

Division of Gastrointestinal and Coagulation Drug Products

MEDICAL OFFICER'S REVIEW OF
SAFETY UPDATE

NDA: 21-200

DATE SUBMITTED: February 28, 2002

SPONSOR: Novartis Pharmaceuticals Corporation
East Hanover, NJ

DRUG: Zelnorm™ [tegaserod maleate] Tablets

PHARMACOLOGICAL CATEGORY: A partial agonist at the serotonin type
4 [5-HT₄] receptors

FORMULATION/ROUTE
OF ADMINISTRATION: Tablets for Oral Administration

PROPOSED INDICATION: Treatment of Constipation-predominant
Irritable Bowel Syndrome (CP-IBS) in
female patients

MATERIAL REVIEWED: Complete Response Package to the
June 15, 2001 non-approvable letter,
including:

- Index
- Draft Package Insert^a/Patient Package
Insert/ Packaging Components^b
- Safety Update of 02/28/2002
- Post-Marketing Surveillance Study
Protocol entitled "Zelnorm
Epidemiological Study"
- Gallbladder Mechanistic Study
protocol/Amendment I
- Risk Management Plan for Zelnorm

a,b) These and Case Report Forms for
Deaths, SAEs and AE Dropouts were
provided in electronic format

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HFD-180

Zelnorm™ [tegaserod maleate] tablets**Review of Safety Update**

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Zelnorm (tegaserod maleate) tablets

Medical Officer Review of 02/28/02 Safety Update

Executive Summary

This review was based on additional safety data received after the sponsor's submission of the Integrated Summary of Safety Update, submitted December 15, 2000. The previous review was that of the June 9, 2000, 120 day Safety Update (SU), which included the ISS in the original NDA. The cutoff date of the present SU is January 15, 2002. Summarized and assessed is information from a) newly completed studies; b) ongoing studies; and c) post-marketing reporting from non-U.S. countries [as of January 25, 2002 tegaserod has been approved for marketing in 18 countries and launched in 4]. The target safety population is women with constipation-predominant IBS (CP-IBS) who were treated with tegaserod for 12 weeks or more in completed studies. Other patients evaluated had conditions such as

A total of 63 studies are complete. There has been little change since the last SU in the database of the CP-IBS in completed D-B trials (12/15/00) SU, n=3659; 02/23/08 SU, n=3670; by now the total number of subjects exposed is 5632. SAEs, dropouts due to SAEs were considered first.

The overall frequency of SAEs in double-blind trials is 1.6% for tegaserod and 1.2% for placebo (unchanged from that reported in the December 2000 SU). For CP-IBS patients, the frequencies of SAEs are similar for tegaserod and placebo (1.6% and 1.1%, respectively). For CP-IBS patients AE dropouts, reported from the Phase III clinical trials, are 7.0% vs. 5.2%. For overall discontinuations due to AEs, the frequency (8.6% vs. 5.6%) is slightly higher dropout rates than reported in the December 2000 SU, due to higher dropout rates seen in the functional dyspepsia trials. From the RCT experience, the most frequently observed AE, were headache (tegaserod = 15%, placebo = 12%) and diarrhea (tegaserod = 11.7%; placebo = 5.4% p < 0.0001).

The emphasis of this review is on the occurrence of abdominal and pelvic surgeries. The information summarized in Appendix 1 shows that these surgeries have been reported in a variety of patient populations, with no consistent pattern. The clinical summaries in Appendix 2 reveal no consistent pattern of events preceding the surgeries as well as a lack of common pathogenesis among these cases. These observations reconfirm those of Dr. Raymond Joseph in his primary review of the original NDA and the medical team leader's (MTL's) secondary review of the numerical imbalance of abdominal and pelvic surgeries between tegaserod and placebo. These observations have been to source of lingering concerns for the medical officer (MO) and MTL. Additional constraints when interpreting these data are: a) abdominal surgical interventions are undeniably increased in this patient population b) although detectable in numbers, the occurrence of those surgeries is not high enough to support the conclusion that **no trend** appears to exist; and c) the difference between tegaserod and placebo has never been statistically significant [although, in reality, this difference does not need to be statistically significant to be of concern].

Although the sponsor disagrees, there is uncertainty and continuing concerns about whether the reported occurrence of surgeries represent a true safety signal that may become a problem once the drug is available and used indiscriminately. These concerns persist, even though the incidence of surgeries was reduced following agreements reached in the re-adjudication meeting, held November 20, 2001, between the Division, the sponsor and the sponsor's consultants. In that meeting, a basic criteria for adjudication was agreed upon. The final re-adjudication of the surgeries was based on the sponsor's newly released information. The re-adjudication process was difficult because it was clear that Novartis did not agree with its own consultants on the adjudication of several of the cases. The Division and the sponsor agreed on the initial adjudication of 9 cases. The sponsor changed its opinion in 5 (Tegaserod = 358/76/24 and 251/42/7; placebo=351/518/19, 251/18/1 and 358/61/23). The Division changed its opinion in 3 (Tegaserod = 358/23/29 and 358/122/4; placebo=358/43/4). At the end, there were 3 cases (Tegaserod =301/112/9 and 358/75/7; placebo= 358/112/22) in which the Division and the sponsor could not agree on. The final number of cases were reduced by the adjudication process but there is still a **numerical imbalance** in the incidence of surgeries: tegaserod, 9/2965=0.30%; placebo, 3/1740 = 0.17%, still p: N.S. **It is not known whether this is a true safety signal or not.**

Our **lingering concerns** may be substantiated by three new reports 1) a case of **sphincter of Oddi spasm**; 2) a case of **bile duct stone** and 3) a case of **cholestatic-hepatocellular** effects, all three from the spontaneous reporting system. These cases are significant because they are **biliary tree adverse events** in apparent association with tegaserod administration.

Randomized Clinical Trial data cannot answer the important question of whether the incidences of surgeries/cholecystectomies represent a **true safety signal**. The Division proposed Post-Marketing epidemiologic evaluations more than 1 ½ years ago that might be useful in answering questions about the significance of these surgeries. The sponsor has agreed to conduct the Division's proposed studies and has proposed a Post-Marketing Survey and a study entitled "Zelnorm Epidemiologic study", which are being reviewed by the Office of Drug Safety (ODS). In addition, the sponsor is currently performing a gallbladder mechanistic study, for which the protocol was submitted previously to the Division for comment and found by the MTL to be adequate.

I. BACKGROUND/INTRODUCTION

Tegaserod is a selective 5-HT₄ receptor partial agonist with promotility effects in the gastrointestinal (GI) tract of experimental animals and humans. Tegaserod is intended for the treatment of constipation-predominant (CP-) irritable bowel syndrome (IBS). The original NDA was submitted on February 11, 2000 and was granted priority review. After review of the evidence from Phase III randomized clinical trials (RCTs) involving patients with CP-IBS, the Medical Officer reviewer Dr. Raymond Joseph, concluded that tegaserod was effective, safe, and well-tolerated and recommended approval of the drug. On June 27, 2000, the Gastrointestinal Advisory Committee gave a positive recommendation for approval. From the RCT experience, the most frequently observed AEs were headache (tegaserod = 15%; placebo = 12%) and diarrhea (tegaserod = 11.7%; placebo = 5.4%, $p < 0.0001$). In his review, Dr. Joseph discussed "**lingering concerns**" regarding lower abdominal pain leading to laparotomy occurring in greater proportion among patients receiving tegaserod than those given placebo. The following was noted at the June 27, 2000 AC meeting:

- a) in the study population, a variety of different gynecological and GI disorders lead to laparotomies;
- b) the frequency of laparotomies by exposure duration was similar for tegaserod and placebo; and
- c) there is no obvious causal relationship or signal that tegaserod affects the frequency of laparotomy.

In agreement with Dr. Joseph's recommendation, the GI Medical Team Leader (MTL) recommended that tegaserod be approved for the treatment of CP-IBS, in women whose primary bowel symptom is constipation. Due to the already mentioned lingering concerns, a large post-approval **epidemiologic study**, to monitor laparotomies in possible association with tegaserod administration was recommended. Tegaserod received an approvable action letter on August 11, 2000. On December 2002, included in a resubmission were results of **Study 358**, which, although showing a not very impressive Δ between the drug and placebo confirmed the efficacy of tegaserod. Dr. Joseph observed a numerical imbalance in the frequency of **cholecystectomies** in patients with CP-IBS. These findings:

- a) have not been frequent enough to be considered trends;
- b) occurred with an incidence that appeared to be within the range expected in this patient population, and
- c) were not (and have never been) statistically significant different

Nonetheless, the occurrence of these events has been given very special attention by all parties involved in the review of the safety profile of tegaserod (See below).

On June 15, 2001 tegaserod received a not approvable letter for reasons that included a numerical imbalance of abdominal surgeries on tegaserod vs. placebo which may reflect

a safety signal and the fact that the risk/benefit profile of the drug could not be established to the Agency's satisfaction. On August 6, 2001, the sponsor submitted a formal dispute resolution request to the Office of Review Management. The Office referred the matter back to the review Division. At a meeting on October 11, 2001, there was disagreement between Novartis and HFD-180 on the adjudication of surgical interventions in clinical trials with tegaserod. There was conceptual agreement re: post-marketing study (being reviewed by ODS), discussion on the design of mechanistic studies for gallbladder, appendix, and ovaries; and agreement to conduct a **joint re-adjudication of abdominal surgeries**. It was noted that if safety concerns could be mitigated, the efficacy data are considered acceptable. In their November 12, 2001 submission, the sponsor provided a detailed plan for discussion/agreement. At a teleconference of November 15, 2001, there was general agreement with the sponsor's proposal for a gallbladder mechanistic study. A re-adjudication of abdominal surgery cases took place on November 20, 2001. The results of this meeting are documented in Dr. Joseph's review of December 19, 2001 [NDA 21-200; Zelnorm: Medical Officer Review on re-adjudication of surgeries]. The difference between tegaserod and placebo has been narrowed with **newly provided information** on a number of cases involved so that on February, 2002, it was: tegaserod = 5/2965 (0.17%); placebo = 1/1740 (0.06%), p = N.S. Disagreement remains re: 3 cases (placebo cholecystectomy, tegaserod hiatal hernia and tegaserod pancreatic cyst). (See Section II. C. c.3 of this review for more details on results of the re-adjudication meeting).

In the present Safety Update review, in addition to general safety and assessment of serious adverse events etc. all cases of abdominal surgery are re-visited. The information is updated and **new surgeries highlighted**. The aim of this approach is to search for a trend that may represent a safety signal. Although other components of the sponsor's complete response package to the June 15, 2001 non-approvable letter are listed and briefly commented upon for completeness, they are being reviewed separately.

II. REVIEW OF SAFETY UPDATE

A. Scope of Material Reviewed

The present SU is an update of the June 9, 2000 120 day SU [which included The Integrated Summary of Safety (ISS) in the original NDA]. Included in the current SU is additional information from safety updates dated March 22, 2000; April 28, 2000; and December 15, 2000 [cut off time August 31, 2000]. Safety data arising from a) newly completed studies; b) on-going studies and c) post-marketing reporting are summarized and assessed. [As of January 25, 2002 tegaserod has been approved for marketing in 18 countries and launched in 4].

The cutoff date of the present SU is January 15, 2002. The SU presents a) all serious adverse events (SAEs, including death) in completed and ongoing trials (pooled); b) all AE dropouts in completed (pooled) and ongoing trials; and c) summary of AEs and laboratory abnormalities in completed trials on an individual study basis.

It is worth noticing that, as requested by the Agency, the SU focuses on a review and appraisal of abdominal and pelvic surgery (**identified in this document as surgeries**), with a focus on those that were re-adjudicated with the Division on November 20, 2001. In addition, all cases of surgeries in double-blind trials of at least 8-week duration that have occurred since the December 15, 2000 SU were unblinded to provide a comprehensive update at this time. Narratives for SAEs and surgeries were given in sponsor's Post-text supplement 3.

It is also important to note that, at the Division's request, the sponsor submitted additional information (i.e. CRFs) of all patients that underwent abdominal or pelvic surgery in the tegaserod clinical program [information submitted on April 20, 2001]. In addition, detailed information on the surgery cases was obtained and used during the November 20, 2001 re-adjudication meeting. As will be discussed later, this new information consisted of **hospital records** including clarifications from investigators in reply to sponsor's inquiries about some individual cases.

B. Clinical Trial Experience: Safety Database (Table 1)

Table 1

**02/28/02 SAFETY UPDATE
Summary of Exposure**

	Initial ISS	ISS + 120 day SU	12/15/00 SU	02/28/02 SU	Total Subjects Exposed
I. Completed Studies [Studies of ≥ 12 week duration]* (CP-IBS Patients)					
Total Number	2665	2892	3659	3670	5632
Treated for ≥6 mo. ^b	418	826	862	862	862
Treated for ≥ 12 mo. ^c	185	187	186	186	186
II. Ongoing Studies					
Total number				2340	
					6240
				3900	

- a) This constitutes the key safety population
- b) These subjects were treated for 180 days; the exposed number exceeds the ICH number of 300 to 600 to detect an event with a frequency of ≥ 0.5%
- c) 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%.

**APPEARS THIS WAY
ON ORIGINAL**

- A total of 63 studies are completed.
- Since the December 2000 SU [Total subjects exposed to tegaserod, n=5086; patients with CP-IBS, n=3659], a total of 10 clinical trials with tegaserod were completed in various indications involving a total of 714 subjects. Of these, 518 originated from two 8-week, double-blind, placebo-controlled, parallel groups, Phase II studies — doses tested: — 4 vs. 12 mg/d, total n = 271; and — doses tested: — 6 vs. 18 mg/d, total n=247]. The remainder 196 subjects came from eight smaller (n=11 to 39 subjects), short-duration (6.5d to 4 weeks) mechanistic or pharmacokinetic studies.
- As summarized in Table 1, the above computation leads to a total of 3670 CP-IBS patients (+ 0.3%) and 5632 (+10.7%) subjects overall on tegaserod. Thus, little safety information has been added since the December 2000 SU.
- The key safety population is based on 10 CP-IBS trials; of these, 6 are double-blind, the other 4 open-label; all are of at least 12 weeks duration.
- A total of 32 studies (14 double-blind, 18 open-label) are ongoing. Included are 6 double-blind studies of at least 8 weeks duration: 2 — [n = 251 randomized by January 2002], 2 — [n=2086], and 2 — [n = 792]. There are also 2 double-blind studies of 4 weeks duration in CP-IBS — n = 510 and — n = 17] and one double-blind 10-month extension study — [n = 102]. Furthermore, also ongoing are 5 — [n = 124], 1 — [n=32], and 14 open-label studies of at least 12 weeks duration [n=2672], and 3 open-label studies of 4 to 8 weeks duration [n = 1401].
- The center of interest of this ISS update is **abdominal and pelvic surgeries**, serious adverse events, and discontinuations due to AEs. Event rates were pooled by combining the numerators and denominators for the selected studies of a database. All post-randomization events of interest that had occurred up to or on 15 January 2002 were taken into account for the numerator¹, including those of patients who were randomized later than 30 November 2001.
- In the ongoing double-blind placebo-controlled parallel group studies of at least 8 weeks duration, the treatment code was broken in 11 patients with surgeries but no for any other patients.

¹ A patient was considered to be safety analyzable if she/he received at least one dose of test medication and relayed safety data.

- Comparisons of proportions between tegaserod and placebo were made using the exact Cochran-Mantel-Haenszel test, stratifying for study.²

Exposure in any studies (Table 2)

- The estimated number of patients exposed for 4, 8, and 12 weeks is presented in this Table, extracted from sponsor's Table 3-2. The actual treatment duration is not available for patients who are still in the study. Therefore, these patients were not counted; i.e. a patient in an ongoing 12-week study who had completed 10 weeks at the time of the cutoff is not counted as a 4- or 8- week completer.³

Table 2
Tegaserod

Exposure Duration for Completed and Ongoing Studies
[Cutoff 15 January 2002]

Length Exposure (At least)	December 2000 SU	Completed Between Dec 2000 And Jan 2002	Total in Ongoing Studies	Total
4 weeks	3936	310	2753	6999 ^a
8 weeks	3601	299	2390	6290 ^b
12 weeks	2666	0	1547	4213 ^c
Any Duration	5071	546	5899	11516 ^d

- Total number of placebo-treated patients
 - 2604
 - 2222
 - 1537
 - 3907

C. Serious Adverse Events

a. Deaths

**APPEARS THIS WAY
ON ORIGINAL**

² 95% confidence intervals for the difference and ratio of proportion were determined based on exact methods (STATXACT). A p-value below 0.05 was considered to be nominally significant. The statistical tests were performed in an explorative way.

³ The sponsor notes that the exposure data are therefore an underestimation. It is further noted that patients entering multiple studies are only counted once.

There have been a total of 3 deaths in the entire tegaserod program. One death (suicide/147/001) in the tegaserod arm of pivotal study B301 was previously reported and considered unrelated to tegaserod. Since the December 2000 SU there were two deaths. Both occurred in ongoing open trials. Narratives of these deaths, as provided by the sponsor, follow.

Tegaserod 12 mg/d

CP-IBS

**Open-label for 12 week followed
by 4 weeks re-treatment in relapsers
Total # of tegaserod patients enrolled: 515 (planned:
600)**

Patient 49/04

This 68 year old female with CP-IBS had a >10 y history of psychiatric problems, treated in the past with antidepressants. She had been under active treatment for psychiatric disorder by her personal physician just prior to study. She began tegaserod treatment on 17-May-01, and committed suicide by overdose of non-test medication and laceration of the wrists on 15-June-01.

The investigator felt that there was no relationship between test medication and her death.

tegaserod 12 mg/d

CP-IBS

**Open-label efficacy and safety for 8 weeks
followed by max. 3 extensions of 12 weeks**

**Total # of tegaserod patients enrolled: 838
(planned: 838)**

Patient 7/33

This 88 y old female with CP-IBS was on treatment with tegaserod 12 mg/d. On 20-Nov-00, the patient started open-label treatment with tegaserod. On Day 118, the patient presented with abdominal pain, and was found to have cholestasis. Abdominal ultrasound showed dilatation of both hepatic and pancreatic ducts, No gallstones were reported. ERCP revealed common bile duct stenosis. Brush cytology specimen showed highly dysplastic cells with suspicion of pancreatic carcinoma. A tent implantation was performed as treatment. On Day _____ days after the last study treatment), the patient died at home of a suspected pulmonary embolism. No autopsy was performed.

The investigator considered that a relationship between the event and the test medication was not suspected, indicating progression of an underlying illness as probable event causality.

The reviewer agrees with the investigators' assessments. The above-described 3 deaths are unrelated to test medication (tegaserod).

b. SAE pattern in double-blind, placebo-controlled studies

In double-blind, placebo-controlled, completed studies, only 6 new SAEs (tegaserod, n = 5; placebo n = 1) were reported. The sponsor presented this information in their Table 4-4, followed by detailed explanation of the actual SAE by body system. In conclusion, the frequencies and patterns in this update (1.7% vs. 1.2) are similar to those reported in the December 2000 SU (1.6% vs. 1.2%).

c. Abdominal and pelvic surgeries

Because this is an important component of the present review, several aspects of this information are considered. Since a good deal of the data have been previously reviewed in some fashion or another, the pertinent information is provided in the form of appendices but details of the joint re-adjudication meeting of November 20, 2001 and new cases, whether surgeries or not, occurring since the time of that re-adjudication meeting, are described within the text of this review.

1) Types of Studies in which Surgeries have been reported

A brief description of the study population (indication), type (main design), length of experimental observation, dose of tegaserod and total number of patients expected to enroll in the trial is given in Appendix 1. Also given is the total number of cases occurring per arm of the study, without adjudication. From this information, it is obvious that surgeries, **including cholecystectomies**, have been reported in all kinds of patient populations, beyond the target population of constipation-predominant IBS. These other populations include _____

_____ There is little long-term experience.

2) Clinical Summaries of all and each of the individual cases of surgery

Although this information is included in Appendix 2 for completeness, no further comments are given because these cases have been the subject of review by Dr. R. Joseph. There was ample discussion of these cases at the below summarized re-adjudication meeting of November 20, 2001 with Novartis, expert consultants and Division representatives' participation.

3) November 20, 2001 Zelnorm Re-adjudication Meeting Outcome

A sponsor's synopsis of each surgery case identified by patient number, type of surgery, patient's age and treatment arm was provided. This information plus Tables and other materials prepared by the Division, were used throughout the re-adjudication process.

The Division and the sponsor concurred on the following basic criteria for adjudication:

1. The surgery was **not solely elective**.

2. Whether there was **new or worsening** pain during the trial.

3. The **temporal relationship** between the onset of the adverse event and the trial.

An extensive discussion followed using the above stated criteria. _____ the sponsor **shed light on existing information** and presented **new information** for several cases. The re-adjudication exercise was made difficult because it was clear that Novartis did not agree with its own consultants on the adjudication of several of the cases.

The cases were divided into the following four categories: **(i through iv)**:

**i) Cases where the Agency and the sponsor agreed (patient number)
[n = 9]**

A. Tegaserod n=7

1. 307/729/7 – hysterectomy
2. 307/721/7 – hysterectomy
3. 351/518/27 – oophorectomy and lysis of adhesions
4. 351/524/1- cholecystectomy
5. 358/132/8 – appendectomy
6. 358/17/48 – cholecystectomy
7. 358/17/48 – cholecystectomy

B. Placebo n=2

1. 301/209/13 – appendectomy
2. 358/64/4 – oophorectomy

These cases will not be discussed any further.

ii) Cases in which the sponsor changed their opinion after adjudication [n=5]

[Basic question –Should a case count as part of the surgical imbalance?]

A. Tegaserod

1. 358/76/24 – This tegaserod case was elective and the sponsor agreed **not** to count it.
2. 251/42/7 – This inguinal hernia case had pain and lower quadrant tenderness before the study. The sponsor agreed **not** to count this case.

B. Placebo

1. 351/518/19/19 – Surgery occurred on day 207 (outside a reasonable time period). The sponsor agreed **not** to count this placebo case.
2. 251/18/1 – Case was solely elective (tubal ligation). The sponsor agreed **not** to count this placebo case.
3. 358/61/23- Cases was solely elective (tubal ligation). Likewise, the sponsor agreed **not** to count this placebo case.

iii) Cases where the Division changed its opinion after joint adjudication [n=3]

A. Tegaserod

1. 358/23/29 – This tegaserod cholecystectomy case was elective (new information) and the Agency agreed **not** to count it.
2. 358/122/4 – This tegaserod cholecystectomy case was also elective (new information) and the Agency agreed **not** to count it.

B. Placebo

1. 358/43/4 – This placebo hysterectomy case deemed to have had a **change in abdominal pain** during the trial and the Agency agreed to count it.

iv) Cases that the Agency and the sponsor could not agreed on [n=3]

Tegaserod- treated cases

301/112/9: This case involved a patient on tegaserod who underwent a pancreatic cyst resection during the study period.

The Division concludes that this case should be included because there is a positive relationship between the onset of the adverse event and treatment. In addition, the Division states that there is no information presented that rule out a possible drug-adverse event relationship.

The sponsor concludes that this case should be excluded because an abnormal LFT was noted at baseline even though the diagnostic ultrasound was not performed until 14 days after study onset. In addition, the sponsor concludes that this case should be excluded because there was no new or worsening of pain by the patient while in the study.

358/75/7: This case involved a patient on tegaserod who underwent Nissen fundoplication for GERD during the study period.

The Division concludes that this case should be included because there is a positive relationship between the onset of the adverse and treatment. In addition, the Agency states that there is no information presented that rule out a possible drug-adverse event relationship.

The sponsor concludes that this case should be excluded because the patient had a history of chronic GERD with Barrett's epithelium and elected to have surgery to treat this previous condition, not a condition resulting from treatment during the study.

Placebo-treated cases

358/112/22: This case involved a patient on placebo who underwent a cholecystectomy **155 days after completion of the study**. The diagnostic ultrasound, which resulted in the surgery, was performed prior to completion of the study.

The Division concludes that this case should be excluded because the temporal relationship does not fit within the criteria for reasonable association of adverse event with drug treatment.

The sponsor concludes that this case should be included because the diagnosis occurred on the last day of the study and this is the only case of biliary obstruction.

**APPEARS THIS WAY
ON ORIGINAL**

As mention in Dr. Joseph's review, at the conclusion of the meeting, the division and the sponsor agreed to leave the adjudication of the last three cases in dispute. The final calculation by the sponsor was: tegaserod 7 cases and placebo 4 cases. The Division concluded that there were: 9 tegaserod cases and 3 placebo cases. Thus, according to the HFD-180 clinical team there continues to be twice as many cases adjudicated to tegaserod in comparison to placebo ($9-3=6$) when these calculations are compared to the sponsor's ($7-4=3$) [Table 3].

Table 3
Cases Included in the 'Numerical Imbalance' after Adjudication

HFD-180 Clinical Team	Tegaserod: Number/possible Total	Placebo Number/possible Total	Difference Between treatments
Sponsor	7/13	4/7	3
Agency	9/13	3/7	6

Table 3 demonstrates that the sponsor agrees to include 7 of the 13 possible tegaserod cases, whereas the Division agrees to include 9 of the 13 possible tegaserod cases. In addition, the sponsor agrees to include 4 of the 7 possible placebo cases whereas the Division agrees to include only 3 of the 7 possible placebo cases.

The Medical Officer reviewer, Dr. R. Joseph notes that Dr. _____ from the _____ was present at the meeting and he reported on the adjudication of the surgical cases by his 'blinded' panel of gastrointestinal consultants which included Dr. _____ from _____, who was also present at the November 20, 2001 meeting. It is worth noting that the consultants were charged mainly with causality with regard to the test medication rather than the mere inclusion/exclusion of the individual cases for consideration of the 'numerical imbalance'.

As Dr. Joseph notes, after the final re-adjudication of the surgeries, which as based on the sponsor's **newly released information**, one is still left with the **numerical imbalance** (tegaserod = 2X vs. placebo 1x) without a clear-cut pathophysiological mechanism or temporal sequence. The Division has repeatedly indicated that no true microscopic evidence of acute inflammation or evidence of gallstone migration has been noted. Additional constraints during the adjudication process have been: a) abdominal surgical interventions are undeniably increased in this patient population; b) although detectable in number, the occurrence of these surgeries is not high enough so that **no trend appears to exist**; and c) the difference between tegaserod and placebo has never been statistically significant.

NOTE: According to the information provided by the sponsor in their Table 4-12 (page 54 of volume 2 of 4 of the February 28, 2002 ISS), as of January 2002, the proportion of surgeries is as follows:

Frequency (number of surgeries/patients treated) of abdominal and pelvic surgery^a in double-blind, placebo-controlled parallel group studies of at least 8 weeks duration in all indications.

	Tegaserod n/N (%)	Placebo n/N (%)	Treatment Difference (95% CI)	p-value ^b	Relative Risk (95% CI)
All Indications (CP-IBS, —)	17/5319 0.32	6/2902 0.21	0.11	N.S.	1.5

^aJanuary 2002: surgeries in December 2000 SU (based on FDA adjudication) and newly reported surgeries (no adjudicated). This includes all newly reported cases (no adjudicated) of abdominal and pelvic surgery in tegaserod double-blind studies, with exception of one still blinded case of appendectomy in ongoing 4-week study — (a trial performed in —)

^bMantel-Haenszel-test, stratifying by study

Abbreviations:

CI: confidence interval; CP-IBS: constipation-predominant irritable bowel syndrome;

In summary, according to the HFD-180 GI Team, at the end of the re-adjudication of surgeries there is an imbalance (smaller than before, but still an imbalance) in the frequency of abdominal surgeries between tegaserod (9/2965=0.30%) and placebo (3/740 = 0.17%) and specifically with regard to cholecystectomy: tegaserod, 5/2965=0.17 and placebo, 1/1740 = 0.06%. From the start, and especially after hearing from their consultants, the sponsor has stated that this difference does not represent a true signal. Dr. Joseph and the MTL have consistently stated and in view of the information reviewed here as well as that from the spontaneous reporting system (See Section II. G. of this review), continue to express **lingering concerns** about a phenomenon that cannot be decided on the basis of the available randomized clinical trial experience. Post-marketing epidemiologic evaluations have been proposed from the beginning. The sponsor has always agreed with this approach. Consistent with their agreement, Novartis Pharmaceuticals Corp. is proposing a Post Approval Epidemiologic study being reviewed by ODS.

As mentioned at the end of section I of the current review, other components of the sponsor's February 28, 2002 complete response package to the Agency's June 15, 2001 non-approvable letter are briefly addressed. This is done for completeness. But they are separately reviewed.

D. Discontinuations due to AEs (Table 4)

The AE dropout rates of completed CP-IBS studies remained very similar to the December 2000 SU. As shown in this Table, in the — indications, — the AE dropout was numerically higher than in CP-IBS (Phase III) trials. This slightly raised the frequency in the pooled database (Table 4).

Table 4
Tegaserod
02/28/02 SAFETY UPDATE

Discontinuations due to adverse events: number (%) of patients in completed double-blind placebo controlled studies of at least 8 weeks duration

Population	Dataset	Tegaserod n/N (%)	Placebo n/N (%)
C-IBS (Phase 3)	Dec 2002	172/2446 (7.0)	83/1589 (5.2)
Pooled indications	Feb 2002	91/885 (10.3)	18/304 (5.9)
		46/385 (11.9)	12/133 (9.0)
		45/500 (9.0)	6/171 (3.5)
Double-blind studies of at \geq 8 weeks: C-IBS (phase 2/3),	Feb 2002	336/3919 (8.6)	115/2061 (5.6)

[

E. Laboratory data in recently completed studies

The two dose-finding studies in _____ (total n = 518) did not show any imbalance in the frequency of abnormal hematology or biochemistry variables between tegaserod and placebo. This was also confirmed in the smaller studies, and is in line with the previous reports⁴ (Table 5-1 and Post-text Suppl 6-11 – 6-14).

F. AEs in recently completed studies

The sponsor provided information from studies _____, not; _____ and smaller PK, studies. But the number of patients in these trials is small to allow drawing meaningful conclusions. It is worth noting that the main additional tolerability data of the recently completed studies stem from these two dose-finding studies in _____. In these trials, diarrhea was the most frequent AE; it was about 3 times higher on the highest tegaserod doses than on placebo. Diarrhea was also the most frequent AE leading to discontinuation. At higher doses diarrhea is not an unexpected AE especially in a population without a mandatory pre-study constipation like _____

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⁴ Sponsor's Table 5-1 and Post-text Suppl. 6--11-6-14

In conclusion, this reviewer agrees with the sponsor that these additional AE data from the recently completed studies are supportive of the safety profile of the December 2000 SU.

- There are data suggesting that tegaserod is well tolerated in patients with mild to moderate impairment of the renal function [tegaserod, n=909; placebo, n=501] but, because of a limited sample size, no conclusion can be made regarding the tolerability of this drug in patients with severe renal impairment (CrCl < 30 mL/min). This lack of information should be addressed in the labeling.

G. Spontaneously reported AEs from approved markets

- As of January 25, 2002 tegaserod has been approved from marketing in 18 countries and launched in 4.
- The sponsor has presented a crude estimate of the number of patients treated with tegaserod from 27th September 2000 (International Birthdate) to 31st December 2001, calculated from the sales volume in kg sold, which was about — On the basis of the daily recommended dose of 12 mg, the estimated patient exposure for that time period was —patient-treatment years.
- Individual reported AEs have been grouped by MedDRA organ classes (a case with more than one reported symptom/diagnosis may thus be counted in more than one organ-class). The most frequently affected organ classes were in decreasing order gastrointestinal disorders (13), nervous system disorders (6), skin and subcutaneous tissue disorders (3), cardiac disorders (2) and general disorders (2).
- The sponsor explains that in the time period of this ISS-update between August 31, 2000 and January 15, 2002, 22 spontaneous cases have been reported for tegaserod, seven of these were reported as SAEs and 15 reports did not fulfill the seriousness-criteria⁵. The 7 SAEs reported as spontaneous reports are summarized in Table 5.

From the post-marketing experience currently there is no cluster of symptoms possibly indicating newly identified adverse events of tegaserod. Taking into account the low number of spontaneous reports received during the review period overall, there is no evidence that the number of reports concerning on particular AR has increased during the months following the first launch of tegaserod. No safety concern has surfaced with tegaserod. In spite of the sponsor's statements, the MTL concludes that the information on spontaneously reported AEs from approved markets is too incipient. No meaningful conclusions can be drawn.

⁵ The criteria for the assessment of seriousness follow the definition of the ICH guidelines E2A/CIOMS and reflect the opinion of the reporting source.

Table 5
Tegaserod
02/28/02 SAFETY UPDATE

Spontaneous reports of serious adverse events

Case Number PHBS/	Age Sex	Dose	AE preferred term as reported	Serious criteria
2001-09618	46/M	12	Abdominal pain	Hospital
2001-10042	56/F	12	Diarrhea aggravated	Disability
2001-10691	53/M	12	Strabismus, diplopia	Med. Significant
2001-11565	24/F	6	Confusion, diarrhea, dizziness, headache, loss of consciousness, nausea, pallor, sweating increased, vomiting (suspected allergic reaction)	Med. Significant
2001-12951	NA/M	6	Frequent bowel movements, diarrhea, gastrointestinal disorder, tenesmus	Med. Significant
2002-00771	25/F	N/A	Peripheral swelling, pain, edema of the fingers Raynaud's like phenomenon	Med. Significant
2002-00760	60/M	12	Cholangitis, cholecystitis, bile duct stone	Hospitalized

NA = not available. This Table corresponds to sponsor's Table 7-1.

- 3 of 7 serious spontaneous reports are classified as unlisted with respect to the Investigator's Brochure: one report of loss of consciousness, diarrhea, sweating, vomiting which may have been an acute hypersensitivity reaction (which was also suspected by the reporting physician) or alternatively a food-intoxication, one report of **strabismus** in which however the patient suffered from underlying neuropathy, and one poorly documented case of questionable Raynaud's symptoms of the fingers. Narratives were provided in Post-text supplement 3.
- As requested by FDA, the clinical database has been reviewed and there have been no reported cases of strabismus. The spontaneous reported case of strabismus is the single such case with tegaserod.
- Additional spontaneously reported AEs from approved markets being reported after the cutoff date to the current SU (cutoff date of August 31, 2002), are being submitted to IND for Zelnorm™ [tegaserod maleate] tablets. One of these, cases from [redacted], is summarized below.

**APPEARS THIS WAY
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Spontaneous report PHBS2002 ~ 02625

- 56-year old-woman
- 6 mg bid tegaserod for 3 days, for irritable bowel syndrome
- patient also treated with lansoprazole for gastritis
- history of cholecystectomy 20 years ago
- onset of colic-like pain on day 3 of tegaserod therapy
- patient stopped tegaserod and hospitalized for further evaluation
- initial abdominal ultrasound showed dilation of bile ducts, common bile duct measured 13 mm; repeat ultrasound next day reported common bile duct measurement of 8 mm
- lab values including liver and pancreatic parameters were normal
- clinical diagnosis of **sphincter of Oddi spasm**
- no ERCP or manometry obtained, and no rechallenge planned
- treated with analgesics and pain resolved within 24 hours
- patient hospitalized for 24 hours
- similar episode occurred 8 years previous, manometry performed at that time and was normal

Reporter: Physician from _____

For this spontaneous report, the reported causality was stated as **possible**. This reviewer recommends to include in the tegaserod labeling this **sphincter of Oddi spasm** case, occurring in possible association with tegaserod administration. This appears to be a case of inappropriate use of the drug. According to the information provided, a similar episode (“clinical diagnosis of sphincter of Oddi spasm”) had occurred 8 years previous although manometry performed at that time had been normal. Until we learn more about how properly to use tegaserod, the drug should be **contraindicated** in patients with a history of sphincter of Oddi spasm or the information should be clearly highlighted in the labeling.

Preliminary information on an additional case reported by Dr. _____ is summarized below. Date of Report 06/07/02.

An 18 year old female patient received tegaserod for approximately 2 weeks for IBS and chronic constipation. She had a history of bipolar affective disease for 4 years for which she was on treatment with **carbamazepine 1600mg/day**. Further concomitant medication was omeprazole 20 mg/day (indication and temporal therapy data unknown). During the second week of Zelmec therapy 3-4 weeks ago she presented with nausea and general discomfort which led her to consult the doctor. The physical examination found not severe pain in right hypochondrium and Dr _____ asked for laboratory tests. Results: Elevated transaminases (approximately 1000mg/dl - which ones not specified), normal bilirubin, gamma-GT elevated, normal blood count. Further tests were performed subsequently for Hepatitis A, B, C and HIV all with negative results. Abdominal ultrasound (liver and gallbladder) found cholelithiasis and cholecystitis, and tegaserod and omeprazole were discontinued and the carbamazepine dose was reduced to 400 mg/day (later after surgery again increased to 800 mg/day). The patient was planned for laparoscopic cholecystectomy and a pre-surgical ultrasound reported cholelithiasis but no choledocholithiasis. Laparoscopic surgery has been performed approx. 16 days ago (about 23rd of May). Afterwards transaminases decreased to 200 (again no further specification). Actual health status

of the patient was satisfactory after surgery and she was in good general health conditions. It is not clear from the information provided so far if Dr. — didn't know about the patient's medical history regarding similar symptoms before or if he explicitly stated that the patient had no similar symptoms before (will be clarified). Regarding causality for cholecystitis and increased transaminases Dr. — stated "yes, possible but not definitive".

This is all information available at present. Hopefully during the next week the sponsor will be able to collect more.

NOTE:

The above-summarized cases from _____, together with case 2002 — 00760 (cholangitis, cholecystitis, bile duct stone) in a 60 y old male patient, are of interest because these are instances of **biliary tree adverse events** in apparent association with the administration of tegaserod. This information should be included in the labeling under the heading "**Adverse Events from Post-Marketing experience.**"

There is one additional spontaneous report from _____ and a new 15-day report from clinical trials, both of which are summarized here. These cases are of interest because they are instances of **colonic events**. The first [PHBS2002 — 05053] is that of a patient with LLQ abdominal pain and hematochezia. The patient stopped tegaserod and upon hospitalization, was diagnosed as having **diverticulitis**. Tegaserod was reintroduced but had to be stopped due to diarrhea. Tegaserod was reintroduced again but again had to be stopped due to diarrhea. Barium enema showed **diverticulitis**. In the other, the patient developed severe LLQ abdominal pain associated with soft and hard stool but neither fever nor rectal bleeding. Test medication was stopped. The clinical diagnosis was that of **nonspecific colitis**. In this case, there was no specific treatment, no endoscopic examination performed, the patient was not hospitalized and the symptoms resolved spontaneously. Tegaserod was restarted without recurrence of symptoms.

**APPEARS THIS WAY
ON ORIGINAL**

Spontaneous report PHBS2002 — 05053

- 65-year old woman
- 6 mg bid tegaserod for 18 days, starting 08 Feb 02, for irritable bowel syndrome
- history of hiatal hernia, Tietze's syndrome (costochondritis), depression, disc herniation and appendectomy
- sigmoidoscopy in 1997 revealed hemorrhoids
- colonoscopy in June 1999 "showed no pathological changes"
- onset of LLQ abdominal pain and hematochezia on day 16 of tegaserod therapy
- patient stopped tegaserod and hospitalized for evaluation
- CT scan showed thickening of sigmoidal wall; WBC elevated at 16.9 diagnosis of **diverticulitis**
- treated with intravenous antibiotics for 4 days, rapidly improved and discharged on 5 Mar 02; oral antibiotics continued until 09 Mar 02
- tegaserod reintroduced 11 Mar 02 for 4 days; stopped due to diarrhea, which was treated with Bioflorin
- tegaserod reintroduced again 20 Mar 02 to 10 Apr 02 (21 days) but again stopped due to diarrhea
- no reoccurrence of abdominal pain or hematochezia with tegaserod rechallenges
- barium enema on 18 Apr 02 (scheduled during hospitalization) revealed "no pathological changes" but showed diverticulosis of sigmoid colon without inflammation
- patient had prior episode of abdominal pain radiating to back which in retrospect may have been episode of diverticulitis, according to reporting physician

New 15 day report from clinical trials since December 2001 ISS update

Report — 02002 — 02969

Patient # — /1702/16 [Study

- 44-year-old Caucasian woman
- 2 or 6 mg bid tegaserod (blinded) for 30 days in extension study, starting 08 Mar 02 (patient had been in core study for 12 weeks treated with either tegaserod 2 mg bid, tegaserod 6 mg bid or placebo)
- history of severe constipation since childhood, history of GERD and hysterectomy
- colonoscopy in Feb 02 reported as normal
- developed severe LLQ abdominal pain associated with soft and hard stool 7 Apr 02
- no fever or rectal bleeding; WBC 11.2, 11 Apr 02 (baseline WBC: 4.9, 15 Feb 02)
- study medication stopped
- abdominal ultrasound showed a thickened descending colonic wall
- clinical diagnosis made of **nonspecific colitis**
- no specific treatment, no endoscopic exams performed, not hospitalized; symptoms resolved spontaneously
- tegaserod restarted on 22 Apr 02 without recurrence of symptoms; subject reported to be doing well on drug (last follow-up 03 May 02)

The reviewer recommends to incorporate in the labeling succinct information on these two cases

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III. Other components of the February 28, 002 complete response Package to the June 15, 2001 Non-approvable letter

A. Draft Package Insert/Patient Package Insert.

These materials which have been assigned to Dr. M. Barreiro for review, are being reviewed under a separate document. Several multidisciplinary intramural sessions/interactions are needed before negotiations with the sponsor regarding their proposed labeling can be scheduled. In the meantime, the reviewer recommends to follow Dr. Joseph's suggestions and include the following in key sections of the labeling.

CLINICAL _____

1. A brief description should be given of the target population that includes patients who had experienced IBS for _____ before randomization.
2. The specific effects of tegaserod on abdominal pain, bloating stool frequency and consistency should be emphasized
3. Results of _____ clinical studies _____ should be summarized.
4. Stress efficacy in females
5. Clarify that efficacy in men is yet to be demonstrated
6. [_____]
7. Stress that although results based on the primary efficacy variable are not very impressive:
 - a) Tegaserod is well differentiated from placebo
 - b) The differences between tegaserod and placebo are sustained based on stool consistency and number of stools/day.

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INDICATIONS AND USAGE:

CONTRAINDICATIONS:

NOTE: Although a strong case for Contraindications is made, these clinical situations may be listed under WARNINGS.

Add

[]

[]

- adhesions?

[]

- Hx of small bowel obstruction

[]

[]

[

]

PRECAUTIONS:



ADVERSE REACTIONS

Add brief section on Post-Marketing experience. Include brief description of the sphincter of Oddi's spasm and the two other biliary tree adverse events occurring in at least possible association with tegaserod.

DOSAGE AND ADMINISTRATION:



- The **Patient Package Insert** (Information for the Patient) was being reviewed by Dr. M. Barreiro, in cooperation with ODS and other disciplines. The review of the PPI will be completed by the MTL.

B. Post-Marketing Surveillance Study

The protocol, entitled "Zelnorm Epidemiological study" is being reviewed by ODS.

C. Gall bladder Mechanistic Study

The protocol for this study was reviewed by the GI MTL and a review signed off in DFS. The study is progressing well.

D. Risk Management Plan for Zelnorm

There are five components to this plan. These include a) objectives, b) target audiences; c) risk determination [the above-mentioned Zelnorm Epidemiological study and the IBS study (a descriptive study on the incidence of abdominal and pelvic surgery in relation to irritable bowel syndrome)]; d) risk communication initiatives [3 different Risk Management Plans for either **low**, **moderate**, or **high** risk determination]; and e) a Risk Management plan evaluation. This document is being reviewed by ODS. Clinical input on the sponsor's proposal was to be provided by Dr. M. Barreiro.

Hugo E. Gallo-Torres, M.D., Ph.D.
Medical Team Leader
HFD-180

cc:

NDA 21-200
HFD-180
HFD-181/PLevineJr.
HFD-180/VRaczkowski
HFD-180/JKorvick
HFD-180/HGallo-Torres
HFD-103/FHoun
HFD- 001/PSeligman/Julie Beitz
HFD-180/JChoudary
HFD-180/LZhou
HFD-715/TPermutt
HFD-440/ACorken
HF-42/MKiester
HFD-430/ABrinker
HFD-870/SDoddapaneni
HFD-870/SAI-Fayoumi
Zelnorm05/15/02/06/11/02/06/12/02

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- _____

An ongoing double-blind, placebo-controlled, parallel group study in _____ designed to last 12 weeks; tegaserod 4, 12 mg/d (896/790); placebo (442/395).

- _____

An ongoing double-blind, placebo-controlled, parallel group, _____ study in _____ designed to last 12 weeks; 2 arms: tegaserod 12 mg/d (260/249); placebo (260/249).

c) Pelvic surgeries in D-B studies

- **Study B307**

The fourth pivotal, Phase III study, as B351, B358 and B301 above: a dose-titration (4 to 12 mg/d), double-blind, placebo controlled: tegaserod, 4 mg/d, n=282; titrate, n=275; placebo, n=284.

- **Studies B358, B358, B351 and B251** [See above]

New Cases since December 2000 SU

- **Study _____**

An ongoing double-blind, placebo-controlled, parallel group 8-week study in _____ tegaserod , mg/d: → 6, 18 (t.i.d.) (77/165); placebo (26/55).

- **Study _____** (See above)

d) Cholecystectomy and biliary-related surgeries in open-label studies

- **Study B209**

An open-label, uncontrolled, 52-week, dose-titration (4 to 12 mg/d) study CP-IBS. The tegaserod titrate enrolled and assessed 567 patients.

**APPEARS THIS WAY
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- **Study B301E1**

Another open-label, uncontrolled, 26-week, dose-titration (4 to 12 mg/d) study in CP-IBS. The tegaserod titrate enrolled and assessed 511 patients.

New cases since December 2000 SU

- **Study _____**

An ongoing _____ study in CP-IBS patients in _____ tegaserod, 12 mg/d, n=118.

- **Study _____**

On ongoing, open-label, 4 to 8 week study, of _____ study in the _____ tegaserod, 12 mg, n=448/750.

- **Study _____**

An ongoing, open-label, 12-month, safety study in _____ patients; tegaserod, 4 to 12 mg, n=220/500

- **Study _____**

An ongoing, open-label, safety and efficacy 8-week, followed by max. 3 extensions of 12 weeks study in IBS patients in _____ tegaserod, 12 mg/d, n=838

e) Abdominal surgeries, other than cholecystectomy, in open-label studies

- **Study B209** (see above)

- **Study B301E01**

- **Study B307E01**

New cases since December 2000 SU

- **Studies _____** (see above)

- **Study _____**

An ongoing, open-label, _____ 12 week study in IBS patients in _____ tegaserod, 12 mg/d, n=212

- **Study _____**

An ongoing, open-label, 4 to 12 week _____ in IBS patients in the — In this trial, 4 weeks after initial treatment. _____

tegaserod, 12 mg/d, n=441/450.

f) Pelvic Surgery in Open-Label Studies

- **Study B204**

An open-labeled, uncontrolled, dose-titration to 24 mg/d; planned duration was 52 weeks but the trial duration was only 26 weeks; tegaserod titrate, enrolled and assessed 170 patients.

- **Studies B209 and B301E01** (See above)

New cases since December 2000 SU

- **Studies [redacted] and [redacted]** (See above)

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Appendix 2 Surgeries

a) Cholecystectomy in double-blind studies

tegaserod 6mg b.i.d.

Patient #351/524/1 [Study B351, C-IBS]

- 51-year-old Caucasian woman
- 6 mg bid tegaserod for 85 days, starting 13 Jan 98
- prior history of chronic RUQ pain, hiatal hernia, hysterectomy
- new onset severe abdominal pain under right breast on Day 45
- exam showed mild epigastric and RUQ tenderness, hospitalized overnight
- workup: ultrasound normal, no gallstones; abnormal biliary scan (ejection fraction reported as 0)
- diagnosis of malfunctioning gallbladder
- laparoscopic **cholecystectomy** on Day 51
- pathology: chronic cholecystitis with cholesterosis
- recurrent pain post-surgery
- patient completed the study

tegaserod 6mg b.i.d.

Patient #358/17/48 [Study 358, C-IBS]

- 38-year-old Caucasian woman
- 6 mg bid tegaserod for 74 days, starting 19 May 00
- prior history of severe heartburn, chronic recurrent RUQ pain with normal ultrasound 1 year before study entry
- adverse events of gastritis and esophagitis on Day 42
- UGI and abdominal ultrasound normal; biliary scan showed poor gallbladder contractility (ejection fraction 13%)
- referred to surgeon on Day 63 for chronic RUQ pain
- elective laparoscopic **cholecystectomy** on Day 71
- pathology: chronic cholecystitis, no stones
- recurrent pain post-surgery
- patient stopped medication on Day 74 and discontinued study to try new medication (Miralax)

tegaserod 6mg b.i.d.

Patient #358/23/29 [Study 358, C-IBS]

- 54-year-old Caucasian woman
- 6 mg bid tegaserod for 85 days, starting 16 Feb 00
- prior history of atypical back pain and new RUQ pain during baseline period
- ultrasound on Day 2, scheduled prior to randomization, showed gallstones
- pain did not worsen during study
- laparoscopic **cholecystectomy** scheduled electively and performed on Day 38
- pathology: multiple stones, no stones in cystic or common bile ducts, no acute inflammation, no wall thickening, chronic cholecystitis
- recurrent pain post-surgery
- patient completed the study

**APPEARS THIS WAY
ON ORIGINAL**

Patient #358/52/15 [Study 358, C-IBS]

tegaserod 6mg b.i.d.

- 30-year-old Caucasian woman
- 6 mg bid tegaserod for 58 days, starting 17 Feb 00
- prior history of atypical back pain, epigastric pain and nausea
- day -28 prior to randomization: increased ALT (68 IU/L)
- day 29: ALT 100 IU/L, AST 47 IU/L, alk phosphatase 145 U/L
- day 30: ultrasound showed large gallstone, thickened gallbladder wall
- discontinued study on day 58
- elective laparoscopic **cholecystectomy** on day 64
- pathology: 3 cm gallstone, chronic cholecystitis
- pain was relieved by surgery

Patient #358/122/4 [Study 358, C-IBS]

tegaserod 6mg b.i.d.

- 37-year-old Caucasian woman
- 6 mg bid tegaserod for 85 days, starting 18 Feb 00
- prior history of GERD, hiatal hernia
- prior history of cholelithiasis one year prior to study; surgery discussed but deferred at that time
- no worsening pain during study
- elective laparoscopic **cholecystectomy** on Day 61 at convenience of patient and surgeon
- pathology: 2 gallstones, chronic cholecystitis
- recurrent pain post-surgery, but milder
- patient completed study

Patient #358/112/22 [Study 358, C-IBS]

placebo

- 37-year-old Caucasian woman
- placebo for 66 days, starting 31 Jan 00
- prior history of RUQ pain, nausea
- mild increase in AST of 43 IU/L on Day -28 prior to randomization
- increased LFTs during study (AST 92 IU/L, ALT 88 IU/L)
- investigator diagnosis was fatty liver and possible drug reaction
- patient discontinued from study on day 66
- abdominal ultrasound ordered on last day of study showed multiple small gallstones
- pain and nausea continued over several months
- episode of abdominal pain, dark urine, acholic stools
- laparoscopic **cholecystectomy** 5 months after study completion
- pathology: multiple gallstones (0.3-0.8 cm), chronic cholecystitis

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Patient # — 23/8 [Study _____]

tegaserod 6mg b.i.d.

- 65-year-old Asian woman
- 6 mg bid tegaserod for 83 days, starting 18 Jun 01
- completed study on 09 Sep 01
- 5 days after study completion, patient developed acute RLQ abdominal pain and nausea
- **appendectomy** performed on 15 Sep 01
- pathology: acute suppurative appendicitis
- did well post-operatively

Patient # — 135/13 [Study _____]

tegaserod 6mg b.i.d.

- 27-year-old Asian woman
- 6 mg bid tegaserod for 88 days, starting 06 Aug 01
- completed study on 02 Nov 2001
- 32 days after stopping medication, patient developed new onset acute RLQ pain
- appendectomy performed on 04 Dec 01
- did well postoperatively

Patient # — 2502/6 [Study _____]

placebo

- 47-year-old Caucasian woman
- placebo for 92 days, starting 30 Oct 01
- history of right inguinal hernia since 1990
- gradual worsening of soreness at hernia site after lifting for several years
- no worsening of symptoms during study
- underwent elective **right inguinal herniorrhaphy** on day 39
- patient completed the study

c) Pelvic surgeries in double-blind studies

Patient #B307/721/2 [Study B307, C-IBS]

tegaserod 6mg b.i.d.

- 37-year-old black woman
- 6 mg bid tegaserod for 93 days, starting 16 Feb 98
- prior history of hysterectomy
- day 75, hospitalized for new onset RLQ pain; CT scan showed possible ruptured right ovarian cyst
- completed study on day 93
- day 100, treated with Danocrine for continued pain; CT scan confirmed presence of ovarian cyst
- day 143, elective hospital admission for persisting RLQ pain and recurrent right ovarian cyst
- underwent **right salpingo-oophorectomy and lysis of adhesions**
- pathology: right ovarian adhesions, benign peritubal cyst, normal appendix
- did well postoperatively

Patient #B307/792/7 [Study B307, C-IBS]

tegaserod 2mg b.i.d.

- 43-year-old Caucasian woman
- 2 mg bid tegaserod for 29 days, starting 13 Oct 98
- prior history of dysmenorrhea, menorrhagia
- multiple prior pelvic surgery: endometrial resection, fibroidectomy, left oophorectomy
- worsening abdominal pain on day 11
- study medication stopped on day 29
- underwent **abdominal hysterectomy** on day 39
- surgical report notes unremarkable uterus, pathology report not available
- postoperative relief of pain but no further follow-up available

Patient #358/76/24 [Study 358, C-IBS]

tegaserod 6mg b.i.d.

- 43-year-old Caucasian woman
- 6 mg bid tegaserod for 85 days, starting 15 Feb 00
- several year history of recurrent RLQ pain, history of hysterectomy
- patient noted RLQ pain during baseline
- saw gynecologist during baseline on 07 Feb 00, ultrasound showed right ovarian cyst
- elective surgery planned for 10 days later (18 Feb 00)
- randomized 15 Feb 00
- preplanned surgery performed on day 3, laparoscopy converted to laparotomy
- **bilateral salpingo-oophorectomy, extensive adhesions, incidental appendectomy**
- patient completed study

Patient #B351/518/27 [Study B351, C-IBS]

tegaserod 6mg b.i.d.

- 13-year-old Caucasian female
- 6 mg bid tegaserod for 85 days, starting 22 Jun 98
- right and left cystectomy 3 months prior to study
- new RLQ pain on day 81, ultrasound in ER on day 83 showed a right ovarian cyst
- completed study on day 85, same RLQ pain persisted
- underwent laparoscopic **removal of right ovarian cyst** and incidental appendectomy on day 89

Patient #B251/18/1 [Study B251, C-IBS]

placebo

- 35-year-old Caucasian woman
- placebo for 84 days, starting 05 Apr 95
- cystoscopy performed on day 72
- completed study on day 84
- elective **tubal ligation and retropubic urethropexy** on day 85

Patient #B358/43/4 [Study 358, C-IBS]

placebo

- 43-year-old Caucasian woman
- placebo for 85 days, starting 07 Feb 00
- history of cholecystectomy, two previous caesarian sections, tubal ligation
- LLQ pain, menorrhagia, dysmenorrhea during baseline
- symptoms worsened during study
- elective surgery planned but patient requested that surgery not be delayed due to increasing pain
- **abdominal hysterectomy and bilateral salpingo-oophorectomy** on day 80
- surgery report: normal appearing uterus with adhesions of left ovary and tube
- patient completed the study

Patient #B358/61/23 [Study 358, C-IBS]

placebo

- 43-year-old black woman
- placebo for 88 days, starting 20 Mar 00
- past history of uterine myomectomy
- elective **tubal ligation** performed 1 day after study completion
- surgery report: 1 cm tear in uterine wall as surgical complication, converted to laparotomy to repair tear with removal of uterine fibroid

Patient #B358/64/4 [Study 358, C-IBS]

placebo

- 43-year-old black woman
- placebo for 85 days, starting 11 Feb 00
- history of caesarian section and tubal ligation
- onset of new moderate pelvic pain and dyspareunia on day 25
- **exploratory laparoscopy with lysis of adhesions** and cauterization of vaginal endometriosis on day 60
- surgery report: adhesions from uterus to bladder with endometriosis involving vagina

Pelvic surgeries in double-blind studies (new cases since December 2000 safety update)

Patient # — 504/3002 [Study _____]

tegaserod 2mg

- 29-year-old Caucasian woman
- 2 mg — tegaserod for 40 days
- several year history of chronic lower abdominal pain
- 2 CT scans for evaluation of pain (most recent CT scan 2 months prior to study) showed small ovarian cysts
- patient experienced her typical lower abdominal pain, similar to previous episodes, on day 32
- ultrasound showed small ovarian cysts
- diagnostic **laparoscopy with lysis of mild adhesions** performed on day 40
- surgery report: essentially normal pelvis with no noted scar tissue, endometriosis or pelvic inflammatory disease, mild saran-wrap type adhesions which were lysed
- patient discontinued study and continues to have same recurring pain 5 months post-surgery

Patient # — 2551/11 [Study _____]

tegaserod 2mg b.i.d.

- 22-year-old Caucasian woman
- 2 mg bid tegaserod for 85 days
- complicated gynecological history: chronic pelvic pain, symptomatic uterine prolapse, recurrent uterine bleeding, endometriosis and multiple pelvic surgeries
- laparoscopic surgery for endometriosis and recurrent pelvic pain every year for past 4 years
- recurrent uterine bleeding and pelvic pain on day 19, similar to previous episodes
- elective **vaginal hysterectomy** on day 25
- pain relived following surgery
- patient completed the study

Patient # — 2560/12 [Study _____]

tegaserod 2mg b.i.d.

- 44-year-old Caucasian woman
- 2 mg bid tegaserod for 85 days
- 2 year prior history of intermittent vaginal bleeding, with normal annual Pap smears
- endometrial biopsy for recurrent intermittent bleeding revealed fragmented adenomyoma with increased mitotic activity
- because of biopsy result, elective **vaginal hysterectomy** performed on day 42
- patient completed study

Patient # — 2534/5 [Study _____]

placebo

- 39-year-old Caucasian woman
- placebo for 85 days
- history of recurrent pelvic pain, ovarian cyst removal 1 year prior to study
- on day 2, patient noted lower abdominal pain similar to previous episodes
- on day 5, patient seen in ER because of worsening pain
- pelvic ultrasound showed a complex 3.5 cm left adnexal mass
- hospitalized on day 7 for increasing pain and evaluation of adnexal mass
- underwent **left salpingo-oophorectomy and lysis of adhesions**
- pathology: hemorrhagic corpus luteum cyst
- pain improved post-surgery
- patient completed study

Patient # — 2546/17 [Study _____]

placebo

- 33-year-old Caucasian woman
- placebo for 7 days
- stopped study drug on day 8 due to missed menses
- pregnancy confirmed and patient discontinued from study
- 29 days later, patient hospitalized for acute abdominal pain
- pelvic ultrasound showed no fetus but an adnexal mass
- **laparoscopy and right salpingectomy** for ectopic pregnancy and hemoperitoneum

d) Cholecystectomy and biliary-related surgeries in open-label studies**Patient #B209/21/6 [Study B209, C-IBS]**

tegasero 6mg b.i.d.

- 68-year-old Caucasian woman
- 6 mg bid tegaserod for 340 days, starting 12 May 97
- 10 months after study start, patient complained of epigastric and back pain
- 8 days after study completed, day 346, abdominal ultrasound showed gallstones
- ALT elevated at 82 IU/L, other LFTs normal
- elective laparoscopic **cholecystectomy** on day 351
- pathology: chronic inflammation and multiple small cholesterol stones

Patient #B209/24/13 [Study B209, C-IBS]

tegasero 6mg b.i.d.

- 35-year-old Caucasian woman
- 6 mg bid tegaserod for 172 days, starting 10 Sep 97
- prior history of epigastric and RUQ pain
- abdominal ultrasound was normal 6 months prior to study
- day 149, patient noted recurrent epigastric discomfort and nausea
- day 154, hepatobiliary scan showed decreased ejection fraction of 6.4%
- elective laparoscopic **cholecystectomy** on day 172
- patient discontinued study
- follow-up showed that same symptoms were recurring post-surgery

Patient #B209/28/31 [Study B209, C-IBS]

tegasero 2mg b.i.d.

- 49-year-old Caucasian woman
- 2 mg bid tegaserod for 116 days, starting 23 May 97
- prior history of hypertension, pulmonary embolism, asthma, dizziness, chest pain
- hospitalized on day 130 for evaluation of chest pain
- study medication was stopped 2 weeks previously
- cardiac evaluations were negative
- abdominal ultrasound showed gallstones
- laparoscopic **cholecystectomy** and incidental appendectomy performed
- 5 days later, patient rehospitalized with bile duct fistula and biloma
- successful drainage of biloma by CT-guided needle aspiration
- uneventful recovery

Patient #B301/E01/172/1 [Study B301E1, C-IBS]

tegasero 2mg b.i.d.

- 43-year-old Caucasian woman
- 2 mg bid tegaserod for 183 days, starting 21 Oct 98
- history of known cholelithiasis and biliary pain prior to study
- hospitalized with symptoms attributed to cholecystitis on day 154
- underwent laparoscopic **cholecystectomy** next day
- uneventful recovery and completed study

**Cholecystectomy and biliary-related surgeries in open-label studies
(new cases since December 2000 safety update)****Patient # — /23/4 [Study — , C-IBS]**

tegasero 6mg b.i.d.

- 45-year-old Caucasian woman
- 6 mg bid tegaserod for 174 days (continuing), starting 29 Mar 01
- multiple prior surgeries including Billroth II partial gastrectomy
- 3 year history of abdominal cramps and nausea
- day 56, abdominal ultrasound showed 2 small gallstones
- day 97, patient consulted surgeon for increasing nausea, no biliary colic
- day 139, elective laparoscopic **cholecystectomy**
- pathology: gallstones, chronic inflammation and adhesions
- post-surgery, nausea improved but abdominal cramping/discomfort persists
- patient is continuing in study

Patient # — /29/1 [Study — C-IBS]

tegaserod 6mg b.i.d.

- 73-year-old Caucasian man
- 6 mg bid tegaserod for 56 days, starting 15 Dec 00
- known history of gallstones 1 year prior to study
- hospitalized on day 34 for acute onset abdominal pain and jaundice
- treated with **ERCP and sphincterotomy**
- did well postoperatively and completed the study

Patient # — /503/9002 [Study —]

tegaserod 2mg b.i.d.

- 39-year-old black man
- 2 mg bid tegaserod for 31 days, starting 05 Oct 01
- history of recurrent upper abdominal pain thought to be functional dyspepsia
- severe upper abdominal pain on day 31
- abdominal ultrasound showed gallstones and thickening of wall
- biliary scan showed no filling of gallbladder
- laparoscopic **cholecystectomy** performed on day 33
- pathology: large stones, acute and chronic cholecystitis
- patient did well postoperatively but discontinued study

Patient death

Patient # — /7/33 [Study — C-IBS]

tegaserod 6mg b.i.d.

- 88-year-old Caucasian woman
- 6 mg bid tegaserod for 117 days, starting 20 Nov 00
- on day 118 (17 Mar 01), patient presented with new upper abdominal pain
- abnormal LFTs: ALT 132 IU/L, APT 170 IU/L, alk phosphatase 537 IU/L, bilirubin 54.8 IU/L
- tegaserod was stopped
- abdominal ultrasound showed dilated pancreatic and biliary ducts, no gallstones
- ERCP showed common bile duct stenosis
- cytology of duct brushings at ERCP showed highly dysplastic cells
- CT scan did not show definite lesion
- pancreatic or ductal cancer suspected
- patient discharged on 10 Apr 01 but readmitted on 28 Apr 01 with recurrent symptoms
- treated by biliary stent placement for biliary drainage
- discharged but did not keep follow-up appointments
- died at home (day 237, 119 days after last dose of study medication) on 4 Jul 01 of suspected pulmonary embolism (no autopsy)

e) Abdominal surgeries, other than cholecystectomy, in open-label studies

Patient #B209/28/6 [Study B209, C-IBS]

tegaserod 6mg b.i.d.

- 58-year-old Caucasian woman
- 6 mg bid tegaserod for 365 days, starting 07 Feb 97
- history of previous small bowel obstruction secondary to adhesions from past hysterectomy
- presented with progressive abdominal distention and hospitalized on day 183
- incomplete response to nasogastric tube drainage and underwent surgical decompression
- **laparotomy with lysis of adhesions and reduction of internal intestinal hernia**
- did well postoperatively and patient completed the study

Patient #B301E01/114/19 [Study B301E01, C-IBS]**tegaserod 2mg b.i.d.**

- 44-year-old Caucasian woman
- 2 mg bid tegaserod for 183 days, starting 08 Dec 98
- on day 166, patient developed new onset lower abdominal pain
- hospitalized on day 168 with diagnosis of appendicitis
- underwent uncomplicated **appendectomy**
- uneventful recovery and patient completed the study

Patient #B301E01/155/3 [Study B301E01, C-IBS]**tegaserod 6mg b.i.d.**

- 56-year-old Caucasian woman
- 6 mg bid tegaserod for 265 days, starting 11 May 98
- on day 224, patient hospitalized with new abdominal pain
- diagnosis of appendicitis and underwent **appendectomy**
- uneventful recovery and patient completed the study

Patient #B307E01/759/1 [Study B307E01, C-IBS]**tegaserod 6mg b.i.d.**

- 43-year-old Caucasian woman
- 6 mg bid tegaserod for 268 days, starting 04 Jun 98
- day 180, elective **repair of chronic abdominal wall hernia** for "esthetic" reasons
- uneventful recovery and patient completed the study

**Abdominal surgeries, other than cholecystectomy, in open-label studies
(new cases since December 2000 safety update)**

Patient # — /46/230 [Study — C-IBS]**tegaserod 6mg b.i.d.**

- 78-year-old Caucasian man
- 6 mg bid tegaserod for 27 days, starting 09 Mar 01
- prior history of left inguinal hernia repair in July 2000
- patient withdrew consent and discontinued study on day 27
- patient stated that he had recent diagnosis of right inguinal hernia by another physician
- study investigator did not agree with diagnosis and found no evidence of inguinal hernia on physical exam
- elective **inguinal hernia repair** performed on 08 May 01

Patient # — /96/480 [Study — C-IBS]**tegaserod 6mg b.i.d.**

- 50-year-old woman (race "other")
- 6 mg bid tegaserod for 93 days, starting 08 May 01
- history of intermittent diverticulitis and recurrent lower abdominal pain
- day 93, hospitalized with increased lower abdominal pain
- tegaserod was discontinued
- nonemergent surgery with **sigmoid resection** on day 114 for diverticulitis

Patient # — 10/5 [Study — C-IBS]**tegaserod 6mg b.i.d.**

- 44-year-old Caucasian man
- 6 mg bid tegaserod for 65 days, starting 05 Jun 01
- — with severe constipation and cor-pulmonale
- day 52, hospitalized with decompensated cor pulmonale and gastroenteritis
- treated with antibiotics and discharged on day 60
- readmitted day 65 with abdominal distention and RLQ mass
- on day 78, an exploratory laparotomy revealed a perityphlitic abscess, possibly secondary to ruptured appendix
- **ileo-cecal resection** performed
- complete recovery

**APPEARS THIS WAY
ON ORIGINAL**

Patient # — /11/2 [Study — C-IBS]

tegaserod 6mg b.i.d.

- 77-year-old Caucasian man
- 6 mg bid tegaserod for 23 days, starting 28 Feb 01
- history of UGI endoscopies since 1992 showing abnormal metaplastic gastric mucosa
- several months before study, patient had weight loss, fatigue and weakness
- medical evaluation continued during study
- day 24, gastroscopy showed extensive cancer
- day 41, **laparotomy** confirmed non-resectable tumor
- palliative chemotherapy planned

Patient # — /41/2 [Study — , C-IBS]

tegaserod 6mg b.i.d.

- 23-year-old Caucasian woman
- 6 mg bid tegaserod for 178 days, starting 09 Feb 01
- history of colonic inertia and severe constipation
- colectomy planned if no response to tegaserod
- therapeutic result not satisfactory and patient discontinued from study on day 178
- day 208, patient underwent elective **partial colectomy**
- uneventful recovery

Patient # — '64/64001 [Study — C-IBS]

tegaserod 6mg b.i.d.

- 60-year-old Caucasian woman
- 6 mg bid tegaserod for 21 days, starting 08 Oct 01
- day 21, patient presented with lower abdominal pain and nausea
- day 23, exploratory laparotomy revealed cecal cancer
- **partial colectomy** performed but lymph node involvement and liver metastasis noted
- chemotherapy planned

Patient : — /3/513/9002 [Study —]

tegaserod 2mg b.i.d.

- 44-year-old Caucasian man
- 2 mg bid tegaserod for 55 days (continuing), starting 25 Sep 01
- day 5, patient developed RLQ abdominal pain
- results of CT scan and ultrasound led to laparotomy for presumed appendicitis
- at surgery, torsion of appendix epiploica noted and **appendectomy** performed
- pathology: no acute appendicitis but hemorrhagic infarct of fat compatible with torsion ischemia
- uneventful recovery and patient is continuing in study

f) Pelvic surgery in open-label studies

Patient #B204/2/8 [Study B204, C-IBS]

tegaserod 2mg b.i.d.

- 32-year-old Caucasian woman
- 2 mg bid tegaserod for 85 days, starting 30 Aug 95
- history of irregular menstrual periods and ovarian cyst rupture 4 months prior to study
- elective **hysterectomy** on day 75
- uneventful recovery and patient completed the study

Patient #B209/11/39 [Study B209, C-IBS]

tegaserod 6mg b.i.d.

- 50-year-old Caucasian woman
- 6 mg bid tegaserod for 334 days, starting 18 Sep 97
- history of irregular uterine bleeding and symptomatic ovarian cysts
- day 334, elective **left oophorectomy** for persisting enlarged left ovarian cyst
- pathology: endometriosis and serous cystadenofibroma (benign)
- surgery complicated by postoperative peritonitis
- investigator stated that surgery was elective and not the result of worsening of patient condition

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Patient #B209/26/6 [Study B209, C-IBS]

tegaserod 6mg b.i.d.

- 46-year-old Caucasian woman
- 6 mg bid tegaserod for 365 days, starting 26 Dec 96
- history of hysterectomy
- hospitalized day 245 for LLQ abdominal pain
- workup with CT scan, ultrasound and barium enema were negative
- readmitted on day 258 for exploratory laparotomy for presumed adhesions
- underwent **bilateral salpingo-oophorectomy, lysis of adhesions and bladder suspension**
- surgical report: multiple adhesions of gut and ovary to left pelvic wall
- uneventful recovery, patient continued study

Patient #B209/28/4 [Study B209, C-IBS]

tegaserod 6mg b.i.d.

- 36-year-old Caucasian woman
- 6 mg bid tegaserod for 365 days, starting 03 Feb 97
- prior history of uterine adenomyosis
- day 306, underwent **hysterectomy and right salpingo-oophorectomy**
- pathology: 3.5 cm ovarian cyst and scattered small cysts, uterine fibroid
- uneventful recovery and patient completed study

Patient #B301E01/114/13 [Study B301E01, C-IBS]

tegaserod 2mg b.i.d.

- 36-year-old Caucasian woman
- 2 mg bid tegaserod for 212 days, starting 08 Sep 98
- history of recurrent irregular menstrual bleeding
- day 212, hospitalized for uterine curettage
- tissue samples showed malignant spindle cell tumor
- **hysterectomy** performed
- pathology: leiomyosarcoma and stroma sarcoma of uterus
- CT scan showed no metastasis and no chemotherapy or radiation treatment given
- uneventful recovery, patient discontinued study

Patient #B301E01/157/5 [Study B301E01, C-IBS]

tegaserod 2mg b.i.d.

- 50-year-old Caucasian woman
- 2 mg bid tegaserod for 268 days, starting 13 Nov 98
- history of uterine fibroids and urinary incontinence
- day 168, elective **hysterectomy and bladder neck suspension**
- uneventful recovery and patient completed the study

Patient #B307E01/749/39 [Study B301E01, C-IBS]

tegaserod 6mg b.i.d.

- 58-year-old Caucasian woman
- 6 mg bid tegaserod for 203 days, starting 06 Nov 98
- history of urinary frequency, dysuria, incontinence and urogenital prolapse
- day 190, elective **repair of urogenital prolapse**
- day 204, **urethral dilatation** for persisting dysuria
- uneventful recovery, patient discontinued study

Pelvic surgery in open-label studies (new cases since December 2000 safety update)

Patient # — /31/1002 [Study — C-IBS]

tegaserod 6mg b.i.d.

- 38-year-old Caucasian woman
- 6 mg bid tegaserod for 316 days, starting 03 Oct 00
- many year history of **dysmenorrhea** and **menorrhagia**
- day 316, elective **abdominal hysterectomy** for definitive treatment of recurrent uterine bleeding
- uneventful recovery

Patient # — /59/5904 [Study — C-IBS]

tegaserod 6mg b.i.d.

- 41-year-old Caucasian woman
- 6 mg bid tegaserod for 77 days, starting 23 May 01
- 5 month prior history of menorrhagia, history of uterine prolapse causing pelvic discomfort
- pessary for uterine prolapse did not provide relief
- day 77, elective **hysterectomy** for chronic uterine complaints
- postoperative course complicated by delay in return of normal urinary bladder function, but otherwise was uneventful

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Spontaneous Reports of Interest

Spontaneous report from _____

Spontaneous report PHBS2002 — J2625

- 56-year old-woman
- 6 mg bid tegaserod for 3 days, starting 06 Feb 02, for irritable bowel syndrome
- patient also treated with lansoprazole for gastritis
- history of cholecystectomy 20 years ago
- unexplained episode of RUQ pain occurred 8 years previously, manometry performed at that time and was normal
- onset of colic-like pain on day 3 of tegaserod therapy
- patient stopped tegaserod and hospitalized 2 days later for further evaluation
- initial abdominal ultrasound showed dilatation of bile ducts, common bile duct measured 13 mm; repeat ultrasound next day reported common bile duct measurement of 8 mm
- lab values including liver and pancreatic parameters were normal
- clinical diagnosis of **sphincter of Oddi spasm**
- no ERCP or manometry obtained, and no rechallenge planned
- treated with analgesics and pain resolved within 24 hours
- patient hospitalized for 24 hours

Spontaneous report from _____

Spontaneous report PHBS2002 — 05053

- 65-year old woman
- 6 mg bid tegaserod for 18 days, starting 08 Feb 02, for irritable bowel syndrome
- history of hiatal hernia, Tietze's syndrome (costochondritis), depression, disc herniation and appendectomy
- sigmoidoscopy in 1997 revealed hemorrhoids
- colonoscopy in June 1999 "showed no pathological changes"
- onset of LLQ abdominal pain and hematochezia on day 16 of tegaserod therapy
- patient stopped tegaserod and hospitalized for evaluation
- CT scan showed thickening of sigmoidal wall; WBC elevated at 16.9
- diagnosis of **diverticulitis**
- treated with intravenous antibiotics for 4 days, rapidly improved and discharged on 5 Mar 02; oral antibiotics continued until 09 Mar 02
- tegaserod reintroduced 11 Mar 02 for 4 days; stopped due to diarrhea, which was treated with Bioflorin
- tegaserod reintroduced again 20 Mar 02 to 10 Apr 02 (21 days) but again stopped due to diarrhea
- no reoccurrence of abdominal pain or hematochezia with tegaserod rechallenges
- barium enema on 18 Apr 02 (scheduled during hospitalization) revealed "no pathological changes" but showed diverticulosis of sigmoid colon without inflammation
- patient had prior episode of abdominal pain radiating to back which in retrospect may have been episode of diverticulitis, according to reporting physician

Spontaneous report from _____

(See page 18)

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New 15 day report from clinical trials since December 2000 ISS update

Report — 02002 — 02969

Patient # — /1702/16 [Study —————]

- 44-year-old Caucasian woman
- 2 or 6 mg bid tegaserod (blinded) for 30 days in extension study, starting 08 Mar 02 (patient had been in core study for 12 weeks treated with either tegaserod 2 mg bid, tegaserod 6 mg bid or placebo)
- history of severe constipation since childhood, history of GERD and hysterectomy
- colonoscopy in Feb 02 reported as normal
- developed severe LLQ abdominal pain associated with soft and hard stool 7 Apr 02
- no fever or rectal bleeding; WBC 11.2, 11 Apr 02 (baseline WBC: 4.9, 15 Feb 02)
- study medication stopped
- abdominal ultrasound showed a thickened descending colonic wall
- clinical diagnosis made of **nonspecific colitis**
- no specific treatment, no endoscopic exams performed, not hospitalized; symptoms resolved spontaneously
- tegaserod restarted on 22 Apr 02 without recurrence of symptoms; subject reported to be doing well on drug (last follow-up 03 May 02)

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Hugo Gallo Torres
6/17/02 02:07:42 PM
MEDICAL OFFICER

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**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW**

Addendum

NDA: 21-200 / N000AZ

Sponsor: Novartis PharmaG Basel, Switzerland

Date submitted: December 15, 2000

Drug: Zelnorm™ (tegaserod)

Pharmacologic Category: A partial agonist at the serotonin type 4
5-HT₄ Receptors

Formulation/Route of Administration: Tablets/Oral Administration

Proposed Indication: Treatment of Constipation-predominate
Irritable bowel syndrome (C-IBS) in
female patients

Material Submitted/Reviewed: Vol. 3-17 (Efficacy and Safety Results
Study B358), Pertinent other Information
And Literatur and (Expert Reviews)

Reviewer: Raymond E. Joseph M.D., F.A.C.P.,
F.A.C.G.

In document N000AZ table 12 should read:

Table 12 Non-adjudicated cases – B358

Treatment	Tegaserod	Placebo
Abdominal or pelvic Surgery	7	4
Laparoscopic Cholecystectomy	4	1
Appendectomy	1	0

Table 14 should read:

Selected SAEs - Adjudicated by the Reviewer - All Phase III Studies

	Tegaserod (n=2,446)	Placebo (n=1,589)
Abdominal Surgery	12 (0.5%)	2 (0.1%)
Cholecystectomy	5	0
Ovarian Cysts	8 (5 – O.R.)*	1 (none – O.R.)
Actual	3	0
Non-	5	1
Appendectomy	1	1
Other	1	0
Syncope	8 (0.3%)	1 (0.1%)
Diarrhea	237	58
Discontinuations	39 (1.6%)	4 (0.3%)

Surgery placebo: (case numbers 301/209/13 and 358/64/4)

Surgery tegaserod: (case numbers 301/112/9, 351/524/1, 358/23/29, 358/132/8, 358/52/15, 358/17/48, 358/122/4, 358/75/7, 307/792/7, 307/721/2, 351/518/27 and 358/76/24)

*[Note]: Of the ovarian cysts only 5 went to the O.R - all from the tegaserod arm

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PRECAUTIONS:

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ADVERSE REACTIONS

Under the **gastrointestinal section** add -

DOSAGE AND ADMINISTRATION:

[]

FINANCIAL DISCLOSURE

I have reviewed the financial disclosure documents for Novartis's Study B358. No disclosable financial information was reported by any of the investigators who participated in the study.

Raymond E. Joseph M.D., F.A.C.P., F.A.C.G.

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/s/

Raymond Joseph
6/15/01 03:15:24 PM
MEDICAL OFFICER

Hugo Gallo Torres
6/15/01 03:20:40 PM
MEDICAL OFFICER
Signed for Lilia Talarico, MD, Division, s Director .

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JUL 25 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA: 21-200

Sponsor: Novartis PharmaG
Basle, Switzerland

Date Submitted: February 11, 2000

Drug: Tegaserod (HTF 919) Zelnac™

Pharmacological Category: A partial agonist at serotonin type 4 (5-HT₄) receptors

Formulation/Route of Administration: Tablets for Oral Administration

Proposed Indication: []

Material Submitted/Reviewed: 212 volumes including

- 1) Index
- 2) Labels and labeling
- 3) Summary
- 8) Clinical Data which included clinical reports of Phase I to II trials, integrated summary of efficacy and integrated summary of safety, drug abuse and overdosing information, and integrated summary of benefits and risks
- 10) Statistical Section
- 11) Case Report Tabulations
- 12) Case Report Forms also a CD ROM was available that contained the CRFs of this study
- 16) Debarment Certification
- 19) Other - which included financial disclosure information
- 20) Pertinent Other Information and Literature References

Reviewer: Raymond E. Joseph, M.D., FACG

EXECUTIVE SUMMARY

Recommendations

Tegaserod hydrogen maleate (Zelmac™ - Novartis) a partial serotonin 5-HT₄ agonist is indicated for treatment of irritable bowel syndrome (IBS) in women whose primary bowel symptom is constipation. Zelmac™ is approvable from a clinical perspective. Zelmac's benefit/risk analysis is favorable when Zelmac is used in women who currently have constipation as their primary bowel symptom. Diarrhea is the main adverse effect; it occurs early and is usually self-limiting. An increased incidence of abdominal surgery and appendicitis has occurred in some patients who took the drug, the significance of which is unclear at present.

Summary of Clinical Findings

A. Brief Overview of Clinical Program

Zelmac™ a partial, randomized, serotonin 5-HT₄ agonist was studied in 3 large Phase III clinical trials (n=2525) for constipation-predominant IBS. The drug was administered orally just prior to a meal b.i.d.

B. Efficacy

Efficacy was demonstrated for females with constipation-predominant IBS in one large double-blind multicenter mostly European trial (301); with support from a multicenter, double-blind U.S. trial (351). The therapeutic gain was modest (8-11%), but sustained and supported by multiple secondary efficacy variables. The primary efficacy variable was a patient's global assessment that included overall well-being, abdominal pain and altered bowel function (i.e. the cardinal features of IBS). There are currently no prokinetic drugs available for the treatment of C-IBS.

C. Safety

The safety testing was adequately addressed in the key safety population. Serious side effects were few and occurred in a similar percentage (1.8%) in the placebo group. The most common AE was diarrhea (11.4% vs 2.4% for placebo). No significant AEs were related to the animal toxicity data. No significant drug-drug interactions were noted. One remaining safety issue is the occurrence of pelvic and abdominal surgery in patients on Zelmac™ vs patients on placebo.

D. Dosing

There is adequate support for the 6 mg po b.i.d. dosage. The dose-response curve is relatively flat over the 4-24 mg range. There are no unresolved dosing issues.

E. Special Population

The drug demonstrated efficacy for females only. Males, minority races and the elderly were not significantly represented in the clinical studies. There is no need for dose adjustment in renal disease. However, the drug should be used with caution in moderate and serious hepatic impairment.

I. BACKGROUND

A. Irritable Bowel Syndrome

1. Background and Diagnosis

For the last three decades, investigators attempted to define irritable bowel syndrome (IBS) using symptom based criteria derived from epidemiological investigations. Table 1 shows the prevalence estimates for IBS from surveys of American and European adults. Prevalence estimates vary, due to the diversity of definitional criteria, as well as the differences in the questions used to elicit the information.

Table 1.
Epidemiological Studies of IBS in American and European Adults

Source	Group characteristics	n (%) (response)	Age (yr)	Diagnostic criteria	% IBS		
					Total	Women	Men
Talley et al.	Olmsted County, MN White=99%	835 (82)	50 (range 30-64)	≥ 3 Manning	12.8	13.6	12.1
				≥ 2 Manning	17.0	18.2	15.8
Heaton et al.	English Urban White=99%	1896 (72)	25-69 (Women) 40-69 (Men)	≥ 3 Manning	9.5	13.0	5.0
Jones and Lydeard	Southern English Mostly white	1620 (71)	20-90	≥ 2 Manning	21.6	24.3	18.7
Drossman et al.	U.S. Householder White=95% Women=51%	5430 (66)	49 ± 16	Rome	9.4	14.5	7.7
Kay et al.	Copenhagen Sex stratified	3608 (79)	Age stratified	Altered bowel habits and pain relieved by defecation	6.6	7.7	5.6
Zuckerman et al.	El Paso, TX White=36% Hispanic=64% Women=66%	905 (99)	30.5 ± 9.3	Altered bowel habits and abdominal pain, constipation, or diarrhea	16.9 (Hispanics) 21.8 (White)	21.7 26.5	7.1 13.9
Taub et al.	College Students-US Black=26.9% Women=62%	1344 (87)	21.2 ± 5.6	≥ 3 Manning	16.9 (Black) 15.0 (White)	19.1 18.0	9.7 9.1

The Manning Criteria (Table 2) was the most widely used during this time. Because there is no biological marker to define this disorder, validation of these criteria has been difficult.

Investigators developed a consensus definition and criteria known as the Rome criteria for IBS and other functional gastrointestinal disorders (Table 2).