CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-200

CHEMISTRY REVIEW(S)

NDA 21-200 (CMC Review #4)

Zelnorm® (Tegaserod Meleate)

Novartis Pharmaceuticals Corporation

Raymond P. Frankewich, Ph.D.
Division of GI and Coagulation Drug Products (HFD-180)

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

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

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative 9

A. Reviewer's Signature 9

B. Endorsement Block 9

C. CC Block 9

Chemistry Review Data Sheet

1. NDA 21-200

2. REVIEW #: 4

3. REVIEW DATE: June 27, 2002

4. REVIEWER: Raymond P. Frankewich, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	February 11, 2000
Amendment	May 5, 2000
Amendment	May 24, 2000
Amendment	August 1, 2000
Amendment	December 20, 2000
Amendment	March 15, 2001
Amendment	April 27, 2001
Telecon	May 24, 2001
Amendment	June 7, 2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	January 30, 2002
Amendment	February 28, 2002

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, NJ 07936-1080
Representative:	Donna M. Vivelo
Telephone:	973-781-3572

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zelnorm®
b) Non-Proprietary Name (USAN): Tegaserod Maleate
c) Code Name/# (ONDC only): HTF-919
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Partial agonist of type 4 (5-HT_4) receptors

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 2 mg, 6 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:

_____SPOTS product – Form Completed

__X__Not a SPOTS product

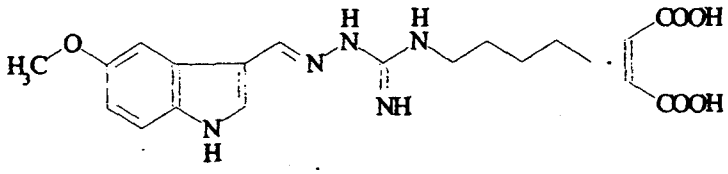
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-(5-Methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate

Molecular formula: $C_{16}H_{23}N_5O \cdot C_4H_4O_4 \equiv C_{20}H_{27}N_5O_5$

Relative molecular mass: 301.4 + 116.1 ≡ 417.5

Structural formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	3	[redacted]	[redacted]	1	Deficient	July 6, 2000	[redacted] withdrawn
[redacted]	3	[redacted]	[redacted]	1	Deficient	July 5, 2000	[redacted] withdrawn
[redacted]	3	[redacted]	[redacted]	1	Adequate	July 3, 2000	
[redacted]	3	[redacted]	[redacted]	1	Adequate	July 3, 2000	
[redacted]	2	[redacted]	[redacted]	1	Adequate	June 21, 2002	

[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: None

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	6/26/2000	-
Pharm/Tox	Acceptable	6/4/2001	Ke Zhang, Ph.D.
Biopharm	Acceptable	7/11/2000	Suresh Doddapaneni, Ph.D.
LNC	NA		
Methods Validation	Pending		
OPDRA	Acceptable	3/10/2001	Alina Mahmud, RPh.
EA	NA		
Microbiology	NA		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

Chemistry Review Data Sheet

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-200

The Executive Summary

I. Recommendations

A. **Recommendation and Conclusion on Approvability**: From a CMC perspective, the application may be approved.

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

II. Summary of Chemistry Assessments

A. **Description of the Drug Product(s) and Drug Substance(s)**: The drug substance is a maleate salt of tegaserod. USAN names exist for both the base and the salt. The drug product is a tablet which contains crospovidone [redacted] One of the drug substance [redacted] to describe their process for the manufacture of [redacted] Drug substance specifications include one related substance acceptance criterion (for compound [redacted] which is above that which is recommended in ICH Q3A [redacted] This acceptance criterion was evaluated by Ke Zhang, Ph.D., Pharmacologist, and was determined to be adequately justified in a memo to this NDA dated June 4, 2001.

B. **Description of How the Drug Product is Intended to be Used**: The drug is indicated for Irritable Bowel Syndrome. Both sizes of tablets are supplied in unit-dose packages (blister packs) which contain 60 tablets in one box (6 strips of 10 tablets). The recommended dosage is 6 mg b. i. d. Tablets should be taken before meals. Proposed expiration dating period of 36 months is determined to be justified (see Stability section of this review). Drug product is to be stored at controlled room temperature with excursions permitted to 15°C-30°C (59°F-86°F).

C. **Basis for Approvability or Not-Approval Recommendation:** In this review, a CMC resubmission dated January 30, 2002 and a labeling submission dated February 28, 2002 are evaluated. The general format for the review is: information from the applicant is reproduced in the appropriate part of the Chemistry Assessment section below, followed by an evaluation of that specific information.

Applicant has adequately addressed issues relating to one of the drug substance intermediates, drug substance specifications, the USAN status of the drug substance, drug products specifications, and stability of the drug product. Recommendations are provided in this review regarding the current labeling. These recommendations are summarized in the Labeling section, and they have been incorporated into the current proposed label and package insert.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

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/s/

Ray Frankewich
6/27/02 04:58:04 PM
CHEMIST

Liang Zhou
6/28/02 02:11:00 PM
CHEMIST

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-200 **CHEM REVIEW #:** 3 **REVIEW DATE:** June 8, 2001

SUBMISSION TYPE	DATES					
	DOCUMENT	CDER	ASSIGNED	REVIEW	NUM	LETTER	ST
AMENDMENT	3/15/01	3/16/01	3/20/01	6/8/01			
AMENDMENT	4/27/01	4/30/01	5/2/01	6/8/01			
AMENDMENT	6/7/01	6/7/01	6/7/01	6/8/01			

NAME & ADDRESS OF APPLICANT:

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME:

Proprietary:	Zelnorm™
Nonproprietary/USAN:	Tegaserod
Code Name/#:	HTF-919
	CAS Registry No. [redacted] : 189188-57-6
	CAS Registry No. [redacted] : 145158-71-0
Chem.Type/Ther.Class:	1P

PHARMACOLOGICAL CATEGORY: Partial agonist of seratonin type 4 ($5\text{-}HT_4$) receptors

INDICATION: Irritable bowel syndrome

DOSAGE FORM: Tablet

STRENGTH: 2 mg, 6 mg

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: X **Rx** ___ **OTC**

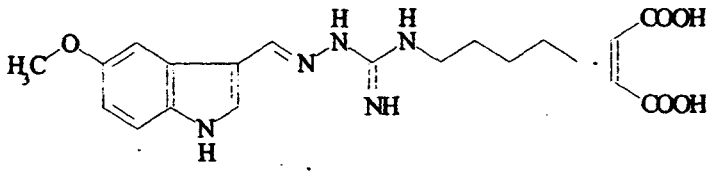
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

3-(5-Methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate

Molecular formula: $C_{16}H_{23}N_5O \bullet C_4H_4O_4 \equiv C_{20}H_{27}N_5O_5$

Relative molecular mass: 301.4 + 116.1 ≡ 417.5

Structural formula:



SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
[redacted]	[redacted]	[redacted]	N/A	7/6/00	-
			N/A	7/7/00	-
			N/A	7/5/00	-
			Adequate	7/3/00	-
			Adequate	7/3/00	-

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:
Pharm/tox discipline reviewers were consulted regarding qualification data for impurities. Also, OPDRA should be consulted regarding issues pertaining to the package labels (see *Drug Product Section*).

REMARKS/COMMENTS:
The original version of this review was completed May 15, 2001. In that version of the review, several deficiencies with both drug substance and drug product were established. These deficiencies were related to the applicant in a telephone conference (telecon) on May 24, 2001. The firm responded to the concerns raised in the telecon

with an amendment submitted by facsimile on June 5, 2001. The amendment was dated June 5, 2001. It was noted in the introductory letter to this amendment that the original hardcopy would be sent to the FDA via overnight express mail the next day. Hardcopy of the amendment arrived and was dated June 7, 2001.

The June 7, 2001 amendment was reviewed and evaluated as part of this review.

The firm has withdrawn the [redacted] Consequently, all the pertinent DMFs listed above have been reviewed, and have been found adequate to support approval of this application.

The firm has recently changed the proprietary name of this drug from "Zelmac" to "Zelnorm".

Three issues involving Drug Substance and three involving Drug Product have been developed as a result of this review. They are listed in the section CMC Comments and Deficiencies, below.

As of July 7, 2000, all of the facilities listed above in sections A2 and B4 have received recommendations of ACCEPTABLE for this submission from HFD-324.

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:
APPROVABLE. See *Summary* on pg. 5 of this review.

Raymond P Frankewich, Ph.D.
Review Chemist, HFD-180

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA #21-200
HFD-180/LTalarico
HFD-180/Div File/NDA #21-200
HFD-180/LZhou
HFD-180/RFrankewich
HFD-181/PLevine
R/D Init by: Lzhou/6-8-01
RF/rpf Draft 6-7-01/**6-8-01**
W:c:\wordfiles\chem\N\21200000.3rf

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/s/

Ray Frankewich
6/8/01 04:34:41 PM
CHEMIST

Liang Zhou
6/8/01 04:43:32 PM
CHEMIST
the application can be approved if the applicant agrees with additiona
l ~~~~~~~~~~~~~~~~~~ and to resolve other issues. Paul : The telecon
could be scheduled to discuss these issues.

DIVISION OF GASTROINTESTINAL AND COUGULATION DRUG PRODUCTS
Review of chemistry, Manufacturing, and Controls

NDA # 21-200 Chemistry Review # 2 Review Date: February 15, 2001

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	08/01/2000	08/02/2000	08/03/2000
Amendment	12/20/2000	12/22/2000	12/27/2000

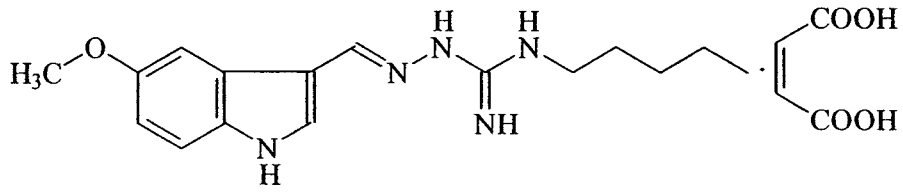
NAME & ADDRESS OF APPLICANT:
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover
New Jersey 07936-1080

DRUG PRODUT NAME

Proprietary:	Zelmac™
Nonpropietary/USAN:	Tegaserod
Code Name #:	HTF-919
Chem.Type/Therapeutic Class:	1/P
PHARMACOLOGICAL CATEGORY:	Partial agonist of seratonin type 4 (5-HT_4) receptors
INDICATION:	Irritable bowel syndrome
DOSAGE FORM:	Tablet
ROUTE OF ADMINISTRATION:	Oral
HOW DISPENESED:	√ RX ___OTC
SPECIAL PRODUCT:	___Yes √ No

CHEMICAL NAME, STRUCRURAL FORMULA, MOLECUALR WEIGHT AND MOLECULAR FORMULA:

3-(5-Methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate
Molecular Formula: $C_{16}H_{23}N_5O \bullet C_4H_4O_4 \equiv C_{20}H_{27}N_5O_5$
Molecular Weight: 301.4 + 116.1 = 417.5
Structural Formula:



APPEARS THIS WAY
ON ORIGINAL

SUUPORTING DCUMENTS

DMF No.	Item Reviewed	Holder	Status	Review Date	Letter Date
[redacted]	[redacted]	[redacted]	Deficient	07/06/00	
[redacted]	[redacted]	[redacted]	None	07/07/00	
[redacted]	[redacted]	[redacted]	Deficient	07/05/00	
[redacted]	[redacted]	[redacted]	Adequate	07/03/00	
[redacted]	[redacted]	[redacted]	Adequate	07/03/00	

RELATED DOCUMENTS: N/A

CONSULTS: N/A

REMARKS/COMMENTS

This review deals with the responses received form the firm (amendment dated August 01, 2000) to the FDA information request letter dated July 24, 2000. The responses were received as two amendments. The December 20, 2000 amendment provided follow-up answers and information to support the initial responses, which were provided in the August 1, 2000 amendment.

Issues of concern still exist in the sections of the application listed below. The specific comments are provided in List of Chemistry Deficiencies and Comments at the end of this review.

For Drug Substance:
- Synthesis/Method of Manufacture
- Regulatory Specifications/Analytical Methods

For Drug Product:
- Container/Closure System
- Drug Product Stability

CONCLUSION
APPROVABLE.

Raymond P. Frankewich, Ph.D.
Review Chemist, HFD-180 –with–

Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
Orig. NDA 21-200
HFD-180/Division File
HFD-180/L.Talarico
HFD-180/RFrankewich
HFD-180/AAlHakim
HFD-820/CHoiberg
HFD-820/SKoepke
HFD-180/CSO/P.Levine
R/D Init by: L.Zhou 2-6-01
RF/rpf Draft 2-5-01/**F/T 2-28-01**
C:\Data\Wordfiles\Wordsponge\NDA\21200000.2aRF

/s/

Ray Frankewich
3/1/01 01:36:48 PM
CHEMIST
Second CMC review of this NDA.

Liang Zhou
3/1/01 01:55:12 PM
CHEMIST
Ali intitially reviewed one of the BC in order to meet deadline when the division made a special request. Both Ray and I will be away.

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-200 **CHEM REVIEW #:** 1 **REVIEW DATE:** July 7, 2000

SUBMISSION TYPE	DATES					
	DOCUMENT	CDER	ASSIGNED	REVIEW	NUM	LETTER	ST
ORIGINAL	2/11/00	2/11/00	2/17/00	7/7/00			
AMENDMENT	5/5/00	5/8/00	5/11/00	7/7/00			
AMENDMENT	5/24/00	5/25/00	6/5/00	7/7/00			

NAME & ADDRESS OF APPLICANT:

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME:

Proprietary: Zelmac™

Nonproprietary/USAN: Tegaserod

Code Name/#: HTF-919

CAS Registry No. [redacted] : 189188-57-6

CAS Registry No. [redacted] : 145158-71-0

Chem.Type/Ther.Class: 1P

PHARMACOLOGICAL CATEGORY: Partial agonist of seratonin type 4 ($5\text{-}HT_4$) receptors

INDICATION: Irritable bowel syndrome

DOSAGE FORM: Tablet

STRENGTH: 2 mg, 6 mg

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: X **Rx** ___ **OTC**

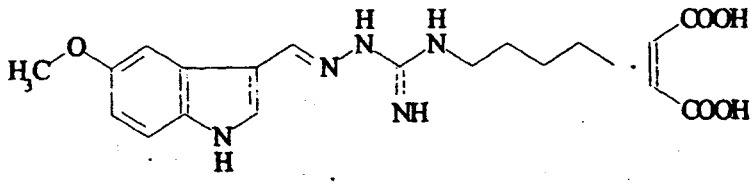
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

3-(5-Methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate

Molecular formula: $C_{16}H_{23}N_5O \cdot C_4H_4O_4 \equiv C_{20}H_{27}N_5O_5$

Relative molecular mass: 301.4 + 116.1 ≡ 417.5

Structural formula:



SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
[redacted]	[redacted]	[redacted]	Deficient	7/6/00	-
[redacted]	[redacted]	[redacted]	None	7/7/00	-
[redacted]	[redacted]	[redacted]	Deficient	7/5/00	-
[redacted]	[redacted]	[redacted]	Adequate	7/3/00	-
[redacted]	[redacted]	[redacted]	Adequate	7/3/00	-

RELATED DOCUMENTS (if applicable): N/A

CONSULTS: N/A

REMARKS/COMMENTS:

Issues of concern have been raised in the sections of the application listed below (the specific comments are provided in Section H, Comments).

For Drug Substance:

[redacted]

CONCLUSIONS & RECOMMENDATIONS:

APPROVABLE.

/S/ 7/11/2000

Raymond P Frankewich, Ph.D.
Review Chemist, HFD-180

/S/ 7/11/00

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA #21-200
HFD-180/LTalarico
HFD-180/Div File/NDA #21-200
HFD-180/LZhou
HFD-180/RFrankewich
HFD-181/PLevine
R/D Init by: Lzhou/6-26-00
RF/rpf Draft 6-23-00/**7-11-00**
W:c:\wordfiles\chem\N\21200007.1rf

Printed by John Gibbs

Electronic Mail Message

Date: 10-Aug-2000 03:28pm
From: John Gibbs
GIBBS
Dept: HFD-820 PKLN 14B31
Tel No: 301-827-6420 FAX 301-827-0878

O: See Below
ubject: NDA 21-200 Tertiary Chemistry Review #1

DA #21-200

rug: Zelmac (tegaserod)

hemical Type/Therapeutic Class: 1P

ype of Letter: Approvable

ertiary Chemistry Review #1

A:	Chem. Rev. #1 (p. 61) and Comment 24 (p.94) found the request for categorical exclusion Not Acceptable.
ER:	Acceptable per EES Detail Report dated 26 June 2000.
icrobiology:	Not applicable. Product is a solid oral dosage form.
rade Name:	Not Acceptable per OPDRA Consult #00-0182 dated 4 August 2000.
ethods Validation:	Due to numerous deficiencies in the analytical methods cited in Chemistry Review #1, methods validation will not be requested until the deficiencies are adequately addressed.
MC:	The chemistry review of the application notes deficiencies in the following areas: a. [redacted] b. [redacted]

For Drug Product:

For the finished product (or both Drug Substance and Drug Product)

- Environmental Assessment
- Methods Validation
- Labeling
- Establishment Inspection

All the DMFs listed above have been reviewed. DMF numbers [redacted] have been found deficient to support approval of this application. More information is needed regarding the [redacted] used for the [redacted] before DMF [redacted] can be reviewed. Information request letters will be issued to the DMF holders whose files are deficient.

As of July 7, 2000, all of the facilities listed above in sections A2 and B4 have received recommendations of ACCEPTABLE for this submission from HFD-324.

Many of the comments are information requests that should not involve generation of additional data. Others are concerns with the validation of analytical methods, which may involve the generation of additional data; however, these should be addressed easily within six months. Accordingly, this application will be found APPROVABLE.

APPEARS THIS WAY
ON ORIGINAL

Zelmac Tablets Original NDA 21-200

Drug Master File References in this NDA

Company	Subject of the DMF	DMF Number	Authorization Letter Date
[redacted]	[redacted]	[redacted]	16-Mar-99
[redacted]	[redacted]	[redacted]	24-Mar-99
[redacted]	[redacted]	[redacted]	28-Jul-99
[redacted]	[redacted]	[redacted]	11-Oct-99
[redacted]	[redacted]	[redacted]	11-Oct-99

APPEARS THIS WAY
ON ORIGINAL

Zelmac Tablets Original NDA 21-200

Central File Numbers for the sites of manufacturing, packaging and control

Site	CFN	Manufacturing	Quality control	Stability	Packaging
Drug Substance					
Novartis Pharma AG Lichtstrasse 35 CH-4056 Basel Switzerland	9611204	X	X		
Novartis Pharma Stein AG Schaffhauserstrasse CH-4332 Stein Switzerland	9692043	X			
Novartis International Pharmaceutical Ltd. Branch Ireland Ringaskiddy, County Cork Ireland	9612715		X		
Novartis Pharmanalytica S.A. Via Serafino Balestra 31 CH-6601 Locarno Switzerland	9614433			X	
Drug Product					
Novartis Pharma Stein AG Schaffhauserstrasse 4332 Stein Switzerland	9692043	X	X		
Novartis Pharmaceuticals Corporation 59 Route 10 East Hanover, NJ 07936	2210396		X	X	
Novartis Pharmaceuticals Corporation 25 Old Mill Road Suffern, New York 10901	2416082		X	X	X
Novartis Pharmanalytica S.A. Viale Serafino Balestra 31 CH-6601 Locarno Switzerland	9614433			X	