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)
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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:

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7. NAME & ADDRESS OF APPLICANT:
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-HT4) 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-pentylcarbazimidine hydrogen maleate

Molecular formula: $C_{16}H_{23}N_2O \cdot C_4H_4O_4 \equiv C_{20}H_{27}N_5O_5$

Relative molecular mass: $301.4 + 116.1 \equiv 417.5$

Structural formula:

![Structural formula image]

17. RELATED/SUPPORTING DOCUMENTS:

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1 Action codes for DMF Table:
CHEMISTRY REVIEW

Chemistry Review Data Sheet

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:

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19. ORDER OF REVIEW (OGD Only)
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. One of the drug substance to describe their process for the manufacture of Drug substance specifications include one related substance acceptance criterion (for compound which is above that which is recommended in ICH Q3A. 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*
WITHHOLD 16 PAGE (S)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

\[\textit{/s/}\]

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

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

APPEARS THIS WAY ON ORIGINAL
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 DOCUMENT   DATES
AMENDMENT 3/15/01            CDER       ASSIGNED REVIEW NUM LETTER ST
AMENDMENT 4/27/01            3/16/01     3/20/01  6/8/01
AMENDMENT 6/7/01            4/30/01     5/2/01   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

Chem.Type/Ther.Class:
CAS Registry No. : 189188-57-6
CAS Registry No. : 145158-71-0
1P

PHARMACOLOGICAL CATEGORY: Partial agonist of serotonin type 4 (5-HT₄) 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: C₁₆H₂₃N₅O • C₄H₄O₄ ≡ C₂₀H₂₇N₅O₅

Relative molecular mass: 301.4 + 116.1 = 417.5
Structural formula:

![Structural formula image]

**SUPPORTING DOCUMENTS:**

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**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 ________ 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.
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 additional and to resolve other issues. Paul: The telecon could be scheduled to discuss these issues.
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of chemistry, Manufacturing, and Controls

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

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

DRUG PRODUCT NAME
Proprietary: Zelmac™
Nonproprietary/USAN: Tegaserod
Code Name #: HTF-919
Chem. Type/Therapeutic Class: 1/P

PHARMACOLOGICAL CATEGORY:
Partial agonist of serotonin type 4 (5-HT₄) receptors

INDICATION:
Irritable bowel syndrome

DOSAGE FORM:
Tablet

ROUTE OF ADMINISTRATION:
Oral

HOW DISPENSED: √ RX  OTC

SPECIAL PRODUCT: Yes  No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT AND MOLECULAR FORMULA:

3-(5-Methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate
Molecular Formula: C₁₆H₂₁N₅O • C₆H₄O₄ = C₂₆H₂₇N₅O₅
Molecular Weight: 301.4 + 116.1 = 417.5

Structural Formula:

![Structural Formula Image]
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RELATED DOCUMENTS: N/A

CONSULTS: N/A

REMARKS/COMMENTS

This review deals with the responses received from 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

APPEARS THIS WAY ON ORIGINAL
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/R.Frankewich
HFD-180/AAl-Hakim
HFD-820/CHOiberg
HFD-820/OKoepke
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

APPEARS THIS WAY
ON ORIGINAL
/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 initially 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

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NAME & ADDRESS OF APPLICANT:
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59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME:
Proprietary: Zelmac™
Nonproprietary/USAN: Tegaserod
Code Name/#: HTF-919
CAS Registry No. : 189188-57-6
CAS Registry No. : 145158-71-0
Chem. Type/Ther. Class: 1P

PHARMACOLOGICAL CATEGORY: Partial agonist of serotonin type 4 (5-HT₄) receptors

INDICATION: Irritable bowel syndrome

DOSAGE FORM: Tablet

STRENGTH: 2 mg, 6 mg

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: X Rx  ____OTC

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

Molecular formula: C₁₆H₂₃N₅O • C₄H₄O₄ ≡ C₂₀H₂₇N₅O₅

Relative molecular mass: 301.4 + 116.1 = 417.5
Structural formula:

![Chemical Structure](image)

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**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:
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.lrf

APPEARS THIS WAY
ON ORIGINAL
Subject: NDA 21-200 Tertiary Chemistry Review #1

DA #21-200

rug: Zelmac (tegaserod)

hemical Type/Therapeutic Class: 1P

type 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.

microbiology: 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. 

b. 
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 ____ have been found deficient to support approval of this application. More information is needed regarding the _________ used for the ________ before DMF ____ 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.
### Zelmac DMFs

#### Zelmac Tablets Original NDA 21-200

**Drug Master File References in this NDA**

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*Appears this way on original*
Zelmac Tablets Original NDA 21-200

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