

FEB 24 2000

NDA 21-200

Novartis Pharmaceuticals Corporation
Attention: Donna M. Vivelo
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Vivelo:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zelmac™ (tegaserod) Tablets

Therapeutic Classification: Priority (P)

Date of Application: February 11, 2000

Date of Receipt: February 11, 2000

Our Reference Number: NDA 21-200

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 11, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 11, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date

action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, Room 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-200

Page 3

If you have any questions, call me at (301) 827-7310.

Sincerely,

/s/ 2/23/00
Paul E. Levine, Jr., R.Ph.
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 21-200

Page 4

cc:

Archival NDA 21-200

HFD-180/Div. Files

HFD-180/P.Levine

DISTRICT OFFICE

Drafted by: PEL 02/ 22/00

Initialed by: J.Dubeau 02/23/00

final: 02/23/00

filename: 21200ACK.doc

/S/2/23/00

ACKNOWLEDGEMENT (AC)

**APPEARS THIS WAY
ON ORIGINAL**

JUN 15 2001

NDA 21-200

Novartis Pharmaceuticals Corporation
Attention: Donna M. Vivelo
Associate Director Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Vivelo:

Please refer to your new drug application (NDA) dated February 11, 2000, received February 11, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zelnorm™ (tegaserod maleate) Tablets.

We acknowledge receipt of your submissions dated August 1, 3, and 8; December 15 and 20, 2000; March 15; April 18, 20, 25, and 27; May 10; and June 5, 7, 13, and 15, 2001. Your submission of December 15, 2000, constituted a complete response to our August 11, 2000, Approvable letter.

We further refer to our meeting with you held on June 14, 2001, to discuss issues related to the efficacy and safety of Zelnorm™.

We have completed our review and find that the information presented is inadequate, and the application is not approvable under section 505 (d) of the Act and 21 CFR 314.125(b). The major deficiencies are summarized below:

1. There is insufficient information about the drug to determine whether tegaserod is safe for use under your proposed indication for the treatment of females with irritable bowel syndrome who have constipation as a predominant complaint _____ (C-IBS). Therefore, we are unable to determine the risk/benefit profile for tegaserod at the proposed to-be-marketed dose. The tegaserod combined clinical trials safety data of studies 301, 307, 351, and 358 may contain a signal for increased risk of surgery secondary to abdominal pain. Surgery, even laparoscopic surgery, carries risks of the surgical procedure and risks of anesthesia and even mortality. The Agency's concern for these risks is increased over our previous safety evaluation performed during your last submission cycle because now there may also be a signal that tegaserod may have a role in the development of symptomatic gallbladder disease. This risk may be further magnified given your proposed indication for use of the drug

in the female IBS population, a population with a high prevalence of gallstones and risk factors that would additionally put them at risk for development of gall bladder disease.

2. The evidence for effectiveness is marginal. Your first submission contained results from studies 301 and 307, which utilized a post-hoc derived outcome variable based on analysis of study 351. Study results for 301 and 307 were conflicting: study 301 was positive and study 307 did not show differentiation from placebo. The approvable letter of August 11, 2000, asked that efficacy be assessed again and that study 358, submitted this cycle, replicate the finding of study 307.
3. The drug effect size is small. In your largest randomized, double-blind, placebo controlled clinical trial, study 358, the effect size is estimated to be around 5% over placebo, which replicates the effect size in 307. The effect size may mean that out of 1,000 patients treated with tegaserod, roughly 50 additional patients would benefit from this drug compared to 1,000 patients on placebo. However, with this small benefit, there may be extra cases of surgery and complications from surgery. Moreover, there is concern that the drug's small effect may be diminishing over time.

In summary, the small effect size, coupled with the outstanding questions about the durability of drug effect and the drug's marginal evidence for efficacy, are overridden by the safety concerns that must be defined, quantified, and evaluated. Postmarketing safety studies, such as those you previously committed to performing during the first cycle, are not appropriate because of our heightened concerns about surgical risk and the role this drug may have in gallbladder disease. Should studies confirm risk, marketing may not be appropriate. Short-term, acute use is not appropriate at this time because studies submitted were not based on this hypothesis and once risks are fully assessed, marketing may not be appropriate.

Clinical Data needed to resolve major deficiencies:

1. Submit data from a large, simple, U.S. study that accurately quantify the risk of abdominal surgery and type of surgery (pelvic, gallbladder/biliary, appendectomy, etc.) showing the product is safe for use under conditions prescribed in the proposed labeling.
2. Submit data that clarify the role of tegaserod in the risk of symptomatic gallbladder disease development, and quantify the risk of gallbladder surgery.
3. Demonstrate that the benefit of the drug outweighs its risks. Should serious risks be confirmed in the above studies, you would be required to demonstrate that tegaserod's benefits outweigh these risks prior to approval. If you pursue your current proposed indication for C-IBS without reference to short or long-term use of tegaserod, you may

be required to demonstrate the effectiveness of long-term administration of tegaserod such that the benefit outweighs the risks. Therefore, your prior commitment to a post-marketing study _____ You may consider



The Agency strongly advises that the protocols for studies fulfilling 1-3 be submitted to the Agency for review and comment prior to initiation. The Agency is amenable to considering your June 14, 2001, request for Advisory Committee discussion on protocols, completed study results, and/or risk management proposals.

We remind you of the following commitments made in your amendment submitted June 5, 2001.

1. To use _____ sourced from the current supplier _____ only;
2. To submit an amendment to qualify any other supplier of _____ beside the current one;
3. To submit to NDA 21-200 a letter of authorization allowing the Agency to reference a Drug Master File (DMF) submitted by _____ the supplier of _____ for the review of NDA 21-200. You indicated in the June 5, 2001, amendment that _____ agreed to submit a type II DMF for the _____ to the Agency by January 2002.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 7. Provide English translations of current approved foreign labeling not previously submitted.

Labeling comments will be provided when the application is otherwise approvable.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, the Agency may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

(See appended electronic signature page)

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Florence Houn
6/15/01 04:55:20 PM

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: March 10, 2001

DUE DATE:
May 18, 2001

OPDRA CONSULT #: 01-0056

TO: Lilia Talarico, MD
Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

THROUGH: Paul Levine, Project Manager
HFD-180

PRODUCT NAME:

Zelnorm
(Tegaserod hydrogen maleate) Tablets
2 mg, 6 mg

Manufacturer: Novartis

NDA #: 21-200

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), OPDRA conducted a review of the proposed proprietary name "Zelnorm" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not object to the use of the proprietary name "Zelnorm".

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

— **FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW**

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

— **FOR PRIORITY 6 MONTH REVIEWS**

OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 4, 2001
NDA NUMBER: 21-200
NAME OF DRUG: Zelnorm
(Tegaserod hydrogen maleate) Tablets
2 mg, 6 mg
NDA HOLDER: Novartis

I. INTRODUCTION

This consult was written in response to a request from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), for assessment of the tradename "Zelnorm", regarding potential name confusion with other proprietary/generic drug names.

On 11/23/98 the firm received approval for the use of the proprietary name "Zelmac" under IND following approval of the name from the Labeling and Nomenclature Committee. On 08/04/01, the proprietary name "Zelmac", submitted under NDA 21-200 was found unacceptable by OPDRA. Subsequently, on 03/02/01, the sponsor submitted the proposed name, "Zelnorm".

PRODUCT INFORMATION

Zelnorm tablets contains tegaserod hydrogen maleate and is indicated for the treatment of patients with irritable bowel syndrome (IBS) who identify constipation as their predominant symptoms. The recommended dosage of Zelnorm is 6 mg twice daily taken orally just prior to a meal. Zelnorm will be supplied in tablets of 2 mg and 6 mg in unit dose boxes of 60 count.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,ii,iii} as well as several FDA databases^{iv} for existing drug names which

ⁱ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

sound-alike or look-alike to “Zelnorm” to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office’s Text and Image Database was also conducted^v. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name “Zelnorm”. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Four product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with Zelnorm. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have any concerns with the name in regard to promotional claims.

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Zelnorm	Tegaserod hydrogen maleate 2 mg and 6 mg tablets (Rx)	6 mg twice daily	
Xeroderm	Lotion: Mineral oil, acetate lanolin alcohol, cetyl alcohol, parabens, imidazolidinyl urea (otc)	Use once daily	S/A, L/A per OPDRA
Zempler	Paracalcitol 5 mcg/ml injection (Rx)	<i>Initial dose:</i> 0.04 to 0.1 mcg/kg (2.8 to 7 mcg) as a bolus dose other day at any time during dialysis. Doses as high as 0.24 mcg/kg (16.8 mcg) have been administered safely.	S/A, L/A per OPDRA
Zemuron	Rocuronium bromide 10 mg/ml injection (Rx)	For IV use only <i>Rapid sequence intubation:</i> 0.6 to 1.2 mg/kg <i>tracheal intubation:</i> 0.6 mg/kg <i>Maintenance:</i> 0.1, 0.15 and 0.2 mg/kg <i>Continuous infusion:</i> Initiate infusion at an initial rate of 0.01 to 0.012 mg/kg/min	S/A, L/A per OPDRA

ⁱⁱ American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

^{iv} COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Zelnorm	Tegaserod hydrogen maleate 2 mg and 6 mg tablets(Rx)	6 mg twice daily	
Sermorelin (Geref®)	Sermorelin 50 mcg powder for injection (Rx)	1 mg/kg administered as a bolus dose	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A separate study was conducted within FDA for the proposed proprietary name to determine the degree of confusion of Zelnorm with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 86 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Zelnorm (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

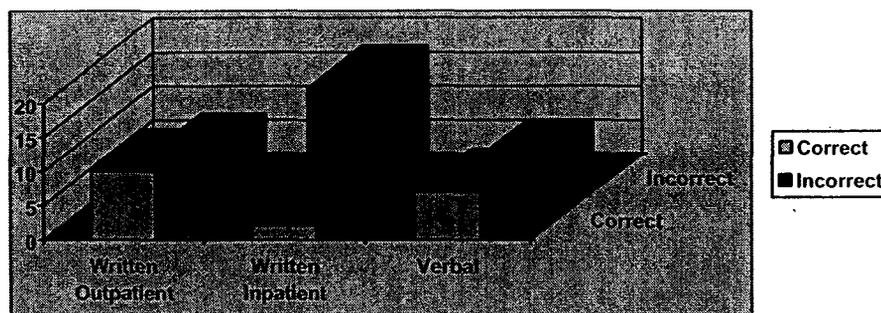
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<i>Outpatient:</i> Zelnorm 6 mg # 36 Sig: 1 po BID x 4 wks	Zelnorm 6 mg Take 1 tablet twice daily for 4 weeks Dispense #36
<i>Inpatient:</i> Zelnorm 6 mg BID	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Zelnorm" response	Other response
Written: Outpatient	28	16 (51%)	10 (63%)	6(37%)
Inpatient	28	18 (64%)	2 (11%)	16 (89%)

Verbal	30	12 (40%)	7 (58%)	5 (42%)
Total:	86	46 (53%)	19 (41%)	27 (59%)



Among participants in the two written prescription studies, 22 of 34 respondents (65%) interpreted the name incorrectly. The interpretations were misspelled variations of “Zelnorm” such as *Zelnorin*, *Zelnoren*, *Zelnorum*, *Zelnomon*, *Zelnormin*, *Zelnoun*, *Zelhorn*, *Zilnorm*, *Zelnorm* and *Zelnormin*. Other participants provided *Zenorun*, *Zelorun*, *Zelhoven*, and *Zelnorue*.

Among verbal prescription study participants, 5 out of 12 study participants (42%) interpreted the name incorrectly. Most of the incorrect name interpretations were phonetic variations of “Zelnorm” such as *Zonorm*, *Zeonom*, and *Zealnorm*.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. Look-alike and sound-alike names

In reviewing the proprietary name “Zelnorm”, the primary concerns raised were related to a sound-alike, look-alike name that already exists in the U.S. marketplace. One product, Zemuron, was believed to be the most problematic in terms of potential medication errors.

OPDRA conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Zelnorm could be confused with Zemuron. However, one study participant provided *Zenorun* as an interpretation which is strikingly similar the approved drug Zemuron. Although there are limitations to the predictive value of these studies primarily due to sample size, we have acquired safety concerns due to positive interpretations. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. The majority of the participants from the verbal and two written prescription studies provided phonetic/misspelled interpretations to the proposed drug name.

Zemuron is a neuromuscular blocker and is indicated for inpatients and outpatients as an adjunct to general anesthesia to facilitate both rapid sequence and routine tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation. Zemuron is available as a 10 mg/mL injection for IV use only. Doses range from 0.45 mg/kg to 1.2 mg/kg. Although Zelnorm and Zemuron do not sound similar, the names look similar when scripted. One participant from the inpatient prescription study provided *Zenorun*, as an interpretation, which is strikingly similar to

the name Zemuron. However, Zelnorm and Zemuron differ in dosage form, dosing frequency and route of administration. In addition, Zemuron is an adjunct for anesthesia that is administered intravenously only by qualified personnel in an appropriately equipped medical setting.

2. _____ analysis

The sponsor contracted with _____ a subsidiary of the _____ to evaluate the name proposed name Zelnorm. Zanosar was found to have a “moderate vulnerability” rating meaning that a moderate risk is associated with the potential confusion of Zelnorm and Zanosar.

Zanosar is an antineoplastic agent used to treat pancreatic islet cell cancer. Zanosar is available for administration by injection only. It is dosed on a mg/m² basis with a specific 5-day dosing schedule every 6 weeks. Given the differences in dosage form, dosing frequency, and route of administration with a lack of convincing look-alike and sound potential, there is insufficient evidence at this time to conclude that the proposed drug name would be confused with Zanosar.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

The labeling and packaging was reviewed on August 1, 2000 with the proposed name “Zelmac” which was found unacceptable.

**APPEARS THIS WAY
ON ORIGINAL**

III. RECOMMENDATIONS

OPDRA does not object to the use of the proprietary name "Zelnorm".

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3231.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Alina Mahmud
4/6/01 01:58:05 PM
PHARMACIST

Jerry Phillips
4/6/01 02:00:45 PM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products		HFD-180
Attention: Melodi McNeil, Project Manager		Phone: (301) 443-0483
Date: May 20, 1998		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: Zelmac		NDA/ANDA# IND —
Established name, including dosage form: No established name. Currently known as HTF 919 Tablets		
Other trademarks by the same firm for companion products: None		
Indications for Use (may be a summary if proposed statement is lengthy): Constipation prone Irritable Bowel Syndrome (C-IBS)		
Initial Comments from the submitter (concerns, observations, etc.): Submission is dated 5/8/98.		

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original IND — ; HFD-180/division file; HFD-180/M.McNeil;

Rev. December 95

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

MM 5/20/98

IND

NOV 23 1998

Novartis Pharmaceuticals Corporation
Attention: Donna M. Vivelo
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Vivelo:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for HTF 919 Tablets.

We also refer to your amendment dated May 8, 1998, serial number 088, requesting our comments concerning "Zelmac[®]" as the proposed proprietary name (trade name) for the drug product.

We have completed our review of your submission and, at this time, have no objection to the use of the proposed proprietary name (trade name) "Zelmac[®]" for this drug product.

If you have any questions, contact Michael Folkendt, Project Manager, at (301) 443-0487.

Sincerely,

/S/ 11-23-98

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival IND
HFD-180/Div. Files
HFD-180/M.Folkendt

Drafted by: mmf/November 20, 1998
Rd initials: L.Talarico 11/20/98
final: 11/23/98
filename: 112098.DOC

/S/ 11/23/98

GENERAL CORRESPONDENCE

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 7/10/00

DUE DATE: 8/4/00

OPDRA CONSULT #: 00-0182

TO:

Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

THROUGH:

Paul Levine
Project Manager
HFD-180

PRODUCT NAME:

Zelmac Tablets
(tegaserod hydrogen maleate)
2 mg, 6 mg
NDA #: 21-200

MANUFACTURER: Novartis

SAFETY EVALUATOR: Peter Tam, RPh.

OPDRA RECOMMENDATION:

OPDRA does not recommend the use of the proprietary name, Zelmac.

APPEARS THIS WAY
ON ORIGINAL

/S/

8/4/2000

11

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk
Assessment
Center for Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 8/1/00
NDA#: 21-200
NAME OF DRUG: Zelmac Tablets
(tegaserod)
NDA HOLDER: Novartis

I. INTRODUCTION:

This consult is in response to a request from the Division of Gastro-Intestinal and Coagulation Drug Products, (HFD-180) on 7/14/00 to review the proposed proprietary name, Zelmac, in regard to potential names conflict with existing proprietary/generic drug names. The goal date is August 11, 2000.

The proposed trade name, Zelmac, was submitted to Labeling and Nomenclature Committee (LNC) on May 28, 1998 under IND _____ and was found acceptable.

PRODUCT INFORMATION

Zelmac tablets contain tegaserod as the hydrogen maleate. It is indicated for the treatment of _____ patients with irritable bowel syndrome (IBS) who identify _____ constipation as their predominant symptoms.

Each 1.385 mg of tegaserod as the hydrogen maleate is equivalent to 1 mg of tegaserod. Zelmac is rapidly absorbed after oral administration; peak plasma concentrations are reached approximately 1 hour after dosing. The absolute bioavailability of tegaserod hydrogen maleate when administered to fasting subjects is approximately 10%.

The recommended dosage of Zelmac is 6 mg bid taken orally _____

Zelmac will be supplied in tablets of 2 mg and 6 mg in _____ Unit Dose box of 60.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{1,2,3} as well as several FDA databases⁴ for existing drug names which sound alike or look alike to Zelmac to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by OPDRA to gather professional opinions on the safety of the proprietary names, Zelmac. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel identified several product names considered to have potential for confusion. The identified products are listed in the following table.

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Zelmac	Tablets, 2 and 6 mg, tegaserod	6 mg bid	
Zomig	Tablets, 2.5 and 5 mg, zolmitriptan	2.5-5 mg and may repeat in 2 hrs. Max. 10 mg/24 hr.	*SA/LA
Zantac	Tablets, 75,150,300 mg, Inj. 25 mg/ml 2,10,40 ml, ranitidine	150 mg bid	*SA
Zyrtec	Tablets, 5,10 mg, Syrup 5mg/5ml, cetirizine	5-10 mg once daily	*SA
Ziac	Tablets, combination of bisoprolol 2.5 mg/HCTZ 6.25 mg	Once daily	*SA

*SA = Sound-alike

*LA = Look-alike

¹ MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

² American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

³ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

⁴ Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

Zomig, Zantac and Zyrtec are the product names that are identified to have the most potential for confusion with Zelmac. They all look-alike and sound alike. In addition, all three products are available in tablet dosage forms. There are no overlapping strengths among the four products. However, Zantac has overlapping dosing intervals as Zelmac at bid dosing. Because of the overlapping dosing interval, there was some concern that Zelmac might be confused with Zantac.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Studies were conducted by OPDRA and involved 91 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Zelmac with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Zelmac (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

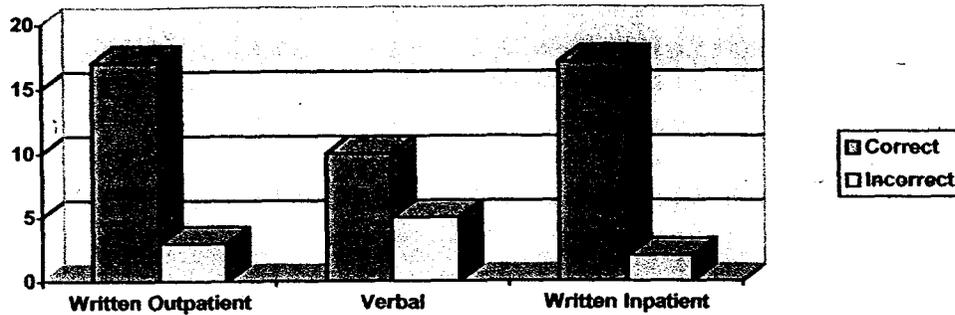
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Zelmac 2 mg #60 Sig: One bid	Zelmac 2 mg Sig: One bid
Inpatient RX: Zelmac 2 mg po bid	

2. Results:

The results are summarized in Table I.

Table I

<u>Study</u>	<u># of Participants</u>	<u># of Responses (%)</u>	<u>Correctly Interpreted</u>	<u>Incorrectly Interpreted</u>
Written Outpatient	31	20(65%)	17	3
Verbal	30	15(50%)	10	5
Written Inpatient	30	19(63%)	17	2
Total	91	54(59%)	44(81%)	10 (19%)



19 percent of the participants respond with incorrect names. The incorrect written and verbal responses are summarized in Tablet II.

Tablet II

Written Outpatient	Incorrectly Interpreted
	Elmac
	Zelmax
	Zolmac
Verbal	Zomax
	Zolmax
	Zomig*
	Soma*
Written Inpatient	Zelniac (2)

* Existing Approved Products

C. SAFETY EVALUATOR RISK ASSESSMENT

Several proprietary product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with the proposed name, Zelmac. They are 1) Zomig, 2) Zantac and 3) Zyrtec. They all share with the letter "Z" and have similar character lengths of either 5 or 6. They are all available in tablet dosage forms and they sound and look alike.

Results of inpatient prescription study indicated that two (out of nineteen) participants interpreted Zelmac incorrectly. There were three (out of twenty) and five (out of fifteen) participants interpreted Zelmac incorrectly in written and verbal outpatient prescription studies. However, one significant finding in verbal prescription study revealed that two participants interpreted Zelmac as Zomig and Soma independently. The fact that the inaccurate interpretations of the proposed name did overlap with two existing approved products is a significant finding in a study with a small sample size. A search in AERS found that there were eight reports of drug maladministration involving Zantac and Zyrtec. These eight drug maladministration reports were all called for Zantac but Zyrtec was inadvertently dispensed. No serious patient outcomes were reported. There was no medication error reported on Zomig confused with either Zantac or Zyrtec.

Due to the phonetic similarities among Zantac, Zyrtec, Zomig and Zelmac, we object to the proposed proprietary name, Zelmac.

CC:

NDA – 21-200

Office Files

HFD-180; DivFiles; Paul Levine, Project Manager, DGCDP

HFD-180; Lilia Talarico, M.D., Division Director, DGCDP

HFD-042; Patricia Staub, Regulatory Review Officer, DDMAC (Electronic Only)

HFD-440; Mary Dempsey, DDREII, OPDRA (Electronic Only)

HFD-400; Jerry Phillips, Associate Director, OPDRA

HFD-400; Sammie Beam, Project Manager, OPDRA

HFD-400; Peter Honig, Director, OPDRA (Electronic Only)

HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (Electronic Only)

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Product Ingredients
Packaging
Stability
c. Other Issues
Validation of Test Methods
Labeling

John J. Gibbs, Ph.D.
Director, DNDC II

Distribution:

O: Bronwyn Collier	(COLLIERB)
O: Paul Levine	(LEVINEP)
O: Melodi McNeil	(MCNEILM)
C: Liang Zhou	(ZHOUL)
C: Raymond Frankewich	(FRANKEWICHR)
C: Florence Houn	(HOUNF)

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-200

Novartis Pharmaceuticals Corporation
Attn: Thomas Koestler, Ph.D.
Sr. Vice President, Drug Regulatory Affairs
59 Route 10
East Hanover, New Jersey 07936-1080

Dear Dr. Koestler:

Please refer to your New Drug Application (NDA) submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zelnorm (tegaserod maleate) Tablets.

We also refer to your letter dated August 6, 2001, received August 7, 2001, containing a request for formal dispute resolution of issues raised in the June 15, 2001, not approvable letter for Zelnorm, and your additional submission dated August 29, 2001. This submission provided information in response to a request made by Ms. Kim Colangelo, Office of Review Management (ORM), to Ms. Sharon Olmstead, Regulatory Liaison, on August 24, 2001.

In your August 6, 2001, letter, you state that the conclusions drawn by FDA concerning the safety and efficacy of your product were unsupported by the data provided in your December 15, 2000, complete response to our August 11, 2000, approvable letter. In addition, you state that these conclusions were raised late in the review process, therefore the interaction between FDA and yourself was limited. We further note that no interaction with the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) and the Office of Drug Evaluation III (ODE III) has occurred since the issuance of the June 15, 2001, not approvable letter.

We have determined that it would be inappropriate for the Director of ORM to consider this matter under formal dispute resolution at this time. Your arguments regarding the issues raised in the June 15, 2001, not approvable letter have not been presented fully to DGCDP and ODE III. We acknowledge your meeting with DGCDP and ODE III on June 14, 2001, but the purpose of that meeting was for DGCDP and ODE III to share their concerns regarding tegaserod's safety and efficacy and their conclusions regarding the overall risks and benefits of tegaserod. Your arguments, including the aggregate analyses provided in the background package of your dispute resolution request, were not fully discussed in that meeting.

Therefore, we are referring this matter back to DGCDP for appropriate action. You may request an end of review conference with DGCDP and ODE III as provided for in 21 CFR 314.102(d). As part of this meeting, we recommend that you consult with DGCDP on the information needed for a complete response to the not approvable letter, some of which may already be contained in your dispute resolution package.

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Page 2

Please contact Mr. Paul Levine, Regulatory Project Manager, at (301) 443-8347 if you have any questions.

Sincerely,

Sandra Kweder, M.D.
Acting Director
Office of Review Management
Center for Drug Evaluation and Research

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/s/

Kim Colangelo
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For Sandra Kweder

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M E M O R A N D U M

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

Date: August 16, 2001

From: Director, Division of Gastrointestinal and Coagulation
Drug Products, HFD-180

Subject: Secondary Review of Zelnorm

To: NDA 21-200

Through: Director, Office of Drug Evaluation III, HFD-103

Zelnorm® is a selective agonist of 5-HT₄ receptors. Activation of these receptors initiates the peristaltic reflex and motor activity of the entire gastrointestinal tract.

NDA 21-200 for Zelnorm was submitted on February 14, 2000 for the treatment of constipation predominant irritable bowel syndrome (C-IBS). The therapeutic aim of Zelnorm was relief of abdominal discomfort/pain and altered bowel habit.

The NDA consisted of three Phase 3 clinical trials (301, 307, and 351). Study 351 was designed with the primary efficacy variable, of Subject Global Assessment (SGA) of relief defined as complete or considerable relief of symptoms =>50% of time at study endpoint (last 4 available weekly SGA responses on treatment or all weekly responses if fewer than 4 weekly scores were available). The preliminary analysis of efficacy of this study failed to show statistical significance. According to the sponsor, the definition of response was too stringent and lacked sensitivity to detect a difference among the treatment groups. The SGA or relief was extended to include complete, considerable or somewhat relief 100% of time at study endpoint. The change was accepted by the GICDP division with the request that the data be presented using both analyses. Efficacy was demonstrated for the Zelnorm regimen of 6 mg/bid when the revised SGA of relief was analyzed post-hoc (SGA or relief 45% for Zelnorm versus 32% for placebo; p=0.008).

The pivotal trial 301 was designed to replicate the post-hoc exploratory analysis results of study 351 using the newly defined endpoints of SGA of relief. Following a 4-week baseline period, patients were randomized to three groups: Placebo, Zelnorm 2 mg/bid or Zelnorm 6 mg/bid. In study 307, patients were randomized to placebo, Zelnorm 2 mg/bid, or to Zelnorm 2 mg/bid and dose titration to 12 mg/day at week 4 if response had been

achieved. Treatment continued for 12 weeks in both studies. After 12 weeks, all treatments were discontinued and patients were observed over a four-week withdrawal period.

The patients recorded daily and weekly efficacy assessment. Four weekly SGAs of relief were entered throughout the duration of the study and five daily assessment of abdominal pain and bowel habit were entered for the last 28 days on treatment in a diary. The primary statistical analyses were by ITT, two-sided and at the 0.05 significant level.

The efficacy results of study 301, determined as global assessment of relief, abdominal pain/discomfort and constipation, showed a response rate of 38% compared to that of 30% for the placebo ($p=0.028$ for both Zelnorm dose regimens). More patients were enrolled than planned in the protocol (20%) which resulted in an increase in the power of the statistical test for efficacy analysis.

Study 307 showed a therapeutic gain of 5% for Zelnorm over placebo, which was not statistically significant. However, different dosing regimen was used in study 307.

Analysis by gender showed no efficacy in the male population, efficacy for females was statistically significant in study 301 and study 351.

A total of 3737 patients received Zelnorm in Phase 2, phase 3 and long-term studies: 826 for 6 months or longer and 167 for 12 months or longer.

Overall incidence of adverse events (AE) including serious AEs (SAE) was similar in the Zelnorm treated groups and in the placebo group and involved mainly the GI system. Diarrhea occurred more frequently in the Zelnorm group.

One third of patients discontinued therapy in the Phase 3 studies: 6.8 and 5.1% discontinued because of AEs in the Zelnorm and placebo groups, respectively.

A total of 46% (10% due to AEs) discontinued treatment in the long-term study.

Unexpected AEs included nine cases of ovarian cysts, 8 in Zelnorm-treated patients and 1 in the placebo group. Five of 8 cysts in the Zelnorm patients required surgery. Ovarian cysts were documented in 5 Zelnorm and 1 placebo patients by surgery or CT scan. A consultation was obtained by the RUDP division. No causal relationship was attributed to the drug by the consultant.

On June 26, 2000, an AC meeting was convened to discuss the efficacy and safety of Zelnorm. The outcome of the meeting was recommendation for approval of Zelnorm 'for the treatment of abdominal pain, discomfort, and constipation in female patients with C-IBS'. The committee did not consider the ovarian cysts and laparatomies as AEs attributable to therapy.

On 8-4-2000, the application was discussed at a CDER review meeting. The consensus outcome of the meeting was that the efficacy was marginal and in need of replication, and that safety concerns needed further assessment.

On 8-11-2000, the FDA (ODE III Office Director) issued an approvable action letter with the request to address the following concerns:

- Submit efficacy and safety results from a study of similar design as 301 with at least 300 patients per arm,
- Provide any additional safety data not previously submitted,
- Submit the results of a study of the 5HT4-receptor status of human appendix and non-gastrointestinal abdominal and pelvic organs compared to human intestinal tissues.

The sponsor was also reminded of the previously agreed upon Phase 4 commitments consisting of:

- A long-term (1 year) maintenance study conducted in the US in women with C-IBS,
- []
- An epidemiologic study of sufficient number of women treated with the recommended dose of Zelnorm to address concerns about the risk of laparotomies, ovarian cysts and appendicitis.

On December 15, 2000, the sponsor submitted a complete response to the approvable letter. The submission included the results of a study (B358) of 1500 females, the updated ISS of 4500 patients, and the results of the receptor study.

Study B358 included 1500 female patients evenly randomized to placebo or Zelnorm 12 mg/d. The study was conducted in the US. Patients were treated for 12 weeks and observed for 4 additional weeks of no-treatment withdrawal period.

The primary efficacy variable was SGA of relief collected weekly. Secondary efficacy variables included weekly assessment of

abdominal pain/discomfort and bowel habit, daily assessment of abdominal pain/discomfort, bloating, and bowel habit.

All analyses for SGA of relief used the last 4 available weekly responses on treatment. Analyses of the diary data used daily scores obtained in the last 28 days on treatment. The primary analysis was done on ITT population.

Seventy-nine percent of patients in each group completed the double blind phase of the study. The reasons for discontinuation were similar in the two groups.

A statistically significantly greater use of laxative during baseline and during the withdrawal period was reported in the Zelnorm patients. Since exploratory analyses of background covariables was prespecified in the study protocol, adjustment for laxative use was performed on the analysis of SGA of relief. The response rate of SGA of relief adjusted for baseline laxative use was 43.5% in the Zelnorm group and 38.8% in the placebo group (p-value= 0.003).

However, the protocol specified unadjusted analysis did not reach statistical significance (p-value=0.059).

Serious AEs were reported in 9 (1.2%) Zelnorm and 5 (0.7%) placebo patients. A total of 84 patients discontinued study for AEs: 49 or 6.4% in the Zelnorm group and 35 or 4.7% in the placebo group. The most frequent AEs involved the GI tract, diarrhea was more frequent in the Zelnorm group most likely secondary to the PD effect of the drug.

Twelve patients in the Zelnorm group and 4 in the placebo group developed abdominal pain leading to abdominal/pelvic surgery; four patients in the Zelnorm group underwent laparoscopic cholecystectomy and 1 patient had appendectomy during the treatment period. One case of ovarian cyst was observed in each treatment group.

In conclusion, the efficacy results of SGA of relief from the three Phase 3 studies show statistically significant difference in favor of Zelnorm only in study B301. According to the Agency statistical reviewer's analysis, the results were not replicated in study B358. Study B358 was positive only if a less conservative analysis was performed by adjusting for laxative use and without corrections for multiple analyses.

The difference in responders' rates in study B307 and B358 were lower than in study 301. Of note, in study B301 the placebo response rate was lower, thus the difference between treatment

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Lilia Talarico
8/17/01 03:54:43 PM
MEDICAL OFFICER

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MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research**

DATE: 7/22/02

FROM: Joyce A Korvick, MD, MPH
DGCDP/ODE III

SUBJECT: **Director (Deputy) Summary Approval Comments
NDA 21-200**

APPLICANT: Novartis Pharmaceuticals Corporation

DRUG: Zelnorm™ (tegaserod)

DIVISION RECOMMENDATION:

The Division recommends approval of Zelnorm™ (tegaserod) for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation. The safety and effectiveness of Zelnorm in men have not been established.

The following phase 4 requests are recommended:

1. A randomized, double-blind, crossover, placebo-controlled study to assess the effects of tegaserod 6 mg bid on gallbladder motility and biliary tract diameter in healthy volunteers and of tegaserod 6 mg bid and tegaserod 12 mg bid on gallbladder motility and biliary tract diameter in female patients with IBS-C (constipation-predominant irritable bowel syndrome), as submitted February 28, 2002 (Gallbladder Mechanistic Study).
2. Zelnorm™ Epidemiological Study, a prospective cohort postmarketing surveillance study, to evaluate the frequency of gallbladder surgeries and other abdominal and pelvic surgeries and procedures, as submitted February 28, 2002.
3. A randomized, double-blind, parallel group, placebo-controlled study to evaluate the intermittent and/or long-term efficacy of Zelnorm™. (Protocol pending)

Regulatory History:

The original Zelnorm new drug application was submitted on February 11, 2000. It was granted priority review status since it would be the first agent approved for the indication of constipation-predominant irritable bowel syndrome. An advisory committee was held

on June 27, 2000, which recommend approval of Zelnorm. On August 11, 2000 an approvable letter was sent to the applicant. Issues that remained to be resolved included the need for an additional efficacy study, additional safety information regarding abdominal/pelvic surgeries, and results of a study of the 5HT₄-receptor status of human appendix and non-gastrointestinal abdominal pelvic organs compared to human intestinal samples. A complete response was submitted on December 15, 2000. This response included the results of an additional U.S. randomized, double blind study of Zelnorm in 1519 women. Because of the continued, unresolved safety issues and the small drug effect size, the risk/benefit of Zelnorm was considered unacceptable and a not-approvable letter was sent to the applicant on June 15, 2001. The applicant submitted a dispute resolution request on August 6, 2001 to the FDA Office of Review Management, CDER. On August 6, 2001 a letter was sent to the applicant denying the request, finding that unresolved safety issues reminded to be discussed between the review division and the applicant. On October 11, 2001 a meeting was held between Novartis and the review division to discuss these remaining issues and what might constitute a complete response to the not-approvable letter dated June 15, 2001. The meetings that followed centered around re-adjudication of the cases of abdominal/pelvic surgery in the phase 3 randomized trials of IBS-C. In addition, discussions regarding phase 4 requirements were held between Novartis and the review division. These lead to the filing of a complete response to the FDA on February 28, 2002. The current submission contained a safety update, proposed protocols for the Mechanistic Gallbladder Study, and an epidemiological study to be conducted post approval. The epidemiological study will explore the possible relationship between abdominal/pelvic surgery and Zelnorm.

Benefit/Risk:

Benefit

The development of Zelnorm for the treatment of IBS-C was challenging due to the waxing and waning nature of the condition, the type of endpoint utilized in the studies and the 12-week duration of treatment studied in a chronic condition. In an end-of-phase 2 meeting held with the applicant on December 9, 1996, the use of a randomized withdrawal study was recommended to the applicant in order to enhance the efficacy evaluation in this functional condition. This type of study design has been recognized by CDER to be useful in the evaluation of efficacy for functional conditions. The applicant's designs did not include a randomized withdrawal phase in any one of the pivotal studies.

During the first review cycle of the original NDA submission, the applicant submitted 3 randomized, double blind, placebo-controlled studies (#351, 301, 307). Study 351 was considered supportive due to the exploratory manner in which the efficacy results were utilized. This study provided the applicant and the FDA the opportunity to further specify and refine the primary endpoint, which was to be applied prospectively in the other pivotal trials. This primary endpoint was a composite of signs and symptoms: a Subject Global Assessment. Patients were classified as responders within a month if they had considerable or complete relief of symptoms for at least two of the four preceding weeks, or if they were at least somewhat relieved for each of the four preceding weeks. It

as felt that this type of endpoint was clinically meaningful and might suggest some durability of effectiveness. The studies were constructed to include a 4-week baseline period (no treatment) followed by a 12-week treatment period (placebo or 6 mg twice-daily dose of Zelnorm). The 12-week response was the protocol specified, primary endpoint. Study 351 showed a 5 % difference in responder rates that was not statistically significant. When analyzed with the new endpoint (post-hoc design) the results became statistically significant. This post-hoc analysis was considered supportive, but could not fulfill the requirement for two positive studies generally required for approval. Study 301 included patients from Europe, South Africa and the U.S., and it showed a 12-week responder rate of 28% (66/240) vs. 39% (95/244) for placebo and Zelnorm, respectively. The difference in responder rates of 11% was a statistically significant result. The other pivotal study that was submitted in this cycle was study 307. This study showed a 12-week responder rate of 38% (88/234) vs. 43% (100/233) for placebo and Zelnorm, respectively. The 5% difference in responder rate was not statistically significant. Study 301 was a positive study supporting the effectiveness of Zelnorm while study 307 was not. In addition, there were concerns that the response was greatest in the first month and that the difference in effect was diminished at the 12 week primary endpoint in each of these studies. This draws into question the durability of the long-term treatment effect of Zelnorm. Therefore, an additional efficacy study was requested at the end of the first review cycle.

Study 358 was submitted in the second review cycle. This was the largest of the four studies conducted. It included 1,519 women studied in the U.S. Study 358 showed a 12-week responder rate of 39% (292/752) vs. 44% (334/767) for placebo and Zelnorm (6 mg twice-daily), respectively. The 5% difference in rates was not statistically significant ($p=0.062$). This borderline p-value fluctuated depending on various adjustments that were made in the analysis. Additionally, while this study had a 4-week withdrawal period, this withdrawal period was not randomized or blinded, and the results were not helpful in determining the durability of effect. This study was not considered to be very strong. However, there was some small effect demonstrated.

As stated earlier, IBS-C is a functional condition and as such creates challenges to endpoint design. However, there is a biologically plausible mechanism of action regarding one aspect of IBS-C that is improvement in gastrointestinal motility. It may be that the primary endpoint that was studied does not adequately reflect the extent of effectiveness of this drug. While the results showed a small difference between Zelnorm and placebo in the 12-week endpoint, this difference was considered to be an adequate clinical effect upon which to base an approval recommendation by the Gastrointestinal Specialists in the review division as well as members of the Advisory Committee, the majority of whom voted for approval during the first cycle. Finally, small trends for improvement were seen in secondary symptomatic endpoints: abdominal pain/discomfort, bloating and increase in the median number of stools. In sum these results were considered supportive of the effectiveness in IBS-C. Since IBS-C is a non-life threatening condition and the benefit appeared to be small, consideration focused on the need to balance the risks in the approval decision. There were unresolved issues regarding the rare, but serious adverse events of abdominal and/or pelvic surgeries, which

were seen in a numerically greater rate in Zelnorm treated patients, compared to placebo treated patients. For these reasons the applicant received a non-approvable letter at the end of the second cycle.

Risk:

It is important to consider the mechanism of action of Zelnorm as it may also contribute to the adverse events of interest. Zelnorm is a 5HT₄-receptor partial agonist. This activity triggers the release of further neurotransmitters such as calcitonin gene-related peptide from sensory neurons. The activation of the 5HT₄-receptors in the gastrointestinal tract stimulates the peristaltic reflex and intestinal secretion as well as inhibits visceral sensitivity. During the first review cycle, 9 reports of ovarian cysts lead the division to focus on the possibility that ovarian cysts were related to treatment with Zelnorm as they occurred in 8 Zelnorm treated patients compared to 1 in placebo treated patient. Review of this issue in consultation with the Division of Reproductive and Urological Drug Products concluded that ovarian cysts are not associated with Zelnorm treatment. In several cases these cysts existed pre-study treatment.

During the second review cycle additional cases of abdominal and pelvic surgery were noted more frequently in the Zelnorm group compared to the placebo group (0.5% [12/2,446] vs. 0.1% [2/1,589], respectively). It is biologically plausible that patients might experience cystic duct or gallbladder contractions leading to exploratory surgery more frequently than IBS patients receiving placebo. Further complicating the issue is the high rate of cholelithiasis in women. It was hoped that the human histological study performed by Novartis might shed some light on the location of the 5HT₄-receptors in the gastrointestinal tract. Further information was requested at the end of the first cycle, but in the second submission it was stated that these biopsies were few and no conclusions could be drawn from this study. Given the increasing evidence regarding the imbalance of this adverse event between Zelnorm and placebo and the small difference in efficacy, as mentioned above, the second review cycle ended with a not-approvable letter because of an unacceptable risk/benefit.

Re-adjudication of the surgical events in the pivotal studies was undertaken subsequently. The applicant employed a blinded expert panel and the FDA reviewed additional clinical data on further clinical follow-up of cases. The result of these reviews and discussions between the sponsor and the applicant resulted in the following rates: FDA analysis found 0.30% (9/2965) in the Zelnorm group vs. 0.17% (3/1740) in the placebo group; Novartis analysis found 0.24% (7/2965) in the Zelnorm group vs. 0.23% (4/1740) in the placebo group. In the end, only 3 cases differed between the FDA and Novartis. This reduced the difference in rates between Zelnorm and placebo. It should be noted that these differences were never statistically significant, however, they were clinically relevant. The result of this re-adjudication has lessened the concern regarding excess cases of abdominal/pelvic surgery possibly associated with Zelnorm, but it has not eliminated it.

The GI Team Leader reviewed a safety update submitted to the final review cycle. There were 3 new cases of interest: a case of sphincter of Oddi spasm; a case of bile duct stone;

a case of cholestatic-hepatocellular effects. All of these cases were from the spontaneous reporting system. These effects make the mechanistic gallbladder study of particular interest.

Conclusions:

Considering the data for risk and benefit as outlined above, the Division feels that the efficacy data are sufficient for approval of Zelnorm (6 mg twice-daily) for short-term treatment (4-6 weeks), with and additional 4-6 weeks in those patients who have a favorable response in the first phase. The limitation to short term treatment is a recommendation as a result of the data that show the effectiveness of Zelnorm was greatest in the first month compared to the 12-week response. This benefit is balanced by a lessened, but continued, concern regarding the possible association of Zelnorm treatment with abdominal/pelvic surgeries. The division feels that it is acceptable to approve Zelnorm at this time with certain phase 4 commitments listed above. These commitments will address the prospective monitoring of abdominal/pelvic surgeries, a mechanistic gallbladder study to determine if Zelnorm increases gallbladder motility potentially leading to symptomatic cholelithiasis, and further study into the actual effectiveness and safety of long-term and/or intermittent therapy for IBS-C. Additional safety measures were taken in labeling recommendations (see below) including a patient package insert, a commitment by the applicant to refrain from direct to consumer advertising in the early marking period, and 15 day submission of cases of abdominal/pelvic surgery in the early post marketing period. These latter two activities will be discussed periodically with the division to determine if and when they can appropriately changed.

Labeling Recommendations:

Specific labeling recommendations included the following:

- The use of "short-term" treatment in the treatment indication section
- Contraindication in patients with a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions
- Precautions against taking Zelnorm in patients who are currently experiencing or frequently experience diarrhea. Immediate discontinuation in patients with new or sudden worsening of abdominal pain.
- Inclusion of the incidence of abdominal surgeries, including cholecystectomy in the ADVERSE REACTIONS section

Joyce A. Korvick, MD, MPH
Deputy Division Director
Division of Gastrointestinal and Coagulation Drug Products
ODE III/CDER
FDA

Note: The reader is referred to primary medical officer reviews as well as team leader memos from review cycles 1-3 for further detail.

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/s/

Joyce Korvick
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MEDICAL OFFICER

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— restrict labeling to a limited duration, and a year-long maintenance study to further study efficacy and safety. These were offered to manage risks of the drug to allow for immediate marketing approval. The company asked for an advisory committee on June 14, 2001, but this request came three days before the action date and it was denied because the meeting could occur after the action letter was issued. Novartis asked on June 15, 2002 to delay the action until after an AC meeting, but this was denied because the decision was ready to be made and, again, the meeting could occur after the decision was issued.

Novartis issued a formal dispute resolution notice to FDA on August 6, 2001 to the Office of Review Management, CDER. Action on the dispute resolution was denied because the company had not sought an end-of-review meeting with the division or office to work out disagreements as its first step. On September 26, 2001, the company requested a meeting with the GI division to go over the end-of-review issues. The meeting with the division and myself occurred on October 11, 2001. At that meeting, FDA proposed that the surgical cases be adjudicated by FDA and Novartis together. In addition, at the meeting a surveillance proposal by Dr. Alex Walker was found to be an acceptable epidemiologic approach post-marketing to track risks of the drug should issues relating to the NDA safety database be resolved. This surveillance proposal was submitted to FDA for comments, which were provided to Novartis by Office of Drug Safety. Over the next few months, adjudication (non-blinded) was concluded on the data using all cases of surgeries in the double-blind trials of at least 8-week duration that occurred since December 15, 2000. The numbers of cases on drug vs. placebo were as follows: FDA found 9/2965 (0.30%) cases of surgery in the drug group versus 3/1740 (0.17%) on placebo; Novartis found 7/2965 (0.24%) cases of surgery in the drug group versus 4/1740 (0.23%) on placebo.

Novartis' submission of February 28, 2002, contained the safety update, revised epidemiologic surveillance program, adjudication of cases as above, and proposed labeling.

Efficacy

The efficacy data are interpreted by FDA to show evidence for efficacy meeting Congress' intent of substantial evidence. The Second Senate Committee Report in 1962 states that differences of responsible opinions of experts qualified by training and experience will exist. There is more than a mere scintilla of evidence and responsible experts might accept what Novartis has presented as adequate, controlled human investigations demonstrating the drug does what it is purported to do. It is also true that other qualified and responsible experts would not accept the data base as evidence for efficacy.

The indication is for short-term use. The data suggest that efficacy wanes. The label clearly states in the trials section that the difference in response rates for drug and placebo was smaller by month 3. The studies were not designed to address the efficacy of this drug for acute exacerbation of IBS-c. I agree to truncating use of this drug after 4-6 weeks and having the company explore how to use this drug long-term. The latter will be done post-marketing because safety concerns are diminished.

The clinical trials section of the labeling clearly shows the results of the three prospectively analyzed data bases at 12-weeks, the defined endpoint of analysis, and confidence intervals. FDA agreed to the company's June 15, 2001 proposal to restrict duration of use in the Dosage and Administration section to 4-6 weeks, when effect size is maximal, with an option to consider another 4-6 weeks if patients responded. FDA requested the indications reflect "short term treatment" given the dosage and administration section. The data at one month (4 weeks) are presented. Because the endpoint variable is a monthly-calculated response, 6 week data (1.5 months) is not presented. 12 week (3 month) data are also presented. On July 10, 2002, FDA agreed to the company's July 9, 2002 proposal to study durability of drug effect and intermittent dosing by conducting Phase 4 studies.

Safety

Some patients will benefit from this drug. Others will do better on placebo with less adverse events. Some patients on drug will have diarrhea, which is the drug's pharmacologic effect. The possible increased risk of surgery with this drug needs further investigation. This will be done post-marketing because the numeric imbalance of cases may not be above the normal variation expected in these studies not powered for safety. For the efficacy to continue outweigh the safety risk should a serious risk, such as surgery, be confirmed, FDA has encouraged development of _____

In the not approvable letter of June 15, 2001, I stated

However, given the disagreement between Novartis and FDA on the numbers of surgical cases and their possible association with Zelnorm, and given the importance of the indication and unmet medical need, readjudication of safety cases was acceptable to pursue. This readjudication lessened the difference between drug and placebo crude incidence for surgical cases and allowed the conflicting evidence for efficacy to be acceptable in light of the safety cases. On January 14, 2002, June 19, 2002, June 26, 2002, and June 28, 2002 in a t-con with Dr. Mathias Hukkelhoven, I stated to Novartis that given the evidence for efficacy is marginal, the effect size is small, the indicated population is very broad, including non-serious patients, the risk-benefit profile is vulnerable to safety concerns. I stated careful marketing of the drug and careful safety monitoring are needed. On January 14, 2002 I suggested at the industry meeting that the surveillance study include some endpoint of benefit to address possible risks uncovered.

The current safety review by Dr. Gallo Torres and the previous ones by Dr. Raymond Joseph are noted for the record. The GI division still has "lingering" concerns about the safety of the drug. The Phase 4 mechanistic study meets the terms of the June 15, 2001 not approvable letter because the study will clarify the role of Zelnorm in the risk of biliary effect and symptoms. This study can be done post-marketing because the safety concern is diminished. Office of Drug Safety has accepted the surveillance protocol, which I also reviewed and commented on. This study will assist in quantifying the risk of surgery in Zelnorm users compared to non-users and meets the terms of the June 15, 2001 not approvable letter. This study is being done post-marketing because the concern for safety has diminished. Labeling contains the adverse events of drug-induced diarrhea and the cases of surgery found in the Phase 3 databases, although causality of surgery is not established. FDA was concerned about claims of ' _____ ' that were proposed in labeling and deleted them. Use of those words would be exceptionally promotional to the GI community, long awaiting a replacement for Propulsid (withdrawn because its indication of treating nocturnal heartburn did not outweigh risk of tachyarrhythmia and sudden death from QT prolongation) and would fuel off-labeled use in a time when marketing needs to further confirm safety.

Novartis marketing officer Mr. Kurt Graves stated on June 19, 2002 that it was not the manufacturer's intention to do DTC until the post marketing surveillance data were reviewed and safety was confirmed. DTC was discussed again on July 3, 2002 in a labeling teleconference call. Novartis restated the above and said that Novartis would "talk" to FDA prior to going DTC. This "talk" was clarified to be contact with the review division prior to a DTC submission to DDMAC. Mr. Graves and Dr. Hukkelhoven were asked by me to explain how and when would "safety be confirmed" in post-marketing and if this "confirmation" could be agreed upon between FDA and Novartis prior to DTC because FDA wanted to include these statements in the approval letter for Zelnorm. In the July 9, 2002 letter from Dr. Hukkelhoven, Novartis states "we understand FDA's perspective on early DTC for Zelnorm and we are fully committed to maintaining our ongoing collaboration with FDA on matters relating to Zelnorm. It is in the spirit of understanding and our continued cooperation with FDA that we indicate our intent not to initiate DTC for Zelnorm during the initial launch phase for the product." "Initial launch" was clarified on July 16, 2002 by Mr. Graves to mean within the first 4-6 months of commercial release. This was agreed to and reiterated in the approval letter.

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