CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-200

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-200

Trade Name Zelnorm Generic Name tegaserod maleate

Applicant Name Novartis Pharmaceuticals HFD-180

Approval Date July 24, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X/

   If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /_X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /_**X**_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_**X**_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_**X**_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_**X**_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_ **X** _/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_ **X** _/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are

there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/ 7/26/02

Signature of Preparer Date

Title: Project Manager

/S/ 7/26/02

Signature of Office or Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

NOVARTIS

Novartis Pharma AG
Basel, Switzerland

Zelmac™ (Tegaserod)

Patent Information

Author(s):	Donna Vivelo
Document type:	Registration
Document status:	Final
Release date:	November 19, 1999
Number of pages:	2

APPEARS THIS WAY
ON ORIGINAL

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for

NDA # 21-200

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	Zelmac™
Active Ingredient(s):	Tegaserod
Strength(s):	2 mg and 6 mg
Dosage Form:	Tablets

A. U.S. Patent Number: 5,510,353

Expiration Date: April 26, 2013

Type of Patent: Compound per se, pharmaceutical composition/formulation and method of use in treating irritable bowel syndrome (IBS)

Patent Owner: Novartis AG
Lichtstrasse 35 CH-4002
Basle, Switzerland

B. The undersigned declares that the above U.S. Patent Number 5,510,353 covers the pharmaceutical composition, formulation and/or method of use of Zelmac™ (tegaserod). This product is the subject of this application for which approval is being sought.

Signed: _____

Zelmac ™ (tegaserod) Tablets
New Drug Application

Debarment Certification

NOVARTIS PHARMACEUTICALS CORPORATION hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

Donna M. Vivelo Date 1/12/00

Donna M. Vivelo
Associate Director
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

1801 LEVINE.

Executive CAC
May 23, 2000

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Ron Steigerwalt, Ph.D., HFD-510, Alternate Member
Al DeFelice, Ph.D., HFD-120, Rotation Member
Jasti Choudary, B.V.Sc., Ph.D., Supervisory Pharmacologist
Ke Zhang, Ph.D., Presenting Reviewer

Author of Draft: Ke Zhang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #: 21,200
Drug Name: Zelmac / SDZ HTF 919
Sponsor: Novartis Pharmaceuticals Corporation.

Background: Zelmac (SDZ HTF 919) is a 5-HT_4 receptor agonist for treatment of constipation-prone irritable bowel syndrome. Zelmac is currently under review in NDA 21,200. There are two oral (in diet) carcinogenicity studies (mouse and rat) submitted in this NDA. SDZ HTF 919 was negative in the mutagenicity studies including *in vitro* chromosome aberration test in Chinese hamster V79 cells, unscheduled DNA synthesis test in rat hepatocytes, a forward mutation assay at HGPRT locus in Chinese hamster V79 cells, and mouse micronucleus test. However, SDZ HTF 919 increased the colonies by 2 fold or (nearly 2-fold) in several assays using the TA1538 (frame shift) strain in the absence of S9 at 75 µg/plate. In this study, SDZ HTF 919 was negative in other frame shift strains of Salmonella typhimurium including TA1537 and TA98. Different batches of SDZ HTF 919 were also tested in Ames tests in five strains of Salmonella typhimurium (TA97a, TA98, TA100, TA102, and TA1535) and the results were negative. In the forward mutation assay in Chinese hamster V79 cells (V79/HGPRT), both frame shift and base substitutions can be detected and SDZ HTF 919 was negative in this study.

Mouse Carcinogenicity Study:

In this study, CD-1 mice (60/sex/group) were treated with SDZ HTF 919 in diet at 0, 60, 200 and 600 mg/kg/day for 2 years. The survival was not affected by the treatment. The terminal body weight was 96, 93 and 81.4% (males) or 94.3, 90.3 and 78% (females) of the control in the low, mid and high dose groups, respectively, suggesting that the high dose of 600 mg/kg/day exceeded MTD. Food consumption was not affected. The treatment with SDZ HTF 919 at high dose produced the

mucosal hyperplasia (8 males and 7 females) and adenocarcinoma (6 males and 2 females) in the small intestine in the high dose group (none in the control, low and mid dose groups). This study is acceptable. On a body surface area basis, the dose of 600 mg/kg/day (1800 mg/m^2/day) is ~203 times the recommended human dose (12 mg/day or 8.88 mg/m^2/day). The ratio of AUC values (parent compound) of mouse ——— ng.h/ml at 600 mg/kg/day at week 4) to human (20.1 ng.h/ml at 12 mg/day) is ———

Rat Carcinogenicity Study:

In this study, SDZ HTF 919 was given to HanIbm Wistar rats (50/sex/group) in diet at 0, 20, 80 and 180 mg/kg/day for 110 weeks (females) or 124 weeks (males). The terminal body weight was 96.5, 88.6 and 75.5% (males) or 93, 86 and 72% (females) of the control in the low, mid and high dose groups, respectively, suggesting that the high dose of 180 mg/kg/day exceeded MTD. The food consumption was slightly lower (11-12%) in the high dose group as compared the control. The mucosal hyperplasia in the small intestine was found in 2 control males and 5 high dose animals (4 males and 1 female). In the original report, the incidence of ovarian cysts (bursal, follicular and luteal) was significantly increased in the treated females as compared to the concurrent control. Subsequent evaluation did not reveal any treatment-related increase in the incidence of ovarian cysts. The treatment with SDZ HTF 919 increased the incidence of benign haemangioma in mesenteric lymph nodes in males (7, 14, 17, 18, and 21 of 50 animals per group in the control1, control2, low, mid, and high dose groups, respectively). The mean background incidence of this tumor was 19.4% (range: 14.5-28% from 8 contemporary studies). The tumor incidence in all treatment groups exceeded the historical values. Sponsor did not consider this was treatment related based on a literature report from studies conducted at least 10 years earlier. (Lymphangioma of the mesentieric lymph nodes was up to 73% in male HanIbm Wistar rats according to a paper reported in Expl. Bio., Med., Vol: 7, pp. 63-71, 1982). It is felt this is not an appropriate comparison group, given the contemporary control data available.

The study is acceptable. The dose of 180 mg/kg/day (1080 mg/m^2/day) in rats is ~122 times the recommended human dose. The ratio of AUC values (parent compound) of rat ——— ng.h/ml at 180 mg/kg/day at week 4) to human (20.1 ng.h/ml at 12 mg/day) is ———

Executive CAC Recommendations and Conclusions:

1. The Committee found that treatment with SDZ HTF 919 produced the mucosal hyperplasia and adenocarcinoma in the small intestine in

mice at the high dose of 600 mg/kg/day.

2. The Committee had a concern over the higher incidence of benign haemangioma in mesenteric lymph nodes in males in the rat study. It was further recommended that whole body haemangioma and haemangiosarcoma be evaluated with statistical analysis. The Division has requested the sponsor to provide the above information along with historical control data for benign haemangioma and haemangiosarcoma (whole body count) in the testing laboratory during 1992 to 1995.

/S/ 06/02/00

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
/Division File, HFD-180
/HFD-181/CSO
/Dr. Choudary, HFD-180
/Dr. Zhang, HFD-180
/ASeifried, HFD-024

APPEARS THIS WAY
ON ORIGINAL

NDA 21-200

Zelnorm (tegaserod maleate) 2, 6 mg Tablets

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant:

Novartis Pharaceutical Corp.
One Health Plaza
East Hanover, NJ 0736-1080

Indication: Treatment of constipation predominant irritable bowel syndrome

Presentation: Blister package of 10 per card/60 per carton

EER Status: Acceptable 26-JUN-2000

Consults: ODS – Tradename: Zelnorm- acceptable 27-JUN-2002
Statistics – none
EA – no consult - waiver requested – granted

CMC Phase IV Commitments: none

The original NDA was received 11-FEB-2000

Note that this is CMC review cycle 3 – following the last review there was an approval recommendation.

The **drug substance** is manufactured by:

Novartis Pharma Inc.
Shuaffhauserstrasse
CH-4332 Stein, SZ

Novartis Pharma Inc.
CH-4002
Basel, SZ

The manufacturing process is well defined and in-process controls are adequate.

Structural characterization of the drug substance was satisfactory. Specifications were found acceptable. Impurities and degradation products were well studies and are

adequately controlled. A re-test period of 18 months is supported by submitted stability data. The stability testing protocol is considered adequate.

Conclusion
Drug substance is acceptable.

The **drug product** is formulated as 2 and 6 mg tablets.

Manufacturer:

Novartis Pharma Inc.
Shuaffhauserstrasse
CH-4332 Stein, SZ

Adequate in-process controls are in place. The proposed regulatory specifications are acceptable including impurities The dissolution test and acceptance criteria were found acceptable by OCPB . Stability data support the proposed 36 month expiry. The stability testing protocol is considered adequate.

Deficiencies were all resolved in the course of the previous review cycles.

The overall Compliance recommendation is acceptable as of 26-JUN-2000.

All associated DMFs are acceptable.

Conclusion
Drug product is acceptable

Overall Conclusion
From a CMC perspective the application should be approved.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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

/s/

Eric Duffy
7/24/02 03:03:25 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

A claim for categorical exclusion from the Environmental Assessment requirements under 21 CFR 25.31(b) - Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph - if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 ppb.

As set forth in 21 CFR Part 25.31(b) [Federal Register, Volume 62, Number 145, dated July, 29, 1998], action on a New Drug Application is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb). "Increased use", as defined in 21 CFR Part 25.5(a), will occur if the drug is "administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity."

Novartis Pharmaceuticals Corporation certifies that this submission for Zelmac 2 mg and 6 mg tablets qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as the concentration of the active moiety, tegaserod hydrogen maleate, will be (significantly) less than 1 ppb.

Further, Novartis Pharmaceuticals Corporation states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21200/000
Stamp: 11-FEB-2000
Regulatory Due: 11-AUG-2000
Applicant: NOVARTIS PHARMS
59 RT 10
EAST HANOVER, NJ 079361080
Priority: 1P
Org Code: 180

Action Goal: 09-AUG-2000
District Goal: 12-OCT-2000
Brand Name: ZELMAC(TEGASEROD HYDROGEN MALEATE)2/6MG
Estab. Name:
Generic Name: TEGASEROD HYDROGEN MALEATE

Dosage Form: (TABLET)
Strength: 2 MG AND 6 MG

Application Comment:
FDA Contacts: P. LEVINE JR (HFD-180) 301-827-7310 , Project Manager
R. FRANKEWICH (HFD-180) 301-827-7310 , Review Chemist
L. ZHOU (HFD-150) 301-594-5765 , Team Leader

Overall Recommendation: ACCEPTABLE on 26-JUN-2000 by M. EGAS (HFD-322) 301-594-0095

Establishment: 2416082
NOVARTIS PHARMA INC (CIBA)
OLD MILL RD
SUFFERN, NY 10901

DMF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: TCM OAI Status: NONE
Estab. Comment: [redacted] WILL NOT BE PERFORMED AT THE SUFFERN, NY FACILITY. PACKAGING OF THE DRUG PRODUCT IN [redacted] CONFIGURATIONS [redacted] BLISTERS) WILL BE PERFORMED AT THIS FACILITY. (on 08-MAR-2000 by R. FRANKEWICH (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAR-2000				FRANKEWICH
OC RECOMMENDATION	08-MAR-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: 9692043
NOVARTIS PHARMA INC (CIBA)
SCHAFFHAUSERSTRASSE
CH-4332 STEIN, , SZ

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
Profile: TCM OAI Status: NONE
Estab. Comment: THE DRUG PRODUCT WILL BE MANUFACTURED AND TESTED FOR RELEASE AT THIS SITE. THIS SITE IS ALSO AN ALTERNATIVE SITE FOR THE [redacted] OF THE DRUG SUBSTANCE. (on 08-MAR-2000 by R. FRANKEWICH (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAR-2000				FRANKEWICH
SUBMITTED TO DO	08-MAR-2000	PS			DAMBROGIOJ
ASSIGNED INSPECTION	09-MAR-2000	PS			EGASM
DO RECOMMENDATION	26-JUN-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
OC RECOMMENDATION	26-JUN-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 2210396
NOVARTIS PHARMA INC (SANDOZ)
59 RT 10
EAST HANOVER, NJ 079361080
DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAR-2000				FRANKEWICH
OC RECOMMENDATION	08-MAR-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: 9611204
NOVARTIS PHARMA INC (SANDOZ)
CH-4002
BASEL, , SZ
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
Profile: CSN OAI Status: NONE
Estab. Comment: DRUG SUBSTANCE MANUFACTURING, [redacted] AND TESTING TAKES PLACE AT THIS SITE. (on 08-MAR-2000 by R. FRANKEWICH (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAR-2000				FRANKEWICH
SUBMITTED TO DO	08-MAR-2000	PS			DAMBROGIOJ
DO RECOMMENDATION	20-MAR-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
BASED ON EI OF 8/28/98					
OC RECOMMENDATION	20-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 9612715
NOVARTIS PHARMA INC (SANDOZ)
RINGASKIDDY/CORK, RINGASKIDDY, EI
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
Profile: CTL OAI Status: NONE
Estab. Comment: THIS IS AN ALTERNATIVE SITE FOR TESTING OF THE DRUG SUBSTANCE. (on 08-MAR-2000 by R. FRANKEWICH (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAR-2000				FRANKEWICH
SUBMITTED TO DO	08-MAR-2000	10D			DAMBROGIOJ
DO RECOMMENDATION	20-MAR-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
BASED ON EI OF 10/23/98					
OC RECOMMENDATION	20-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 9614433
NOVARTIS PHARMANALYTICA SA
LOCARNO, , SZ

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAR-2000				FRANKEWICH
SUBMITTED TO DO	08-MAR-2000	GMP			DAMBROGIOJ
DO RECOMMENDATION	09-MAR-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
BASED ON EI OF 3/98					
OC RECOMMENDATION	13-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment

DMF No: AADA:
Responsibilities:
Profile: OAI Status: NONE
Estab. Comment: THIS FACILITY WILL (on 07-MAR-2000 by R. FRANKEWICH
(HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAR-2000				FRANKEWICH
OC RECOMMENDATION	08-MAR-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

APPEARS THIS WAY
ON ORIGINAL

Demographic Worksheet

Application Information *(Enter all identifying information for the submission pertaining to this summary)*

NDA Number: 21-200 **Submission Type:** N/A (pilot) **Serial Number:** N/A (pilot)

Populations Included In Application *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

Category		Number Exposed To Study Drug		Number Exposed To Study Drug		Number Exposed To Study Drug
Gender	Males	ca. 1,152	All Females	ca. 10,364	Females >50	Not calculated
Age:	0-≤1 Mo.	None	>1 Mo.-≤2Year	None	>2-≤12	None
	12-16	None	17-64	ca. 9,638	≥65	ca. 684
Race:	White	ca. 88%	Black	ca. 8%	Asian	Not calculated
	Other	ca. 4%				

Gender-Based Analyses *(Please provide information for each category listed below.)*

Category	Was Analysis Performed?				Was gender-based analysis included in labeling?	
			If no is checked, indicate which applies or provide comment below		Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☒
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☒

Is a dosing modification based on gender recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒Sponsor ☒FDA

Age-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?				Was age-based analysis included in labeling?	
			If no is checked, indicate which applies or provide comment below		Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☒
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐

Is a dosing modification based on age recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒Sponsor ☒FDA

Race-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?				Was race-based analysis included in labeling?	
			If no is checked, indicate which applies or provide comment below		Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☒
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☒

Is a dosing modification based on race recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒Sponsor ☒FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:

a) In the I & U Section the statement that S + E of Z in men have not been established, is included.; b) Total # of patients studied, by age, is included under Geriatric Use. Also under subpopulation: there is a paragrapgh stating that no age effect on the PK of tegaserod. ; c) Under subpopulations, a statement that data were inadequate to assess the effect of race on the PK of tegaserod, has been included.

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

/s/

Hugo Gallo Torres
7/24/02 01:24:17 PM

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-200 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: February 28, 2002 **Action Date:** July 24, 2002

HFD 180 **Trade and generic names/dosage form:** Zelnorm (tegaserod maleate) Tablets

Applicant: Novartis Pharmaceuticals, Inc. **Therapeutic Class:** 1P

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: **"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."**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☑ **No: Please check all that apply: ____Partial Waiver __X__Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ **kg**____ **mo.**____ **yr.** 17 **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.** 0 **Tanner Stage**____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☑ **There are safety concerns**
- ☑ **Adult studies ready for approval**
- ☑ **Formulation needed**

Other:____

Date studies are due (mm/dd/yy): January 2, 2004

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

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

/s/

Paul Levine
7/25/02 10:25:14 AM
CSO

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21200	**Trade Name:**	ZELMAC(TEGASEROD HYDROGEN MALEATE) 2/6MG
Supplement Number:		**Generic Name:**	TEGASEROD HYDROGEN MALEATE
Supplement Type:		**Dosage Form:**	Tablet; Oral
Regulatory Action:	AE	**Proposed Indication:**	for the treatment [redacted] female patients with irritable bowel syndrome (IBS). The safety and effectiveness of Zelmac in men have not been established.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Infants (1-24 Months)
_X_Other Age Groups (listed): [redacted]
____Children (25 Months-12 years)
____Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
07/24/00 - Studies will be requested in response to PPSR submitted March 27, 2000.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, PAUL LEVINE

/S/ 8/9/00

Signature Date

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Levine

Food and Drug Administration
Rockville MD 20857

SEP 5 2000

Dr. med. Christiane Klein
Osterhofenerstr. 5
94550 Künzing
Germany

Dear Dr. Klein:

Between June 13 and June 15, 2000, Ms. Linda S. Leja, representing the U.S. Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # HTF-B301-E-00) of the investigational drug, Zelmac (tegaserod) tablets, performed for Novartis Pharmaceuticals Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

We understand that your study was not conducted under a U.S. Investigational New Drug Application. However, from our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent U.S. Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Leja during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Levine

Food and Drug Administration
Rockville MD 20857

AUG 17 2000

Peter Haeck, M.D.
Boerhaaverstraat 1
Stadskanaal 9501 HE
Netherlands

Dear Dr. Haeck:

Between June 19 and June 22, 2000, Ms. Linda S. Leja representing the U.S. Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # HTF-B301-E-00) of the investigational drug, Zelmac (tegaserod), performed for Novartis Pharmaceuticals Corp. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent U.S. Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Leja during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855 U.S.A.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Levine

Food and Drug Administration
Rockville MD 20857

AUG 17 2000

Italo Fumagalli, M.D.
Via Della Pace 3
6600 Locarno, Switzerland

Dear Dr Fumagalli:

Between June 26 and June 29, 2000, Ms. Linda S. Leja representing the U.S. Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # TF-B301-E-00) of the investigational drug, Zelmac® (tegaserod) performed for Novartis Pharmaceuticals Corp. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections, designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to pertinent U.S. Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Leja during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855 U.S.A.

APPEARS THIS WAY
ON ORIGINAL

Levine

MEMORANDUM

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

DATE: July 17, 2000

/S/ 07/24/00

FROM: Hugo E. Gallo-Torres, M.D., Ph.D., Medical Team Leader
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 21-200 - ZELMAC™ (tegaserod; HTF 919):
Recommendations for Regulatory Action

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

/S/ 7-25-00

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

With this memorandum justification for our recommendation for regulatory action for NDA 21-200 - Zelmac™ (tegaserod) is transmitted. We hope you will concur with our recommendation for approval.

I. INTRODUCTION

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder seen by physicians. IBS is characterized by a number of clinical features and varying severity of symptoms which wax and wane. The most frequent symptom reported by IBS patients is abdominal pain but, for a number of patients, bowel disturbances are the most prominent symptoms. These disorders are believed to result from dysregulation of intestinal motor, sensory, and CNS function (brain-gut dysfunction). This results in increased sensitivity to painful distentions in the small bowel and colon. The numerous neurotransmitters found in brain and gut that have effects on pain control, GI motility, emotional behavior and immunity include: the enkephalins, substance P, calcitonin gene-related peptide, nitric oxide, **5-HT**, cholecystokinin and others. Approaches involving 5-HT are but one of many possibilities of intervention.

The diagnosis of IBS is a **diagnosis of exclusion**. Now-a-days, the preferred approach is identification of IBS using positive symptom criteria (ex. the Manning criteria, the Rome criteria) and a limited diagnostic screen. Four symptomatic subgroups are recognized, depending on the predominant symptom(s): constipation (C-IBS), diarrhea (D-IBS), alternating constipation/diarrhea (C/D-IBS) and pain/gas/bloating. The duration of exacerbations and remissions for these clinical presentations has not been adequately studied but it is customary **to recommend clinical trials of 12-week duration**. Until recently, no drug had been found efficacious in IBS. Efficacy and safety were recently demonstrated with LOTRONEX™

(alosetron hydrochloride; GR68755), a 5-HT_3 receptor antagonist, for the treatment of female patients with **D-IBS**. In NDA 21-200, Novartis has presented evidence of ZELMAC™ efficacy and safety in the treatment of female patients with **C-IBS**.

ZELMAC™ (tegaserod, HTF 919) is a partial agonist at serotonin type 4 (5-HT_4) receptors, characterized as an oral GI pro-motility agent that stimulates peristaltic reflex and intestinal secretion as well as inhibits visceral sensitivity. The sponsor's NDA submission was granted priority review.

II. JUSTIFICATION FOR PRIORITY REVIEW

Novartis PharmaG requested and was granted, accelerated review of NDA 21-200. In granting this request, the Division considered that, in comparison to existing therapies, tegaserod represents a significant therapeutic advance (with an apparently acceptable profile) as a first line monotherapy for the significant population of female patients with constipation predominant IBS. In short, no commercially available agent in the United States has been shown to have proven efficacy in the treatment of women with C-IBS.

III. BRIEF REVIEW OF THE EVIDENCE IN NDA 21-200

Only certain items are highlighted here. A more detailed review of the evidence submitted by the sponsor is found in the separate reviews by different disciplines: Medical (Dr. R. Joseph), Statistics (Dr. S. Castillo), Biopharm. (Dr. Doddapanini) and Pharmacology/Toxicology (Dr. K. Zhang). In the present secondary review, clinical issues, based on Drs. Joseph and Castillo reviews, are emphasized.

A. EFFICACY

As explained in both the MO and the statistical review after post-hoc analysis of study 351, an additional protocol amendment was submitted before breaking the blind in studies 301 and 307. The **new** subject Global Assessment (SGA) of relief definition of responder was:

> **"completely relieved" or "considerable relieved" for at least 50% of the last 4-weeks of treatment, or at least "somewhat relieved" for all of the last 4 weeks of treatment**

It is worth noting that the Division found it **acceptable** to add the somewhat relief category to the definition of responder. As explained by Dr. M. Camilleri, the sponsor's consult, this category is clinically meaningful because it captures an event (IBS manifestation) that is happening in an eminently subjective fashion 100% of the time. It is also noted that the SGA of relief became the only primary efficacy variable since the SGA of abdominal discomfort/pain was changed from a primary to a secondary efficacy variable. As explained in Dr. Castillo's statistical review (July 6, 2000, page 6), the sponsor's rationale for eliminating the SGA of abdominal discomfort/pain as a primary efficacy variable and retaining it as a secondary efficacy

variable was that there are inherent problems with the use of the VAS. This is a plausible explanation. The reliability of the VAS as a tool to measure efficacy outcome in many although not all situations is being questioned. This is especially true in those situations where the therapeutic gain is not very large. There are inherent patient potential difficulties in translating the experimental subject's experiences to the scale. There are also constraints when attempting to define clinically/statistically meaningful response on the VAS.

The comments and conclusions are based mainly, although not exclusively, on the response to the primary efficacy parameter summarized in Table 1. It is realized that these conclusions are not based on the initially stipulated protocol analyses. However, it must be stated that, even in the year 2000, tools to satisfactorily assess efficacy of drugs in C-IBS are **still under development and yet to be standardized.**

In addressing the general issue of tegaserod's efficacy in the treatment of C-IBS, this reviewer attempts to answer a set of seven questions.

1. **Was efficacy demonstrated?**

- YES

This conclusion is supported by the voting at the June 26, 2000 meeting of the AC in answer to the question: has efficacy been demonstrated in both men and women with constipation predominant IBS?

Men: YES 0 NO 8 Women: YES 6 NO 2

2. **Recommended claim(s)-indicated population(s)?**

- Efficacy has been demonstrated only in women.
- The recommended claim is for the treatment of irritable bowel syndrome in women who identify _____ constipation as their predominant symptoms.
- Efficacy has not been demonstrated in men.

3. **How shown? (What were the major trials and endpoints, statistical significance?)**

Using proportion of subjects with global assessment of relief (**new definition**), efficacy was demonstrated in Study 301. Both the 2 mg b.i.d. and the 6 (or 2 to 6) mg b.i.d. dose levels were shown statistically to be significantly different from placebo, with a p-value of 0.028. These data in pivotal study 301 are supported by a post-hoc analysis of study 351 for the 6 (or 2 to 6) mg b.i.d. dose level, but not replicated in study 307 (Table 1).

For the 6 (or 2 to 6 mg) b.i.d. dose, the dose recommended by this reviewer, the majority of results of secondary efficacy variables, derived from daily diary data at endpoint (ITT population), also demonstrate efficacy (Table 2). This Table shows results from pivotal study 301 and supportive study 351. For simplification of presentation purposes, results for the

2 mg b.i.d. dose (not the recommended dose) and those from Study 307 (inconsistent results and generally recognized as a negative trial) are not included in this Table.

TABLE 1
NDA 21-200
Proportion of Subjects With Global Assessment of Relief
(New Definition)[a]

Study	Tegaserod (mg b.i.d.)		PL	Therapeutic gain[b] [p-value][c]	
	2	6 or 2 to 6		2 mg vs PL	6 or 2 to 6 mg vs PL
351	40%	45%	32%	7% [N.S.]	13% [0.008]
301	39%	38%	30%	9% [0.028]	9% [0.028]
307	38%	42%	37%	1% [N.S.]	5% [N.S.]

From S. Castillo, Ph.D., Statistical Review and Evaluation, July 6, 2000
a: At least 50% of the SGAs at endpoint with COMPLETE or CONSIDERABLE relief or all (100%) of the SGAs at endpoint with at least SOMEWHAT RELIEF (i.e. complete, considerable or somewhat).
b: Responder rate with tegaserod minus (-) responder rate with PL.
c: p-value adjusted using: Hochberg's multiple comparison procedure adjusting for two doses in studies 351, 301 and 307 for the new definition of SGA of Relief.
NOTE: Six patients are not included in the ITT population of study 307 and only United States centers are included in the ITT population of study 351.

In pivotal study 301 and supportive trial 351, for the parameter at least "somewhat relieved" for SGA of relief (ITT population) the effects of tegaserod (Fig. 1) **persisted** for the 12-week duration of the trial.

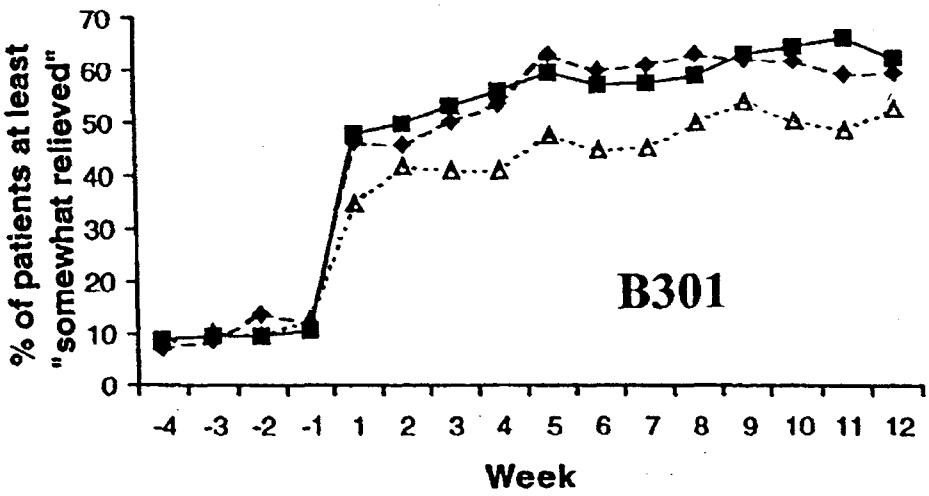
The effects of the drug on secondary parameters of efficacy were **consistent** with those observed with the primary efficacy parameters. These effects were exemplified by two clinically important secondary efficacy parameters depicted in Fig. 2, a) the weekly number of bowel movements (upper panel) and b) the weekly mean stool consistency (lower panel).

TABLE 2
NDA 21-200

Secondary Efficacy Variables Derived from Daily Diary Data at Endpoint
(ITT Population)

VARIABLE	STUDY 301		STUDY 351	
(Mean percent change from baseline in)	Tegaserod 6 or 2 to 6 mg b.i.d.	PL	Tegaserod 6 or 2 to 6 mg b.i.d.	PL
SIGNIFICANT PAIN[a]	-18.6% [N.S.][c]	-10.4%	-16.9% [0.017]*	3.9%
SIGNIFICANT BLOATING[a]	-8.3% [N.S.]	4.0%	-15.1% [0.006]*	-5.6%
NO BOWEL MOVEMENTS[a]	-22.5% [0.013]*	-19.2%	-31.2% [0.002]*	-21.4%
BOWEL MOVEMENTS[a]	54.6% [0.009]*	42.0%	69.3% [<0.001]*	44.8%
HARD OR VERY HARD STOOL[a]	13.7% [N.S.]	15.0%	11.3% [0.003]*	18.9%
CONSISTENCY SCORE BETWEEN 3 and 5[a]	69.8% [0.009]*	76.0%	76.3% [N.S.]	74.3%
NORMALIZED BOWEL HABIT[b]	65.5% [N.S.]	68.9%	76.6% [N.S.]	69.1%

a) Assessed either as number or days, or number of days with the secondary variable
b) Proportion of patients with
c) p-value (nominal p-value) are presented for the comparison between the tegaserod dose and placebo at endpoint
* Indicates a statistically significant difference compared to placebo based on Holm's multiple comparison procedure, adjusting for two doses, at significant level of <0.05.



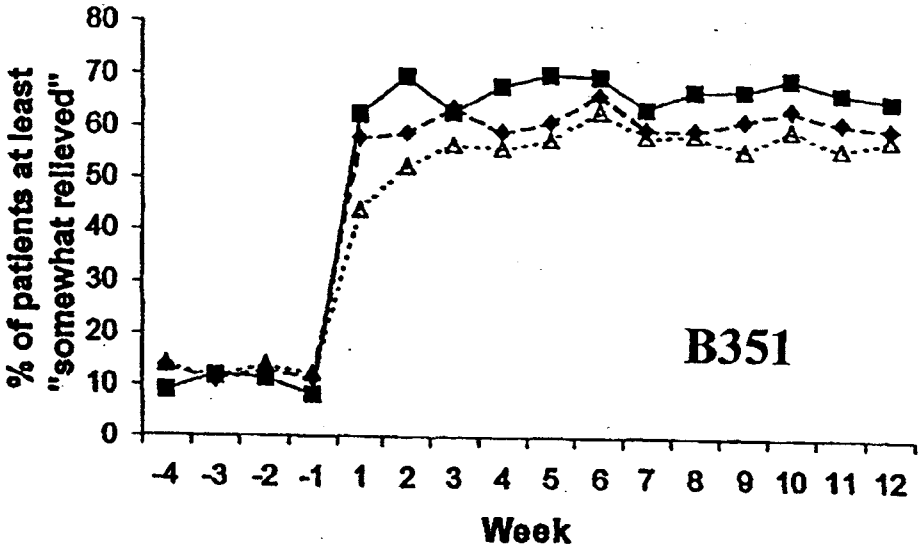


Fig. 1. - Weekly percentage of patients with at least "somewhat relieved" for SGA of relief (ITT Population).
Upper panel = Study 301
Lower panel = Study 351

4 mg/d — 12 mg/d — placebo

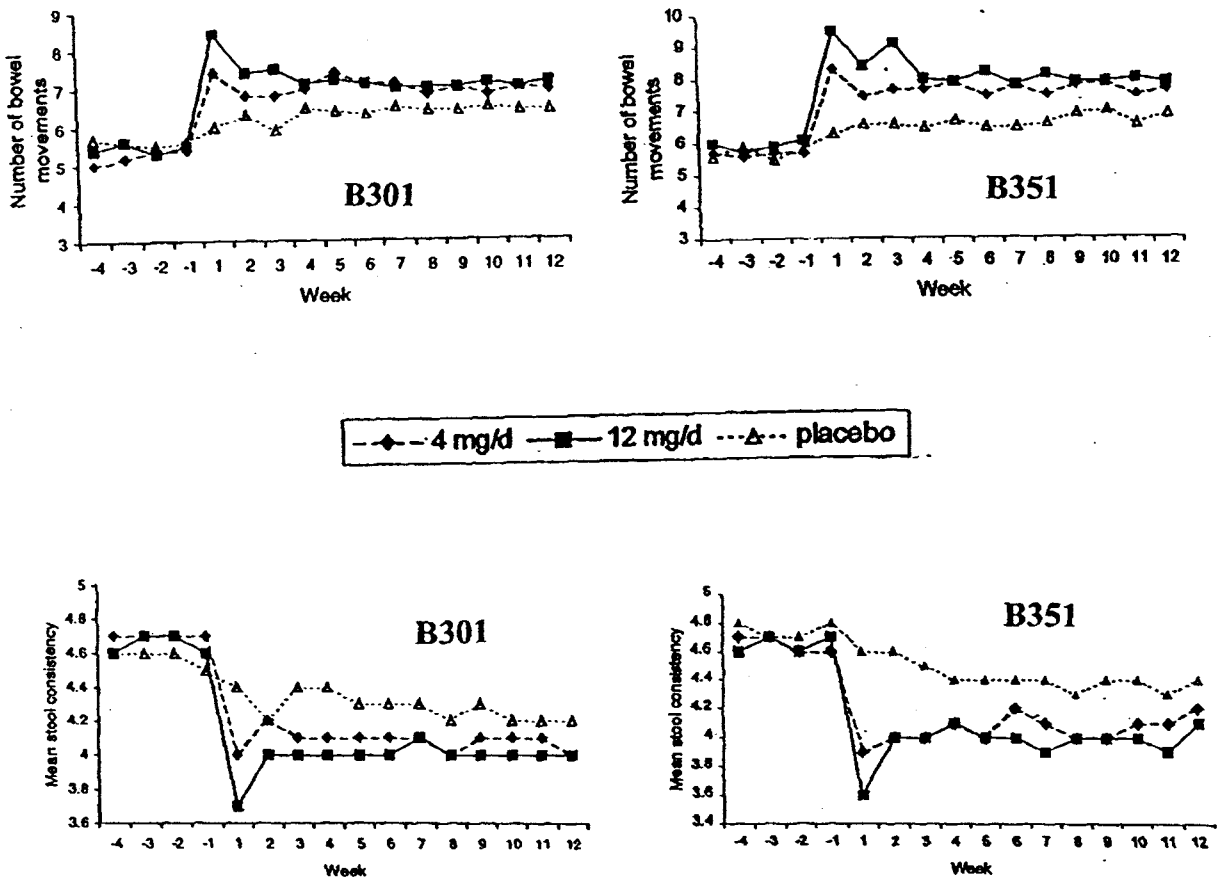


Fig 2. - Effects of tegaserod on secondary parameters of efficacy. Number of Bowel Movements (Upper Panel) and Mean Stool Consistency (Lower Panel)

4. Size of treatment effect?

For the recommended dose level, the size of treatment effect [therapeutic gain, defined as responder rate with tegaserod minus (-) responder rate with PL, Table 1] was 9% in pivotal study 301 and 13% in supportive trial 351. A smaller clinically insignificant therapeutic gain (5%) was seen in pivotal study 307; this difference from placebo was not statistically significant.

5. Relationship of studied endpoints to patient benefit - was only one aspect of the disease studied?

The endpoints studied were very much related to patient benefit and, essentially, attempted to cover all main aspects of C-IBS. As explained in Dr. Castillo's statistical review (JUL 6, 2000; page 4-5), the patient recorded all efficacy assessments in a diary. Three weekly assessments - Subject Global Assessment (SGAs) of relief, abdominal discomfort/pain and bowel habit - and four daily (intensity of abdominal pain/discomfort, intensity of bloating, frequency of bowel movements and average stool consistency) assessments were made by the patient throughout the 16-week study duration.

For the main efficacy outcome, **SGA of relief**, the patients responded weekly to the following question:

> ***"Please consider how you felt this past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain and altered bowel habit. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during the past week?"***

Answers:

COMPLETELY RELIEVED		**CONSIDERABLY RELIEVED**
SOMEWHAT RELIEVED	**UNCHANGED**	**WORSE**

In addition, the definition of responder took into account: a) the number of days with laxative use during treatment period is $\leq$5 and no laxative use during the last 28 days of treatment; b) duration of exposure to test medication is $\geq$28 days and c) at least one post-baseline SGA of relief.

All in all, fifteen secondary efficacy variables were analyzed (Dr. S. Castillo's Statistical Review and Evaluation, JUL 6, 2000, page 8).

6. How does efficacy relate to other drugs available for indication?

IBS is the most common functional gastrointestinal disorder seen by general physicians. IBS is characterized by a number of clinical features and probably comprises a cluster of different conditions. Although the most frequent symptom reported by IBS patients is abdominal pain, for a number of patients, bowel disturbances are the most prominent symptoms.[1] The symptoms of

[1] [M. Delvaux, J. Frexinos. A European Approach to Irritable Bowel Syndrome Management. Can. J. Gastroenterol. 13Suppl.A: 85A-88A (1999)].

IBS wax and wane. Although consensus has not been reached, research to date indicates that symptoms of IBS are generated by quantitative differences in motor reactivity of the gut and increased sensitivity to stimuli (distension) or spontaneous contractions. There is also increased sensitivity to normal intestinal function (e.g. spontaneous migrating motor complexes), as well as an increased or unusual area of somatic referral of visceral pain.[2]

There is no "gold standard" treatment for IBS. No commercially available agent in the United States has been shown to have proven efficacy in the treatment of C-IBS. Specifically, in constipated female IBS patients, no agent has been shown to be of proven benefit in the treatment of the patient's most bothersome symptoms of abdominal pain, associated with constipation [decrease stool frequency and/or increased stool consistency (harder stools)].

One of the major obstacles to demonstrate drug efficacy in IBS is the **high placebo response rate** in these patients. Although not clearly differentiated between C-IBS and D-IBS or alternating IBS, this placebo response has been reported to vary from 30% to 88%, according to the AGA.[3] Strictly speaking, a number of agents in the US are labeled for the treatment of IBS or symptoms of IBS. Most are described as **"adjunctive treatment"** while others, such as LIBRAX (a combination of the antidepressant Librium with the anticholinergic clinidium bromide) have the qualifier that they are **"possibly effective"**. This reflects the market introduction of these products prior to establishment of the current regulatory standards for providing substantial evidence of effectiveness. In a recent review article, M. Camilleri[4] concluded that current therapies targeted on the predominant symptoms of IBS (meaning diarrhea, constipation, or abdominal pain/bloating) are **"moderately successful"**. It is also of interest to mention Marvin M. Schuster's statement in another recent review article.[5]

It is to be noted that, in February 2000, Glaxo Wellcome received approval of LOTRONEX™ (alosetron hydrochloride) oral tablets, administered twice-a-day for up to 12 weeks, for the treatment of IBS in women over 17y of age whose predominant bowel symptom is diarrhea (D-IBS). Alosetron is a 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist. As indicated in Dr. David Hoberman's Statistical Review and Evaluation of NDA 21-107 for LOTRONEX™, according to the pivotal protocols (S3BA3001 and 3002), the **primary clinical endpoint** was the patient's weekly response in a diary to the question:

> ***"In the past 7 days, have you had adequate relief of your Irritable Bowel Syndrome pain discomfort (YES/NO)?"***

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[2] Because the mechanisms of central interpretation of afferent signals are not known, it is also not known whether psychological or neurophysiological mechanisms work singly or together in the perception of incoming signals.

[3] [Gastroenterology 112:2120-2137 (1997)].

[4] [M. Camilleri. Review article: clinical evidence to support current therapies of irritable bowel syndrome. Aliment. Pharmacol. Ther. 13 Suppl 2: 48-53 (1999)].

[5] **"given the many visceral afferent innervations and the even greater complexity introduced by the dynamic interaction of these factors (both of which remain poorly understood) - it is easy to see why no effective treatment for IBS has yet evolved".**

In NDA 21-107, the primary analysis compared the number of **"monthly responders"**.[6] Both pivotal trials (S3BA3001 and SB3A3002) provided statistically significant evidence that alosetron is active in the relief of pain/discomfort IBS in women (primary endpoint). Both trials suggested that the treatment differences is manifested by the number of patients who responded in all 3 months. Ca. 40% of patients who started the trial on alosetron achieved adequate relief for all 3 months, whereas for patients assigned to placebo the proportion was 25 **[therapeutic gain=15%]**.

7. Issues with effectiveness - how resolved?

At his presentation to the June 27, 2000 AC, the Medical Officer listed the following efficacy issues, which were amply considered by members of the committee: a) pain was not adequately assessed as an efficacy endpoint [this was also listed as one of the two "inadequacies" in Dr. Castillo's Statistical Review], b) overall difference between drug and PL group is 8%; c) efficacy in males not established; and d) potential "confounding" effects of laxatives. To these, this reviewer adds a fifth issue (e) tegaserod response as a function of geographical location and f) a sixth, lack of response in study 307.

a) Pain is indeed an essential component of IBS. When analyzed independently, no statistically significant difference was seen in pivotal studies 301 and 307. However, when pain was analyzed **as a component of SGA of relief** along with well-being and altered bowel function, a clinically relevant approach to assess effects on pain, abdominal pain was statistically significant for the assessments in pivotal study 301 and supportive study 351.

b) Although the overall difference between drug and PL was *ca.* 9%, this difference increased when the data were analyzed as a function of gender. This was shown with both dose levels of tegaserod and in both pivotal study 301 and supportive study 351 [only data for the recommended dose (6 or 2 to 6 mg b.i.d.) are displayed]:

Subject Global Assessment of Relief

Tegaserod	Study 301		Study 351	
(mg b.i.d.)	Overall	Women Only	Overall	Women Only
6 or 2 to 6	9% [0.028]	12% [0.012]	13% [0.008]	15% [0.004]

Source: Table 5.1 (page 17) vs Table 5.4 (page 20) in Dr. S. Castillo's Statistical Review and Evaluation. Depicted are the therapeutic gains (tegaserod vs placebo) and the corresponding adjusted p-values.

The observed 12% therapeutic gain in pivotal study 301 and 15% in supportive study is not only statistically significant (p=0.012 and 0.004, respectively) but

[6] Defined as patients who indicated "adequate relief" for at least 2 weeks out of the month. Thus a patient could be a responder for any of months 1, 2 or 3

also clinically meaningful. This is because the patients in these clinical trials had long-standing recalcitrant disease, which makes it difficult to show efficacy.

c) The proportion of male patients included in the clinical trials averaged only 15%. The response to Zelmac™ in this gender group was not different compared to placebo. This lack of differentiation from placebo may be due to an inadequate sample size. In addition this finding raises the question of whether C-IBS is different in males.

d) It is theoretically possible that the use and timing of laxatives may influence the response of the SGA of relief. In the clinical trials, laxative use, including bulking-agents, was allowed. Although there was similar qualitative consumption between the tegaserod group and placebo, the issue of concomitant laxative use is somewhat unsettled. This is because quantitative differences - which may arise in spite of a well-executed randomization process - may affect outcome in constipation study patients.

e) In the clinical trials, the proportion of patients as a function of geographic location, is summarized in Table 3.

TABLE 3

STUDY	DOSE (mg/day)[a]	Geographic Location (% of patients)
I. Phase II dose-ranging		
B251 [n=547]	–24	US (54%) Europe (43%), Canada
II. Phase III Efficacy/Safety		
B351 [n=799]	4, 12	US (97%), Canada
B301 [n=881]	4, 12	Europe (90%), US, S. Africa
B307 [n=845]	4, 4-12	US (66%), Europe (32%), Canada
III. Long-term Safety		
B209 [n=579]	4-12	Europe (50%), US (41%), Canada

Source: Novartis' Briefing Document to AC meeting of June 27, 2000, EF3.

a) Divided into two daily doses.

One consideration is whether efficacy in the US population has been demonstrated, being that in B307, a negative study, two-thirds of the patients originated from the US while 32% came from Europe. A member of the GIAC - one of the two who did not recommend approval of the drug - suggested an additional clinical study in the US. The efficacy results in relation to the data displayed in Table 3, can be summarized as follows. As pointed out in

Dr. Joseph's MOR (page 20), from Study B251 (54% of patients from US), it was concluded that there was consistency between the data in the SGA and the diary variables. In this trial, the – mg/d dose was not differentiated from placebo; 4 mg/d appeared to be an effective dose; the dose-response was flat over the 4 mg/d to 24 mg/d dose-range. In supportive study B351, 97% of the patients came from the US. Although the bulk of the patients (90%) in pivotal study B301 were from Europe, there is no reason to suspect that C-IBS among American patients is different from Europeans. No pronounced differences in the proportion of women and men with IBS are found when comparing US [redacted] to European populations [redacted] [Table 1 in Dr. Joseph's MOR, page 3].

f) There are no plausible explanations for the lack of response to tegaserod in pivotal study 307, just conjectures. In this trial, the placebo response was highest compared to the other two. During the June 27, 2000 AC meeting it was commented that 307 may have had a faulty design. It was speculated that titration of the dose from 4 to 12 mg/d may prime the 5-HT_4 receptor with the lower dose. This phenomenon would blunt the response to the higher dose. As a consequence, one would not get the same efficacy results shown when one starts with the 12 mg de novo.

B. SAFETY

1. Adequacy of safety testing: number of exposed patients/duration?

The procedures to gather, assemble, analyze and report adverse events and related safety information were all adequate. The number of C-IBS patients exposed as well as the duration of exposure is summarized in Table 4. In the Integrated Summary of Safety (ISS) plus the 120 day Safety Update, the number of patients treated exceeded those recommended in the ICH efficacy guideline E1A.[7]

[7] International Conference on Harmonization efficacy guideline E1A: The extent of population exposure to assess clinical safety: For drugs intended for long-term treatment of non-life-threatening conditions (March 1995).

TABLE 4
Summary of Exposure
C-IBS patients
(studies of ≥12 week duration)[a]

	ISS	ISS + 120 day SU	Total Subjects Exposed[b]
Total number	2665	2892	3737
Treated ≥ 6 mo.	418	826[c]	826
Treated ≥ 12 mo.	185	187[d]	187

a) This constituted the key safety population.
b) Includes subjects from all completed studies.
c) These patients were treated for 180 days; the exposed number exceeds the ICH number of 300-600 to detect an event with a frequency of ≥0.5%.
d) In the ISS, 302 of these patients were treated for 335 days. The exposed number exceeds the ICH number of ≥100 to detect an event with a frequency of ≥3%,

The clinical studies contributing safety data included the two Phase II trials (B251 and B202), the three Phase III studies (B351, B301 and B307) and long-term studies of either ≥6 mo. or ≥12 mo. duration. In the ISS the number of patients receiving at least 6 months treatment was 418; in the 120 day SU, this number was increased by 408 [total=826]. Disposition of these patients was as follows.

- 80% to 84% of patients completed the Phase III trials as planned; 6.8% of tegaserod-treated patients discontinued treatment because of AEs compared with 5.1% in the PL group. There was no evidence of a dose response.

- The proportion of patients completing Phase II trials was similar to those of the Phase III trials (discontinuation due to AEs, tegaserod=8.3%; PL=9.3%). The AE-related discontinuation rate (1.9%) was lower in the tegaserod – mg/day group than in the other dose levels drawn from Phase II Study B251 (8% to 10%).

- In the long-term (L-T) trials in IBS, the completion rate was lower at 39%. This was partly due to the premature termination of B204. In study B209, which was completed as planned, 54% of the patients completed the trial. Overall, in the two studies combined, 10% of patients discontinued because of AEs.

2. Serious side effects? Discuss frequency. Monitoring recommendations.

One death (suicide /147/001) in the tegaserod 4 mg/day group in study B301 was unrelated to tegaserod.

When all completed studies are considered, the frequency of serious adverse events (SAEs) was 2.05% (70/3510) in the tegaserod group and 1.5% (18/1185) in the PL group. This difference is to be expected because of the longer duration of exposure in many tegaserod patients. As

pointed out in Dr. Joseph's MOR (page 85), in the pooled Phase II or III studies the incidence of SAEs with tegaserod was similar to that seen with PL:

	Incidence of SAEs	
Studies Pooled	Tegaserod	PL
Phase II	1.9%	3.3%
Placebo	1.8%	1.6%

Laparotomies are discussed later in this review. The MOR (page 85) gives a detailed description of the distribution of SAEs per organ system. Dr. Joseph points out that GI disorders were the most frequently reported SAEs and that these consisted mostly of recognized symptoms of IBS considered serious because the patients had to be hospitalized for a diagnostic work-up. In his review of the SU, Dr. Joseph gives a detailed appraisal of events occurring in L-T studies B301-E-01 and B307-E-01, all of which had already been described in the ISS.

3. Common side effects? Frequency?

As pointed out in the MOR by Dr. Joseph, in the **Phase III trials**, the most frequently reported AEs were either GI symptoms which would be expected in IBS patients (abdominal pain, diarrhea, nausea, flatulence, dyspepsia, constipation) or general disorders (such as headache or back pain). Diarrhea was more frequent in the tegaserod than in the PL group (11.75 vs 5.4%; $p<0.0001$].

In the **Phase II studies**, similar although slightly higher AEs predominated perhaps due to more frequent visits (every 2 weeks in study B251) and duration longer than 3 months (26 weeks in study B202). Abdominal pain, headache, nausea and dizziness occurred at similar frequencies among tegaserod-treated patients in comparison to those receiving PL. But the frequency of diarrhea (28% vs 15%) or flatulence (16% vs 11%) was higher in those given tegaserod.

The **L-T studies** showed AEs at similar frequencies and types as those observed in the Phase II-III studies.

4. Relationship of side effects to known animal toxicity?

As mentioned above, with tegaserod, the most frequently reported AEs were either GI symptoms, which would be expected in IBS patients or general disorders, such as headache or pain. These manifestations are not related to known animal toxicity, but the observed diarrhea may be an exaggeration of the main pharmacological effects of the drug. Tegaserod stimulates the peristaltic reflex and intestinal secretion and inhibits visceral sensitivity. *In vivo* pre-clinical studies have shown that the drug enhances basal motor activity and normalizes impaired motility throughout the GI tract.

5. Drug-drug interaction potential? How manageable?

As pointed out in Dr. Joseph's MOR, page 13, studies with human liver microsomes indicated a very low potential of tegaserod to inhibit CYP2C8, -2C9, -2C19, -2E1 and -3A4. More effects

seemed to be mediated by CYP1A2 and -2D6 but further studies conducted using these izoenzymes did not reveal clinically relevant drug-drug interactions. According to these observations, the major circulating metabolite of tegaserod did not show any potential for inhibition of cytochrome P450 isoenzymes *in vitro*.

6. Exposure in trials vs probable marketing exposure-duration and magnitude? Is the ratio adequate?

The duration of exposure in the pivotal clinical trials [B301, B307 and B351] was only 12 weeks (preceded by a 4-week run-in period). Although this is the length of time usually recommended to demonstrate efficacy in IBS trials, once available in the market the drug is likely to be taken for longer periods of time. This is because IBS is a very chronic condition [the patients in the tegaserod pivotal clinical trials had had IBS for 10y or more]. In addition, the design of the pivotal clinical trials did not include a follow-up (no drug treatment) observation period after discontinuation of the drug. There is no information about how quickly do the IBS constipation and abdominal pain symptoms return in these patients and whether - as proposed by some observers - there might be a rebound effect once the drug is discontinued. This is why, a post-approval one-year maintenance trial, details to be agreed upon with the sponsor, is recommended.

The efficacy/safety ratio is acceptable.

7. Effect of trial exclusions on safety profile vs expected marketed population?

By necessity, patients with diseases/conditions that affect bowel transit and those planning to use drugs or agents that affect GI motility and/or perception, were not included in the clinical trials. Examples of the first are gastric, small bowel or colonic resection, history of colon cancer, diabetes mellitus (insulin dependent and/or associated with neuropathy), known history of inflammatory bowel disease, Hirschsprung's disease, scleroderma, etc. In the clinical trials, colonoscopy or sigmoidoscopy [plus double-contrast barium enema if patients were >50y of age], performed no longer than 5y prior to screening, was an entry requirement. Some incidental GI pathology is to be expected if patients with normal but old (>5y) colonoscopic/ sigmoidoscopic findings are prescribed the drug. Drugs that affect GI motility and/or perception that were not allowed in the clinical trials but that patients may be taking when tegaserod is prescribed include: prokinetics (such as metoclopramide), erythromycin (accelerates gastric emptying), opioids (although in the clinical trials, sporadic use of codeine-containing analgesic was allowed), anticholinergics, 5-HT_3 antagonists (ondansetron, granisetron, dolasetron), antispasmodics (e.g. peppermint oil, mebeverine), serotonin re-uptake inhibitors and tricyclic antidepressants (although - at "constant doses" - these were allowed throughout the trials). When given concomitantly with tegaserod and perhaps depending upon the dose, etc. it would not be surprising that some of these drugs may interact with this C-IBS drug.

8. Recommended warnings?

NONE

9. How does safety relate to other drugs available for indication?

Strictly speaking, no other drug has been shown of proven efficacy for the treatment of C-IBS. Therefore, this consideration does not seem to apply.

10. Unresolved safety issues?

This reviewer hesitated to discuss **laparotomies** under the heading of "unresolved safety issues" but it seems that a secondary review without addressing this issue might be incomplete. A more appropriate heading for this topic might be "lingering concerns". These lingering concerns are regarding lower abdominal pain leading to laparotomy occurring in greater proportion among patients receiving ZELMAC™. In his MOR (pages 86 to 90) Dr. Joseph addresses the subject of ovarian cysts. An introduction is followed by a list of medications associated with ovarian cyst formation and a detailed description of 9 cases in the original submission, reported in apparent association with tegaserod **[n=8]** in comparison to PL **[n=1]**. Of these, 5 of the tegaserod cases but not the PL case, underwent surgery. All of these 5 (3 in L-T study 209 and 1 each in study 307 and 351) received tegaserod 12 mg/day. Each one of these cases was carefully examined by the MO who concluded that ovarian cysts may not be related to drug as cause and effect. This reviewer agrees with this conclusion. A consult from Urology arrived at the same conclusions. The sponsor submitted feedback from a medical expert in endocrinology, Dr. Bruce Carr, Professor and Director of the Division of Reproductive Endocrinology at the Southwestern Medical Center, Dallas who concluded that the reported cases of ovarian cysts are due to different etiologies and are considered unrelated to test medication. The issue was further discussed at the June 27, 2000 AC meeting on ZELMAC™ at which time Dr. Carr, invited by the sponsor, addressed the issue. Dr. Carr concluded that there was no treatment-related ovarian cysts in rat toxicity studies up to 6 months, in dog toxicity studies up to 12 months or in mouse carcinogenicity study or after reevaluation in the rat carcinogenicity study. He pointed out that there was no histopathological evidence of hormonal perturbation in any studies. Dr. Carr also examined the issue of tegaserod and laparotomies. He mentioned that a) in the study population, a variety of different gynecological and GI disorders led to laparotomies; b) the frequency of laparotomies by exposure duration was similar for tegaserod and placebo; and c) that there was no obvious causal relationship or signal that tegaserod affects the frequency of laparotomy.

In spite of all these explanations by the sponsor and his consultant and the fact that the AC viewed this as not a problem, this reviewer shares the MO's lingering concerns. It is worth noting that some of the laparotomies were due to **appendicitis** while others were the result of **adhesions**. Although the latter are relatively common, appendicitis is less and less common in the US. Due to these lingering concerns, a large post-approval, **epidemiologic study** to monitor laparotomies in possible association with tegaserod administration is recommended.

C. Dosing

The dose-response curve is relatively flat over the 4 to 24 mg/d range. According to the sponsor, the recommended dosage of Zelmac™ (tegaserod hydrogen maleate) is 6 mg po b.i.d. taken just prior to a meal. Dr. Jospeh agreed with this recommendation. This reviewer notes that this tegaserod dose is adequately supported by results of pivotal study B301 and supportive trial B351.

There are no unresolved dosing issues.

D. Special Populations

As discussed under III. A, above, tegaserod demonstrated efficacy for females only. These findings should be reflected in the indication section of the labeling. Males, races other than Caucasian and the elderly were not appropriately represented in the clinical trials. There is no need for dose adjustment in patients with renal disease. The drug should be used with caution in patients with moderate or severe hepatic impairment.

IV. RECOMMENDATIONS FOR REGULATORY ACTION

Tegaserod (Zelmac™) is a partial agonist at serotonin type 4 (5-HT_4) receptors, characterized as an oral GI pro-motility agent that stimulates persistaltic reflex and intestinal secretion as well as inhibits visceral sensitivity. In agreement with Dr. R. Joseph's recommendation, this reviewer is recommending that tegaserod be approved for the treatment of C-IBS, in women whose primary bowel symptom is constipation. This recommendation is based on the MOR review of the evidence presented by the sponsor and the findings on efficacy and safety summarized in the present memorandum where answers to 7 important questions regarding efficacy and 10 questions related to safety are provided. This approach allows a global efficacy assessment to be compared with the properly characterized safety profile of the drug.

Most aspects of tegaserod efficacy and safety seem clear at this point. It is effective only in females with C-IBS. Using the new primary efficacy parameter definition, (a patient's global assessment that included overall well-being, abdominal pain and altered bowel function) the therapeutic gain (against placebo) is not very great (9% to 15%). Nonetheless, tegaserod is undoubtedly differentiated from placebo. The efficacy effects are sustained and supported by multiple clinically important secondary efficacy variables. The very convincing results of pivotal study B301 are supported by those from study B351. This therapeutic gain is not dissimilar to that seen with the recently approved drug for the treatment of D-IBS in women.

Tegaserod is also safe and well-tolerated. Safety evaluations were adequately addressed in the key safety population. The few SAEs reported occurred in a similar proportion of patients as in the placebo group. Most of these involved the GI tract and consisted mostly of recognized symptoms of IBS. In Phase III trials, the most commonly reported AE was diarrhea [tegaserod=11.7%; placebo=5.4%; p<0.0001]. This safety information has been addressed in the labeling. The latter, as well as recommended Phase IV studies are addressed separately.

In this reviewer's opinion, the totality of evidence is in favor of the drug for efficacy. The safety ratio is still acceptable. No major issues remain unresolved.

We hope that we have provided sufficient information to justify an approval action.

July 24, 2000

/S/

Hugo E. Gallo-Torres, M.D., Ph.D.
Medical Team Leader

cc:
NDA 21-200
HFD-180
HFD-180/LTalarico
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-181/PLevine
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APPEARS THIS WAY
ON ORIGINAL