sponsor
	III	(b) (4)		7	N/A	-	Bottle packaging dropped by sponsor
	III	(b) (4)		4	N/A	-	-
	III	(b) (4)		1	Adequate	23-FEB-2010	-
	III	(b) (4)		4	N/A	-	-
	III	(b) (4)		1	Adequate	19-FEB-2010	-
	III		(b) (4)	7	N/A	-	Bottle packaging dropped by sponsor

[1] Action codes for DMF Table:
1 – DMF Reviewed.
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2 –Type 1 DMF
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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,139	FTY720D Capsules for the Treatment of Multiple Sclerosis
IND	57,293	FTY720A for the Treatment of Prophylaxis of Organ Rejection
IND	70,407	FTY720 for the Treatment of Hepatitis C

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending.	-	X. Yan
EES	Acceptable.	03-FEB-2010	M. Stock
Pharm/Tox	Pending.	-	R. Siarey
Biopharm	Pending.	-	J. Lai
LNC	N/A	-	-
Methods Validation	Method validation by FDA laboratory not needed.	20-JAN-2010	W. Wilson-Lee
DMEPA	Objection to proposed tradename, Gilenia®.	05-MAY-2010	F. Duffy
EA	Categorical exclusion granted.	31-AUG-2009	W. Wilson-Lee
Microbiology	N/A	N/A	N/A

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Chemistry Review for NDA 22-527

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, we cannot recommend approval for fingolimod capsules 0.5 mg. During the review cycle, we identified the proposed shelf-life limit (NMT (b) (4)) for the drug product degradant (b) (4) as exceeding the ICH qualification threshold (NMT 1.0%). We informed the pharm/tox review of this issue and asked for a final recommendation as to whether or not the (b) (4) is qualified at (b) (4) based on nonclinical studies. To date, the pharm/tox review team has not provided a final recommendation concerning this issue and therefore, CMC cannot offer a final recommendation concerning approval of this NDA. If the pharm/tox review team recommends approval of the proposed (b) (4) shelf-life limit, no further action from CMC will be needed. However, if the pharm/tox review team does not consider the (b) (4) qualified at the proposed (b) (4) limit, the sponsor will need to revise the drug product regulatory specification and submit the revised specification for review prior to our final CMC recommendation.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

We have no CMC Phase 4 commitments at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Fingolimod hydrochloride, a novel synthetic sphingosine analogue, is an S1P-receptor modulator that reversibly traps a proportion of lymphocytes in the lymph nodes, thereby reducing their recirculation in the bloodstream and the central nervous system. The drug substance is a white to practically white powder. During development of the drug substance, the base and (b) (4) salts of fingolimod were manufactured and tested for stability, solubility and polymorphic properties. Based on this testing, the hydrochloride salt was chosen for further development. It exhibited the best solubility characteristics in both water and 0.1 N HCl and the best stability characteristics with a standard excipient mixture.

Fingolimod hydrochloride (b) (4) is the desired form used throughout the toxicity and clinical program. (b) (4)

The sponsor manufactures fingolimod in (b) (4)

The structural elucidation data support the proposed structure of fingolimod hydrochloride. The identity and quality of the drug substance is assured through appropriate in-process controls and adequate final drug substance specification. The drug substance specification includes tests and acceptance criteria for description, particle size distribution, color and clarity of solution, identity (IR and XRPD), chromatographic purity (HPLC), residual solvents, heavy metals, (b) (4), assay (HPLC), chloride assay, and microbiological purity. All analytical methods are validated for their intended use. Novartis proposes a (b) (4) retest period for the drug substance.

Fingolimod 0.5 mg hard gelatin capsules are an immediate release dosage form for oral administration. The 0.5 mg strength drug product is a size 3 capsule with a white, opaque body and a bright yellow, opaque cap that contains white to practically white powder. The capsule has a "FTY 0.5 mg" radial imprint (b) (4) on the cap and two radial bands imprinted on the body with yellow ink. All of the formulation excipients as well as the capsule and ink components comply with compendial or regulatory standards. The drug product does not contain any novel excipients.

The manufacturing process is straightforward and consists of (b) (4), encapsulation, and packaging. The drug product quality is controlled through appropriate in-process controls and final product specification. The drug product specification includes tests and acceptance criteria for appearance, (b) (4) identification (TLC, HPLC), single-point dissolution, degradation products (HPLC), assay (HPLC), uniformity of dosage forms by content uniformity, and microbial purity. All analytical procedures are appropriately validated for their intended use. The commercial packaging is blister packs. Novartis proposes a 24 month expiry for this product when stored in the commercial packaging at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF), protected from moisture.

B. Description of How the Drug Product is Intended to be Used

Fingolimod capsules are indicated 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 physical disability. The recommended daily dose 0.5 mg fingolimod. Fingolimod 0.5 mg capsules are for oral administration once daily, with or without food. Fingolimod capsules are supplied in blister packs as a carton of 28 capsules (b) (4) or as a physician sample (one blister strip of 7 capsules in a carton).

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, we cannot recommend approval of fingolimod capsules 0.5 mg, pending a recommendation from pharm/tox regarding the proposed shelf-life limit for the drug product degradant (b) (4) The sponsor adequately responded to our requests and provided information demonstrating that the manufacturing processes consistently produce drug substance and drug product of adequate quality.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson-Lee

B. Endorsement Block

WWilson-Lee: 30-JUN-2010
MHeimann: 30-JUN-2010
RSood: 30-JUN-2010

10 page(s) have been Withheld in Full immediately following this page as B4 (CCI/TS)

C. CC Block

TBouie
HToumet

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/

WENDY I WILSON
06/30/2010

RAMESH K SOOD
06/30/2010

NDA 22-527
Quality Review #1

Fingolimod Capsules
0.5 mg

Novartis Pharmaceuticals Corporation

Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Quality Assessment
For
Division of Neurology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22-257

2. REVIEW: 01

3. REVIEW DATE: 30-APR-2010

4. REVIEWER: Wendy I. Wilson, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None.	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	16-MAR-2010
Amendment	11-MAR-2010
Amendment	21-DEC-2009
Amendment	24-JUL-2009
Original	16-JUN-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, NJ 07936-1080
Representative:	Mara Stiles, RBRM, Drug Regulatory Affairs
Telephone:	862-778-3771

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Gilenia® (proposed)
b) Non-Proprietary Name (USAN): Fingolimod Hydrochloride
c) Code Name/# (ONDQA only): FTY720
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Treatment of Relapsing-Remitting Multiple Sclerosis

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 0.5 mg

13. ROUTE OF ADMINISTRATION: Oral

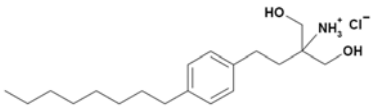
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2-amino-2-[2-(4-octylphenyl)ethyl]propan-1,3-diol hydrochloride
Mol. Formula: $C_{19}H_{33}NO_2 \bullet HCl$
Mol. Weight: 343.93 (HCl salt); 307.48 (free base)



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Chemistry Review for NDA 22-527

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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(HPLC), chloride assay, and microbiological purity. All analytical methods are validated for their intended use. Novartis proposes a (b) (4) rest period for the drug substance.

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C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, we recommend a complete response for fingolimod capsules 0.5 mg, pending response to our information request and labeling. We sent 10 additional comments to the sponsor on 07-MAY-2010 regarding recommended changes to the drug substance and drug product controls (see Section III of this review). The assessment of the qualification of one drug product degradant by the pharm/tox review team is also pending.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson-Lee

B. Endorsement Block

WWilson-Lee: 30-APR-2010
MHeimann: 07-MAY-2010
RSood: 11-MAY-2010

90 page(s) have been Withheld in Full immediately following this page as B4 (CCI/TS)

C. CC Block

DHenry
HToumet

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WENDY I WILSON
05/12/2010

RAMESH K SOOD
05/12/2010