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May 21, 2001

Janet Woodcock, MD,
Director
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Woodcock:

Pursuant to 21 C.F.R. § 10.20 and 10.30(d), Novartis Pharmaceuticals Corporation ("Novartis" or the "Company") submits this letter in response to and in opposition to the March 22, 2001 Citizen Petition submitted by Public Citizen regarding Novartis' New Drug Application (NDA) for tegaserod maleate tablets ("tegaserod"). Tegaserod -- Novartis' investigational drug for the treatment of abdominal pain, discomfort and constipation in female patients with Irritable Bowel Syndrome (C-IBS) -- is under review at the Food and Drug Administration ("FDA") Division of Gastrointestinal and Coagulation Drug Products (the "Division"). An approvable letter was issued by the Division on August 11, 2000 in response to the tegaserod NDA.

Novartis believes that the public health and safety of its products are of the utmost importance. In the case of tegaserod, clinical data from more than 4,500 patients have

demonstrated its safety and efficacy in treating this debilitating disorder. Data from these clinical trials have been scrutinized by a number of experts, including FDA's Gastrointestinal Drugs Advisory Committee (the "Advisory Committee") and two independent experts retained by FDA. Following Novartis' comprehensive meeting with the Advisory Committee on June 26, 2000 (the "Advisory Committee Meeting"), the Advisory Committee recommended that FDA approve tegaserod.

Despite the compelling data supporting tegaserod's approval and the Advisory Committee's positive recommendation, Public Citizen has urged FDA not to approve tegaserod because, according to Public Citizen, tegaserod has "questionable efficacy and has potentially serious adverse effects." The clinical record for tegaserod, however, refutes such claims.

As for safety and Public Citizen's unsubstantiated claim that tegaserod causes the formation of ovarian cysts, clinical studies have demonstrated that there is no difference between tegaserod and placebo with regard to the incidence of ovarian cysts. In short, the extensive safety data collected provide strong evidence that there is no causal link between the administration of tegaserod and the formation of ovarian cysts.

Similarly, the efficacy of tegaserod is clearly supported by the clinical record and has been demonstrated in two double-blind, placebo-controlled studies. Public Citizen's contrived allegations that Novartis manipulated efficacy data in an attempt to deceive FDA simply is absurd.

Furthermore, Public Citizen ignores the fact that the substance of its product safety and efficacy claims was covered by FDA and Novartis during the Advisory Committee Meeting. (See May 24, 2000 Novartis Advisory Committee Briefing Document ("Novartis Briefing Doc.") reprinted from http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3627bla.pdf (Ex. A), June 26, 2000 FDA Preliminary Medical/Statistical Review ("FDA Briefing Mat."), reprinted from http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3627b1b.pdf (Ex. B), and Transcript of June 26, 2000 Advisory Committee Meeting on Tegaserod ("Adv. Comm. Tr.") reprinted from http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3627tla.pdf, 3627t1b.pdf, 3627t1c.pdf (Ex. C)). In addition, following the Advisory Committee Meeting, Novartis submitted to FDA an additional study of 1,500 female patients that confirmed the safety and efficacy of tegaserod.

As will be discussed in greater detail below, the allegations and claims hurled by Public Citizen reflect an incomplete, outdated and distorted understanding of the clinical data relating to tegaserod. Public Citizen's attempt to besmirch Novartis and the clinical record for tegaserod in this regard lacks all credibility. And, Public Citizen's shameful efforts to trivialize Irritable Bowel Syndrome ("IBS") are an affront to the up to 40 million patients who suffer from this life-altering condition. (Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: A technical review for practice guideline development. *Gastroenterology* 1997;112:2120-2137 (Ex. D); Lynn RB, Friedman LS. Irritable Bowel Syndrome. *N Engl J Med* 1993; 329:1940-1945 (Ex. E)).

SAFETY

The primary focus of Public Citizen's claims regarding the safety of tegaserod is centered on its analysis of clinical data considered by the Advisory Committee relating to the incidence of ovarian cysts. A review of these clinical data, however, reveals the specious nature of Public Citizen's claims.

In connection with the Advisory Committee Meeting, Novartis shared clinical data which demonstrated no increased risk of ovarian cysts to patients treated with tegaserod compared to those on placebo.[1] (Novartis Briefing Doc. at 87-89; Adv. Comm. Tr. at 101-108, 154-58). Novartis provided clinical data on the eight adverse event reports of ovarian cysts reported in the tegaserod-treated patient group. (Adv. Comm. Tr. at 101-109; Novartis Briefing Doc. at 87-89). In addition, Novartis presented the Advisory Committee with the opinion and analysis of an expert endocrinologist who closely examined the relevant case reports, medical histories and pathology reports relating to the adverse event reports. (Adv. Comm. Tr. at 101-108). Specifically, the expert concluded that four of the cases did not involve or demonstrate the existence of ovarian cysts; the expert diagnosed these cases as follows:

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[1] In addition, preclinical studies do not suggest the presence of treatment-related increases in ovarian cysts. (Adv. Comm. Tr. at 106). In fact, an expert panel retained by Novartis has reviewed the animal data in rats and has concluded that there is no treatment-related increase in the incidence of ovarian cysts. (Id.) The preclinical data were provided to the Division and presented in connection with the Advisory Committee Meeting. (Id.)

- cystadenofibroma (a benign ovarian tumor)[2];
- pelvic adhesions without a cyst;
- peritubal cyst (most likely a congenital defect); and
- abdominal pain without further evidence to support the presence of a cyst.

(Id.; see also Adv. Comm. Tr. at 154-58).

Of the four remaining cases, two of the cases involved patients who were known to have a history of ovarian cysts prior to entry in the studies.[3] (Adv. Comm. Tr. at 104; Novartis Briefing Doc. at 88). The other two cases involved patients with newly occurring ovarian cysts. (Adv. Comm. Tr. at 104). One patient was diagnosed with a polycystic ovary ("PCO"). (Id.) PCO is not a disorder associated with abdominal pain or development of large cysts. (Id.) The other patient was diagnosed with a cyst or ovarian follicle that arose during the patient's menstrual cycle and regressed in a subsequent cycle. (Id.)

Of the eight adverse event reports of ovarian cysts, five patients underwent surgery.[4] (Adv. Comm. Tr. at 104-105, 154-55; see also FDA Briefing Mat. at 16). Following surgery, three of the five patients were found not to have ovarian cysts. (Adv. Comm. Tr. at 103-105,

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[2] This patient had a ten-year history of ovarian cysts. (Adv. Comm. Tr. at 155)

[3] Following surgery, one of the two patients was found to have appendicitis with incidental drainage of an ovarian cyst and the second patient was diagnosed with adenomyosis and ovarian cyst. (Adv. Comm. Tr. at 104).

[4] Based upon a pooled analysis of clinical data to date, there is no difference in the frequency of pelvic surgeries, regardless of type or cause, between tegaserod and placebo treated patients (0.1% tegaserod vs. 0.2% placebo).

155-56). The remaining two patients were known to have a history of ovarian cysts prior to entering into the studies. (See Footnote 3).

After reviewing the clinical data and considering the information presented by Novartis, the Advisory Committee, as well as the two experts retained by FDA, unanimously agreed that there was no cause for concern over the preclinical and clinical data regarding the incidence of ovarian cysts. (Adv. Comm. Tr. at 225-26).

Following the Advisory Committee meeting, Novartis submitted to the Division an additional study of 1,500 female patients showing no adverse event reports of ovarian cysts in the tegaserod-treated group.[5] In a pooled analysis of all controlled, double-blind studies, submitted to the Division in December 2000, there was no difference in the tegaserod-treated group versus placebo with regard to the incidence of ovarian cysts (0.13% tegaserod vs. 0.12% placebo). Overall, the prevalence of ovarian cysts found in the clinical trials is consistent with that found in the general population. (Borgfeldt C, Andolf E. Transvaginal sonographic ovarian findings in a random sample of women 25-40 years old. *Ultrasound Obstet Gynecol* 1999 May; 13(5): 345-50 (Ex. F)).

Public Citizen's attempt to artificially heighten concern over other adverse events reported by patients treated with tegaserod is equally unpersuasive. In this connection, Public Citizen claims that the incidence of diarrhea and syncope (fainting) reported in

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[5] One patient was diagnosed as having an ovarian cyst during the baseline period before treatment with tegaserod and received treatment for the cyst during the study period.

patients treated with tegaserod provides additional grounds for not approving the drug. The clinical data, however, do not support such claims.

At the time of the Advisory Committee Meeting, Novartis presented Phase III clinical data on the incidence of diarrhea. (Novartis Briefing Doc. at 76-77; Adv. Comm. Tr. at 111, 114-15). These data demonstrated that 12% of patients receiving tegaserod 12 mg/d reported diarrhea as an adverse event compared with 5% of patients receiving placebo. (Novartis Briefing Doc. at 76-77, 88-89; Adv. Comm. Tr. at 111, 114-15, 147-48; FDA Briefing Mat. at 16). Corresponding figures for severe diarrhea were 4% (tegaserod) and 2% (placebo). (Adv. Comm. Tr. at 111). Overall, the discontinuation rate due to diarrhea was low (2.1%) among the tegaserod-treated patients. (Novartis Briefing Doc. at 77, 88-89; Adv. Comm. Tr. at 111-112, 114-115, 149; FDA Briefing Mat. at 16, 17). In most cases, the diarrhea occurred early -- with approximately half of the cases occurring in the first week of treatment -- was most often observed as a single episode, and resolved with continued therapy. (Novartis Briefing Doc. at 76-77; Adv. Comm. Tr. at 111-112, 150, 228-29). Importantly, there were no serious adverse reactions due to diarrhea that required hospitalization for dehydration or electrolyte abnormalities. (Adv. Comm. Tr. at 227-28). All of these data were reviewed and considered by the Advisory Committee.[6] (Id. at 109-118, 150, 226-29).

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[6] Following the Advisory Committee Meeting, Novartis submitted additional data on the incidence of diarrhea from a 1,500 all-female-patient study that had been completed. Data from that study were consistent with what had been observed in the other Phase III clinical studies. Clinical data to date demonstrate that 9% of patients receiving tegaserod 12mg/d reported diarrhea as an adverse event compared with 5% of patients receiving placebo. Corresponding figures for severe diarrhea are 3% (tegaserod) and 1% (placebo). Based upon all Phase III data, the discontinuation rate due to diarrhea is 1.6%.

All reported cases of syncope were carefully reviewed. (Novartis Briefing Doc. at 82-83). No case was found to be associated with QTc prolongation or ventricular arrhythmias. (Novartis Briefing Doc. at 82-83, 86-87, 89). Data submitted to the Advisory Committee showed that syncope had been reported in 0.5% of tegaserod patients and 0.1% of placebo patients. (Id. at 82-83; FDA Briefing Mat. at 16; Adv. Comm Tr. at 149). In the recently completed 1500 patient study, there were no adverse event reports of syncope in the tegaserod-treated group and one report of syncope in the placebo group. Based upon clinical experience to date, syncope has been reported in 0.3% of tegaserod-treated patients and 0.1% placebo-treated patients.

Furthermore, more than 10,000 ECGs in the Phase III program -- a majority of which were obtained at the approximate time of maximal drug concentration (T_{max}) (the concentration level of drug in the blood stream) -- were centrally analyzed and reviewed in a blinded fashion by an independent expert cardiologist retained by Novartis. (Novartis Briefing Doc. at 85-87; Adv. Comm. Tr. at 113-14). The results of this analysis showed tegaserod to have no deleterious effects on the ECG, specifically no effects on the QTc interval or other ECG intervals, and no difference in arrhythmias were observed between tegaserod and placebo. (Novartis Briefing Doc. at 85-87, 89; Adv. Comm. Tr. at 113-14; FDA Briefing Mat. at 16).

As for Public Citizen's comparison of tegaserod to cisapride, a mixed 5-HT_3 antagonist and 5-HT_4 agonist, and Lotronex® (alosetron hydrochloride), a 5-HT_3 antagonist, in an attempt to predict the incidence or type of adverse events, such an exercise is

symptom-based efficacy variables of IBS. Thus, the third study provides additional supportive evidence of efficacy.[8]

The allegation by Public Citizen that Novartis deceived FDA by altering the end points of two blinded trials in order to lower the threshold for efficacy is outright prevarication. At the time of the initiation of the tegaserod Phase III program, there was no consensus in the regulatory and medical communities as to the appropriate outcome measure to be used in IBS studies. (See Veldhuysen Van Zanten SJD, Talley N, Bytzer P, et al. Design of treatment trials of functional gastrointestinal disorders. *Gut* 1999; 45 (Suppl. II): II69-II77 (Ex. H); Adv. Comm. Tr. at 30). During this period, Novartis conducted three large, randomized double-blind, placebo-controlled studies in support of tegaserod (B301, B307 and B351). All patients enrolled in the studies met the internationally recognized Rome diagnostic criteria for C-IBS.[9] (Novartis Briefing Doc. at 17; Adv. Comm. Tr. at 33, 78-85, 120). After consulting with FDA and an advisory panel of academic experts retained

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[8] The efficacy of tegaserod and the results of studies B301 and B351 were fully reviewed with FDA and the Advisory Committee (Novartis Briefing Doc. at 20, 27-46, 59-72; FDA Briefing Mat. at 1-9, 17; Adv. Comm. Tr. at 28-94, 120-24, 130-38, 141-42, 144-47, 159-65, 216-22).

[9] These criteria require the presence of abdominal discomfort or pain relieved by a bowel movement or associated with a change in the frequency or consistency of stools. (Novartis Briefing Doc. at 17; Drossman DA, Thompson WG, Talley NJ, et al. Identification of subgroups of functional gastrointestinal disorders. *Gastroenterology Int.* 1990; 3:159-72 (Ex. I); Adv. Comm. Tr. at 33). In addition, for C-IBS, patients are required to have 2 of the following $\geq$25% of the time: <3 bowel movements/week, hard/lumpy stools or straining with a bowel movement. (Novartis Briefing Doc. at 18; Adv. Comm. Tr. at 33). Number of bowel movements is one of several indicators of constipation. Thus, given the fluctuating nature of IBS symptoms and the presence of other constipation symptoms (e.g., hard stools, straining), not all patients would be expected to have on average <3 bowel movements/week during the 4-week baseline period. (Id.) All patients however were required to have demonstrated abdominal discomfort or pain during the baseline period in order to confirm the diagnosis of IBS. (Adv. Comm. Tr. at 33).

by the sponsor, Novartis utilized two primary outcome measures for these trials -- the SGA of relief and the SGA of abdominal discomfort and pain.[10] (Novartis Briefing Doc. at 16; Adv. Comm. Tr. at 159-60; see FDA Briefing Mat. at 1-2). The Agency was fully briefed on, and concurred with, these parameter changes as set forth in protocol amendments for the tegaserod clinical trials.

The results of the first study completed (B351) showed a trend in favor of tegaserod on the primary efficacy variables and statistically significant improvements on multiple secondary efficacy variables. (Novartis Briefing Doc. at 20, 27-36; Adv. Comm. Tr. at 41-45, 57, 61). These results suggested that the "response" definition used in the study may have been too stringent to allow for the detection of a treatment effect. (Id.) As a result, Novartis met with experts in gastroenterology and statistics and with FDA to discuss and mutually agree upon an appropriate definition of "response" for the ongoing Phase III trials. (Adv. Comm. Tr. at 45).

Based on these discussions, and in agreement with FDA, the original SGA of relief was modified and adopted as the definition of response for the primary efficacy variable in the remaining, rigorously blinded Phase III studies. (Novartis Briefing Doc. at 17, 20-21, 36;

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[10] In addition, patients were permitted to use (non-bulking) laxatives as rescue medication, if they had no bowel movements for 4 days associated with bothersome abdominal discomfort. (Novartis Briefing Doc. at 18; Adv. Comm. Tr. at 34). As a result, laxative intake was considered to be a potential confounding influence. At the request of FDA, laxative use was factored into the final statistical analysis of the primary efficacy variable to account for its potential confounding influence. (Novartis Briefing Doc. at 23; Adv. Comm. Tr. at 37, 49-50). The statistical methodology was thoroughly reviewed at the Advisory Committee Meeting. (Adv. Comm. Tr. at 37, 49). The additional study of 1,500 female patients (B358) submitted to FDA following the Advisory Committee Meeting also factored laxative use into the efficacy analysis.

FDA Briefing Mat. at 4-5; Adv. Comm. Tr. at 32, 48). The SGA of abdominal discomfort and pain was retained as a secondary efficacy variable. (Id.) Thereafter, a protocol amendment was prepared and submitted to FDA, and the remaining studies (B301 and B307) were subsequently unblinded. (FDA Briefing Mat. at 2, 4-5; Novartis Briefing Doc. at 17, 20; Adv. Comm. Tr. at 131, 134-35, 144-45).

In this context, the SGA of relief is in accord with the recent recommendations of an independent consensus panel convened to examine and recommend the appropriate design of clinical trials investigating treatments for functional gastrointestinal disorders (Rome II Committee on the Design of Treatment Trials for the Functional Gastrointestinal Disorders). (See Veldhuysen Van Zanten SJD, Talley N, Bytzer P, et al. Design of treatment trials of functional gastrointestinal disorders. *Gut* 1999; 45 (Suppl. II): II69-II77 (Ex. H)). The Rome II Committee recommended that the primary outcome measure used in IBS trials should "integrate the contribution of a disparate group of symptoms." (Id.) The SGA of relief clearly satisfies such requirements.

Novartis' modification of the definition of response was appropriate in all respects. Aside from the fact that FDA reviewed and approved the modification, redefining response criteria in a protocol amendment prior to unblinding of a study is in full compliance with accepted statistical and clinical trial principles. (ICH harmonised tripartite guideline: statistical principles for clinical trials. 5.1: prespecification of the analysis. *Federal Register* September 16, 1998; 63 (179):21-22). Furthermore, like Public Citizen's safety claims, this matter was fully reviewed and discussed at the Advisory Committee Meeting. (Adv. Comm.

Tr. at 28-62, 130-47, 159-65). Subsequent to the Advisory Committee Meeting, Novartis provided further proof of efficacy with the submission of an additional recent study of 1,500 female patients (B358).

* * *

IBS is a chronic disorder often associated with significant disability and impairment of quality of life. To date, despite the millions of patients who suffer from this debilitating disorder, no medication has proven to be safe and effective in treating IBS patients who suffer from abdominal pain, bloating and constipation as their main symptoms. Clinical studies have demonstrated tegaserod to be safe and effective for the treatment of abdominal pain, discomfort and constipation in female patients with IBS. In particular, data from two double-blind, placebo-controlled studies have demonstrated its efficacy in treating this debilitating disorder. Furthermore, the Advisory Committee and two independent experts agree that the clinical data do not support a causal link between the administration of tegaserod and the formation of ovarian cysts. For all of the foregoing reasons, tegaserod has a favorable risk-benefit profile that strongly supports approval. In this connection, we look forward to working with FDA toward final action on the tegaserod NDA.

I certify that to the best of my knowledge, information and belief that the statements made in this submission are true and accurate.

Respectfully submitted,

NOVARTIS PHARMACEUTICALS CORPORATION

By: _____

Dorothy P. Watson
Vice President, General Counsel

Enclosures (Submitted To Dockets Management Branch Only)

cc: Dockets Management Branch (HFA-305)
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May 21, 2001

Dockets Management Branch (HFA-305)
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Rockville, Maryland 20852

Dear Madam/Sir:

Pursuant to 21 C.F.R. § 10.20 and 10.30(d), Novartis Pharmaceuticals Corporation ("Novartis" or the "Company") submits for filing an original and four copies of its comments in response to and in opposition to the Citizen Petition filed by Public Citizen concerning Zelmac (tegaserod). Also enclosed are copies of materials referenced in Novartis' submission document.

We understand that Public Citizen's petition was submitted to Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research, and that an official docket has not been established as of yet for Public Citizen's petition. In this connection, kindly file the enclosed papers to the appropriate docket at the time a docket number is assigned to Public Citizen's petition.

Should you have any questions regarding this matter, please do not hesitate to contact me.

Very truly yours,

NOVARTIS PHARMACEUTICALS CORPORATION

By: _____
Mark D. Plinio
Pharmaceuticals Counsel

MDP/rva
Enclosures
cc: Janet Woodcock, MD