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Public Citizen



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Joan Claybrook, President

March 22, 2001

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

Dear Dr. Woodcock:

Public Citizen, a nationwide consumer organization with about 145,000 members, hereby strongly urges the Food and Drug Administration (FDA) not to approve the drug tegaserod (Zelmac, Novartis Pharmaceuticals), a drug for the treatment of constipation-predominant Irritable Bowel Syndrome (IBS) because of its highly questionable efficacy and because of serious safety concerns. According to information we have received from the FDA, tegaserod has been associated with eight cases of ovarian cysts in women in clinical trials, all on the highest dose of this drug. All eight developed symptoms in association with the use of tegaserod and five underwent hospitalization and surgery. FDA reviewers estimated that the risk of cysts was three times higher in tegaserod recipients than in placebo recipients. The true incidence of cyst induction is unknown because there was no ultrasonographic monitoring. These ovarian cysts might have been expected since, in animal studies, tegaserod caused a statistically significant, dose-related increase in their incidence.

In addition to ovarian cysts associated with symptoms, the drug also has questionable efficacy: none of the three pivotal trials demonstrated efficacy, as judged by the original, predetermined primary clinical endpoints. When it was seen, after the fact, that there was no significant improvement for either of the two original efficacy endpoints in the first completed trial, Novartis cunningly altered the endpoints for the other two ongoing (but still blinded) trials, eliminating one endpoint and redefining the other in a manner that created a lower threshold for declaring improvement. However, even this manipulation produced only one pivotal trial with a statistically significant result, and that result was only half of what Novartis had expected. There is no reason, other than wishful thinking, to

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Ralph Nader, Founder

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suggest that the "positive" trial should be given more weight than the "negative" trial in terms of deciding if the drug is actually efficacious.

Tegaserod is a drug to be marketed for constipation-predominant IBS, yet many of the patients in the trials were not constipated. The internationally recognized Rome Criteria for IBS constipation stipulate that patients have less than three bowel movements a week. In these trials, a large number of patients had five or more bowel movements per week. (This is in part due to regression to the mean, not uncommon when studying relapsing conditions.)

In sum, tegaserod was not tested in the appropriate patient population, appears to have very questionable efficacy, and has potentially serious adverse effects. Only a minority of patients "respond" and the absolute benefits conferred (compared to placebo) are not clinically significant. These minor benefits for a few must be weighed against the significant dangers of the drug and the ill-defined and non-life-threatening nature of IBS. The recent experience with the drug Lotronex, another drug for IBS (diarrhea-predominant), where pre-approval evidence of ischemic colitis was ignored, is an example of what can happen when warning signs from clinical trials are dismissed, particularly for marginally effective drugs. If the FDA approves this drug, it may well have to be withdrawn because of the high probability of seeing more cases of ovarian cysts once the drug reaches the less-carefully monitored and less healthy population at large.

There is an urgency in evaluating this petition since a decision on the approval of tegaserod is expected to occur soon: Novartis has received an "approvable" letter (August, 2000) with final approval dependent on submission of additional clinical data that were expected to be at FDA in December 2000. We therefore look forward to a prompt response to this petition.

MECHANISM OF ACTION

Tegaserod is thought to work by binding as an agonist to 5-hydroxytryptamine₄ (5-HT₄) receptors. (5-HT₄ is one of a family of 5-HT [serotonin] receptors.) Novartis was asked at the Advisory Committee meeting on tegaserod if there were 5-HT₄ receptors outside the gastrointestinal tract. The company responded that it had not looked, but that a literature survey had not revealed any 5-HT₄ receptors in the ovary.¹ Novartis later stated at the Advisory Committee meeting that there were 5-HT₄ receptors in atrial (heart) tissue.²

Public Citizen's own literature search uncovered multiple 5-HT₄ receptor sites, both peripheral and central, including a study by Novartis itself on 5-HT₄ receptors in human brain.³ The peripheral organ systems where the 5-HT₄

¹ Dr. Bruce Carr, Novartis; Advisory Committee Transcript for Zelmec; June 26, 2000, p.108.

² Dr. Hans Pfannkuche, Novartis; Advisory Committee Transcript for Zelmec; June 26, 2000, p.117.

³ Hoyer D, Fehlmann D, Langenegger D et al. High affinity of SDZ HTF-919 [tegaserod] and related molecules for calf and human caudate 5-HT₄ receptors. *Annals of the NY Academy of Sciences*

receptor is important include: the gastrointestinal tract, where it affects smooth muscle tone, mucosal electrolyte secretion, and the peristaltic reflex; the urinary bladder, where it modulates cholinergic/purinergic transmission; the heart, where it produces positive inotropy and tachycardia (potentially triggering arrhythmias); and the adrenal, where it stimulates release of cortisol, corticosterone, and aldosterone.⁴ (One study done in cells isolated from the human ovary found that a related 5-HT receptor [5-HT7] is involved in progesterone production.⁵)

Because tegaserod can bind to 5-HT4 receptors in many organs of the body, it is capable of causing adverse effects over a wide range of tissues. Clearly, this is a very complex area, and until the experiment is done to specifically look for 5-HT4 receptors in the human and rat ovary, the mechanism of cyst formation will not have been adequately evaluated.

SAFETY

For this part of the petition, we have utilized the data in the FDA Preliminary Medical/Statistical Review, the Gastrointestinal Drugs Advisory Committee Meeting Transcript (June 26, 2000), and a literature review.

OVARIAN CYSTS

Toxicity Data

Female rats treated with tegaserod for two years developed ovarian cysts at all three doses tested (20, 80 and 180 mg/kg/day). Twelve percent, 14%, and 20% of the animals, respectively, developed ovarian cysts, compared to 0-4% of control rats.⁶ The lowest dose tested was 16 times the exposure of humans, calculated on a surface-area basis. The fact that the incidence of ovarian cysts was still substantially elevated at the lowest dose tested makes it likely, if not certain, that ovarian cysts would have occurred at even lower doses, had these been studied.

A Medline search for papers on chemically-induced ovarian cysts in rats over the ten-year period 1990-2000 yielded only six chemicals: dehydroepiandrosterone,⁷ estradiol,⁸ human chorionic gonadotropin,⁹ valproate,¹⁰

molecules for calf and human caudate 5-HT4 receptors. *Annals of the NY Academy of Sciences* 1998;861:267-8.

4 Hegde SS, Eglen RM. Peripheral 5-HT4 receptors. *FASEB Journal* 1996;10:1398-407.

5 Graveleau C, Paust HJ, Schmidt-Grimminger D et al. Presence of a 5-HT7 receptor positively coupled to adenylate cyclase activation in human granulosa-lutein cells. *Journal of Clinical Endocrinology and Metabolism* 2000;85:1277-86.

6 FDA Preliminary Medical/Statistical Review; June 26, 2000, p.17.

7 Anderson E and Lee GY. The polycystic ovarian (PCO) condition: apoptosis and epithelialization of the ovarian antral follicles are aspects of cystogenesis in the dehydroepiandrosterone (DHEA)-treated rat model. *Tissue Cell* 1997;29:171-89.

8 McCarthy GF, Farookhi R, Brawer JR. Plasma gonadotropin patterns characterizing the development of polycystic ovaries in the estradiol valerate treated rat. *Canadian Journal of Physiology and Pharmacology* 1990;68:28-33.

RU-486,¹¹ and epidermal growth factor.¹² Since only a relatively small number of chemicals are known to cause ovarian cysts in animals, this finding should be taken very seriously. It would be inexcusable if the supplementary data generated by Novartis for FDA did not include prospective ultrasound monitoring for ovarian cysts.

Human Data

General: Ovarian cysts were also an adverse reaction in women. Ovarian cysts associated with symptoms occurred in eight patients on tegaserod and one patient on placebo in the four major clinical trials discussed in the Medical/Statistical Review (three 3-month trials: B351, B307, and B301 and one long-term trial without a control group: B209).¹³ The nine cases were ones in which women with cysts had enough pain to require medical intervention; how many cases of asymptomatic cysts were present in these women is unknown since there was no monitoring. While the sponsor has sought to dismiss many of these as unrelated to the drug, the fact is that they occurred disproportionately in the treated group of a blinded, randomized trial. The most straightforward explanation for a positive relationship in such a trial is usually that it is causal.

Non-surgical ovarian cysts: Information was not submitted on these four cases (three in the treated and one in the placebo groups) except to state that one treated patient and the one placebo patient had cysts due to Polycystic Ovarian Disease.

Surgical ovarian cysts: Of women with cysts, only women taking tegaserod required surgery (five of eight cases in the treated groups) and all cases were in high-dose women (see Table 1). Nevertheless, Novartis' investigators listed four of five of these cases in the New Drug Application as "unrelated" to the study drug and one of five "unlikely related"¹⁴. Adequate evidence for these categorizations was not provided. Of these five surgical cases, only two had pathology reports submitted to the FDA. All five of the surgical cases appeared after women had been on the drug for at least three months: three of five cysts were in the long-term, open-label study (B209) and occurred after 8, 10, and 11 months of tegaserod. The other two occurred near the end of 12-week studies (B307 and B351) (see Appendix 1).

9 Bogovich K, Clemons J, Poretsky L. Insulin has a biphasic effect on the ability of human chorionic gonadotropin to induce ovarian cysts in the rat. *Metabolism* 1999;48:995-1002.

10 TaubLL E, Isojarvi JI, Harbo HF, et al. Long-term valproate treatment induces changes in ovarian morphology and serum sex steroid hormone levels in female Wistar rats. *Seizure* 1999;8:490-3.

11 Ruiz A, Aguilar R, Tebar AM, et al. RU486-treated rats show endocrine and morphological responses to therapies analogous to responses of women with polycystic ovary syndrome treated with similar therapies. *Biology of Reproduction* 1996;55:1284-91.

12 Christiansen JJ, Vinter-Jensen L, Nielsen K. Systemic treatment in the rat with epidermal growth factor causes polycystic growth of the ovaries. *APMIS* 1996;104:147-52.

13 Dr. Raymond Joseph, FDA; Advisory Committee Transcript for Zelmec; June 26, 2000, p.154.

14 FDA Preliminary Medical/Statistical Review; June 26, 2000, Appendix.

TABLE 1: OVARIAN CYSTS ASSOCIATED WITH SURGERY

Study No.	Duration	0 mg	4 mg	12 mg
B351	12 weeks	0/267	0/265	1/267
B301	12 weeks	0/288	0/299	0/294
B307	12 weeks	0/284	0/282 ¹	1/275
B209	Variable	N/A	N/A	3/460 ²

¹ patients received 4 mg for four weeks and were increased to 12 mg for remaining eight weeks if they had not responded

² estimate based on 80% of 570 patients receiving 12 mg tegaserod for at least 10 months¹⁵

The rate of occurrence of cysts (both those associated with surgery and those not) was estimated in the Medical/Statistical Review to be three times higher in the treated groups than in placebo recipients. The reviewers felt that "further evaluation" was required.¹⁶ There is no evidence in the documents which FDA has made public that further evaluation has been done (e.g., periodic ultrasound tests on women in new studies).

As is the case for animals, only a few drugs appear to cause ovarian cysts in humans and their occurrence appears to be a rare event, based on a survey of Medline reports. Polycystic ovaries have been reported in women taking valproic acid,¹⁷ and ovarian cysts have been reported in women taking tamoxifen as treatment for breast cancer.¹⁸ This argues for taking the finding of increased incidence of ovarian cysts very seriously.

DIARRHEA

Diarrhea was the most common pre-approval adverse event and was seen in 11 to 12% of treated and 5% of placebo patients in pivotal trials.¹⁹ Severe diarrhea (mean duration seven days) was present in 2% of placebo compared with 4% of treated patients; it accounted for discontinuations in therapy in 0.4% of placebo and 1.6% of treated patients. The long-term open label study (B209) had "again headache and abdominal pain being the two most common adverse events," with a 15% rate of diarrhea.²⁰

15 Dr. Martin Lefkowitz, Novartis; Advisory Committee for Zelmac; June 26, 2000, p.112.

16 FDA Preliminary Medical/Statistical Review; June 26, 2000, p.16.

17 Isojarvi JI, Laatikainen TJ, Pakarinen AJ et al. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *New England Journal of Medicine* 1993;329:1383-8.

18 Mourits MJ, de Vries EG, Willems PH et al. Ovarian cysts in women receiving tamoxifen for breast cancer. *British Journal of Cancer* 1999; 79:1761-4.

19 Dr. Martin Lefkowitz, Novartis; Advisory Committee Transcript for Zelmac; June 26, 2000, p.111.

20 Dr. Martin Lefkowitz, Novartis; Advisory Committee Transcript for Zelmac; June 26, 2000, p.112.

SYNCOPE

Syncope (fainting) occurred in 0.5% of tegaserod patients and 0.1% of placebo patients.²¹ Syncope was a cardiac adverse effect seen with cisapride,²² also a partial 5-HT₄ receptor agonist. Cisapride was later largely withdrawn by the manufacturer due to cardiac arrhythmias. Novartis performed ECGs in patients on tegaserod and stated that they found no effect on the length of the QT interval,²³ an adverse effect which can cause arrhythmias and fainting. However, as in the case of ovarian cysts, the finding of syncope was dismissed with little effort made to investigate a possible mechanism.

EFFICACY

As mentioned, three randomized, placebo-controlled studies were conducted in support of tegaserod: B351, B301, and B307. All were 12-week, randomized, double-blind, placebo-controlled trials in men and women. In addition to placebo, Studies B351 and B301 used two tegaserod doses (4 and 12 mg) for the entire 12 weeks, while Study B307 had one group on 4 mg for the entire 12 weeks and another on 4 mg for 4 weeks followed by 12 mg for 8 weeks, if they had not responded to the 4 mg dose. All studies excluded "diarrhea-predominant" IBS patients. Each week, patients completed a questionnaire recording their IBS symptoms. The primary questions asked were the Subject's Global Assessment (SGA) of "relief" and SGA of "abdominal discomfort/pain." Permitted responses for SGA of relief were completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. This is, of course, a highly subjective and rather vague outcome measure. Bulking agents were permitted during the entire study; laxative use was permitted but had to be recorded.²⁴ (A much better design would have limited the patient population to those who were non-responsive to an adequate trial of bulk-forming laxatives.)

Study B351 was completed first. However, neither dose resulted in a statistically significant improvement over placebo for either of the two pre-defined primary efficacy measures (SGA of relief and SGA of abdominal discomfort/pain).²⁵ As a result of the lack of significant improvement in B351, Novartis dropped the criterion of SGA of discomfort/pain and relied completely on SGA of relief, which was broadened from "considerable or complete relief at least 50% of the time during the last 4 weeks on treatment" to also include "*OR somewhat, considerable, or complete relief for all of the last 4 weeks on treatment*"²⁶ (italics added). The addition of the "OR" condition, by definition,

21 FDA Preliminary Medical/Statistical Review; June 26, 2000, p.16.

22 Tonini M, De Ponti F, Di Nucci A et al. Review article: cardiac adverse effects of gastrointestinal prokinetics. *Alimentary and Pharmacologic Therapeutics* 1999;13:1585-91.

23 Dr. Martin Lefkowitz, Novartis; Advisory Committee Transcript for Zelnorm; June 26, 2000, pp.113-114.

24 Dr. Sonia Castillo, FDA; Advisory Committee for Zelnorm; June 26, 2000, p.134.

25 Dr. Sonia Castillo, FDA; Advisory Committee for Zelnorm; June 26, 2000, p.135.

26 FDA Preliminary Medical/Statistical Review for Zelnorm; June 26, 2000, p.5.

lowered the threshold for declaring relief. These changes in endpoints applied to the two ongoing, but still blinded, trials (B301 and B307). The extent of the data manipulation is illustrated by the fact that in B351 the response rate increased from 29.4% (original efficacy definition) to 38.9% (new efficacy definition) for the 4 mg group, and from 26.2% to 45.7% (a near-doubling) in the 12 mg group.

Using the original efficacy definition, SGA of relief was not statistically significantly improved in either B301 and B307 at either dose (4 or 12 mg) compared to placebo. Even the redefined single efficacy variable failed to produce a statistically significant result for either dose in B307.

With the new efficacy variable, B301 showed a statistically significant 9% and 8% absolute increase over placebo at 4 mg and 12 mg, respectively, an extremely modest, non-dose-related result. Novartis had based its sample size calculation on a 15% improvement compared to placebo.²⁷ Importantly, the placebo effect was stronger than the drug effect: about three-quarters of the reduction in symptom severity in B301 was due to the placebo effect (an extra 8% to 9% more than the 30% due to placebo).

²⁷ Dr. Martin Lefkowitz, Novartis; Advisory Committee for Zelmac; June 26, 2000, p.63.

TABLE 2: SUBJECT GLOBAL ASSESSMENT OF RELIEF IN MALE AND FEMALE PATIENTS COMBINED²⁸

Study	Original Efficacy Definition ¹			New Efficacy Definition ²		
	4 mg	12 mg	Placebo	4 mg	12 mg	Placebo
B351						
Response	29.4%	26.2%	22.1%	38.9%	45.7%	33.3%
Gain ³	7.5%	4.1%		6.0%	12.4%	
Adjusted p ⁴	0.200	0.370		0.314	0.016 ⁵	
B301⁶						
Response	27.8%	26.2%	20.5%	38.8%	38.4%	30.2%
Gain ³	7.6%	5.5%		9.1%	8.3%	
Adjusted p ⁴	0.056	0.116		0.033 ⁵	0.033 ⁵	
B307⁶						
Response	25.5% ⁷	26.5%	28.2%	38.3% ⁷	42.2%	37.0%
Gain ³	-3.0%	-1.4%		0.8%	6.0%	
Adjusted p ⁴	0.703	0.703		0.837	0.284	

¹ "considerable or complete relief at least 50% of the time during the last 4 weeks on treatment"

² includes both above "OR somewhat, considerable, or complete relief for all of the last 4 weeks on treatment"²⁹

³ percent difference between the drug and placebo group at end of study (taking into account center effect)

⁴ adjusted for two doses and for multiple comparisons

⁵ statistically significant (p<0.05)

⁶ pivotal trial

⁷ patients received 4 mg for four weeks and were increased to 12 mg for remaining eight weeks if they had not responded

28 FDA Preliminary Medical/Statistical Review for Zelmec; June 26, 2000, p.3.

29 FDA Preliminary Medical/Statistical Review for Zelmec; June 26, 2000, p.5.

POST-HOC META ANALYSIS (INCLUDING GENDER ANALYSIS)

As part of its application, Novartis submitted an assessment of tegaserod's efficacy that combined the results of all three randomized trials (both sexes) using a statistical technique called meta analysis. FDA reviewers felt the meta analysis to be unjustified because.³⁰

- a) it was not pre-specified in the protocol;
- b) this tactic would constitute a single trial necessitating a second trial;
- c) "statistical significance of post-hoc, pooled results is problematic;"
- d) the decision to pool was based on the non-significant results of one pivotal trial, B307;
- e) B351 was not a pivotal trial and should not be pooled with others;
- f) the studies were not homogeneous concerning 1) ethnic composition, 2) percentage of participating primary, secondary, and tertiary centers, and 3) baseline use of laxative;
- g) the primary endpoints were not the same;
- h) the design of B307 was different from other two (B307 had titration from 4 mg to 12 mg, while the other trials had only fixed doses);
- i) B307 should be analyzed using the original definition of relief because the original definition was used to determine if the patient was to be up-titrated after 4 weeks treatment;
- j) "the 4-12 mg dose titration in B307 [4 mg for first 4 weeks and 12 mg for next 8 weeks if patients failed to respond to the 4 mg dose] cannot be combined with 4 mg group for the month 1 pooled analyses and then with the 12 mg group for the at endpoint pooled analyses;"
- k) the sample size of each study was large so pooling was not necessary;
- l) "studies are not independent because the same U.S. principal investigators participated in two of the three studies;"
- m) pooling leads to an overall result that is not a useful guide to physicians.

For these reasons, presumably, the Preliminary Medical/Statistical Review did not include the results of Novartis' meta-analysis; we find these critiques of the methodology by FDA to be very compelling.

The company also presented a meta analysis of efficacy broken down by gender. The critique of the overall meta analysis (see a-m above) would apply as well to the gender meta analysis. The FDA Statistical Reviewer, however, did perform an analysis by gender for each of the separate randomized, placebo-controlled clinical trials. This analysis found no evidence of efficacy in males; in fact, in some studies, their IBS worsened. For females, there was some efficacy in B301, but not in B307 (see Tables 3 and 4 and Appendices 2-4).

³⁰ FDA Preliminary Medical/Statistical Review for Zelmac; June 26, 2000, p.11.

TABLE 3: EFFICACY IN MALES (% difference from placebo)

Study	Original Definition		New Definition	
	4 mg	12 mg	4 mg	12 mg
B351	5.6%	0.60%	-2.0%	-2.1%
B301 ¹	5.5%	-5.2%	0.48%	-7.8%
B307 ¹	-16% ²	-10%	0.09% ²	5.0%

TABLE 4: EFFICACY IN FEMALES (% difference from placebo)

Study	Original Definition		New Definition	
	4 mg	12 mg	4 mg	12 mg
B351	8.9%	5.2%	8.8%	15% ³
B301 ¹	7.6% ³	7.9% ³	10% ³	11% ³
B307 ¹	0.38% ²	0.43%	1.5% ²	5.2%

¹ pivotal trial

² patients received 4 mg for four weeks and were increased to 12 mg for remaining eight weeks if they had not responded

³ statistically significant ($p < 0.05$)

A similar gender effect was seen with the IBS drug, Lotronex. Even though that Advisory Committee concluded unanimously that efficacy in males had not been demonstrated, Lotronex was still prescribed to men despite the absence of demonstrable effectiveness. Indeed, three of the 43 cases of ischemic colitis associated with Lotronex reported to FDA occurred in men. We are concerned that the same thing could happen in this case. Furthermore, lack of efficacy in males increases doubts of any efficacy, even in females.

DEFINITION OF PATIENT POPULATION

In addition to questionable efficacy, the definition of the patient population used in these studies did not conform to the internationally accepted Rome Criteria for IBS constipation. One member of the Advisory Committee stated that Novartis enrolled those with an average of five or more bowel movements a week and that these patients had "not that firm of a stool,"³¹ whereas the Rome Criteria for IBS constipation called for an average of less than three movements a week. It appears that patients were entered into the study based on meeting the Rome Criteria, but that their condition spontaneously improved during the four-week run-in period, prior to the administration of tegaserod or placebo, to the point that many did not have constipation at all. Some patients even had a "diarrhea component,"³² according to an Advisory Committee member, which Novartis justified as their intent since "by not having strict stool consistency criteria" they could "enroll patients who would likely get the drug in clinical practice . . ." The problem is that now practitioners cannot know with confidence

31 Joel Richter, M.D., FDA consultant, Advisory Committee Transcript for Zelmac; June 26, 2000, p.79.

32 Martin Lefkowitz, M.D., Novartis, Advisory Committee Transcript for Zelmac; June 26, 2000, p.80.

in whom the drug has been tested and thus cannot make well-informed decisions about whom to treat.

LAXATIVE USE

Laxative use was a further confounding factor noted by the FDA's Medical and Statistical reviewers. Novartis did not adjust for laxative use which the FDA concluded "inflates responder rates in all treatment groups."³³ As mentioned above, the confounding effect of laxatives would have been better dealt with by limiting trial participants to those individuals who were found to be non-responders to bulk-forming laxatives.

CONCLUSIONS

SAFETY: Before approval is granted for tegaserod, Novartis should be required to investigate further the incidence of ovarian cysts, prospectively, using ultrasonography. In addition, Novartis should be required to conduct assays for the presence of 5HT4 receptors in rat ovaries; an analysis for receptors in human ovary should be made on those women with surgery for ovarian cysts. A pharmaceutical company should not be allowed to sweep aside issues relating to human safety by rationalizing them as "unrelated" to the drug (particularly after the unequivocal evidence that tegaserod causes ovarian cysts in animals), but should provide solid scientific data to back up any claims of safety.

Although Novartis dismissed the possibility that ovarian cysts are drug-related, there is evidence for the opposite view: only high-dose, long-term treatment produced cysts requiring surgery in women in the clinical trials (12 mg/day for ≥ 3 months) (see Table 1).

Had a requirement for a stronger showing of safety been in effect previously, many drugs, including the recently withdrawn Lotronex, would not have been approved and then withdrawn after harming additional patients. (In clinical trials, Lotronex caused ischemic colitis severe enough to require hospitalization, but the problem was dismissed by Glaxo Wellcome as having no relation to drug treatment.)

EFFICACY: The bottom line is this: according to the original protocol's definitions, none of the three double-blind, randomized clinical trials showed evidence of efficacy. Once Novartis saw this lack of efficacy in its first completed trial, it dropped one of the two primary endpoints and broadened the other. This kind of data manipulation is unacceptable. Obviously, a company should not be allowed to cherry-pick those outcomes most likely to cast its drug in a favorable light. These contortions had the effect of making the first trial significant on one outcome variable, but since the endpoint was changed post-hoc, the trial was no longer considered "pivotal". Even with the benefit of this carefully constructed

33 FDA Preliminary Medical/Statistical Review for Zelnac; June 26, 2000, p.13.

endpoint, only one of the two remaining pivotal trials had statistically significant results (an 8%-9% increase over placebo), only about half of what the company had used for its sample size estimates and overshadowed by the placebo effect. Thus, even with redefined endpoints, we have one positive and one negative trial with no scientific rationale to accept results from one over the other. Moreover, in neither pivotal trial was there evidence of efficacy in males (regardless of the definition of endpoints) and in females only one trial showed (modest) efficacy.

IBS is a poorly defined disease, which, although capable of causing significant distress in some individuals, is neither progressive nor life-threatening. If approved, the use of this drug will spread to less healthy and more poorly monitored populations, and, as prescribing extends beyond the 3-month duration of the double-blind clinical trials, there will almost certainly be an increase in the number and severity of adverse events, as has occurred in the longer, open-label clinical trial. The lack of testing in a truly constipated population, the inability to replicate efficacy results, and the worrisome incidence of ovarian cysts in both humans and animals should tip the risk-benefit equation against approving this drug. Because the FDA has already sent an approvable letter to Novartis, it is urgent that this petition be evaluated quickly, before any final decision is reached.

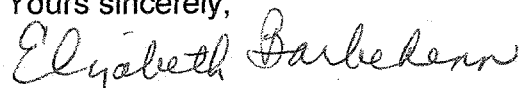
ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Yours sincerely,



Elizabeth Barbehenn, Ph.D.
Research Analyst



Peter Lurie, MD, MPH
Deputy Director



Sidney M. Wolfe, MD
Director
Public Citizen's Health Research Group

APPENDIX 1: CASE REPORTS OF OVARIAN CYSTS ASSOCIATED WITH SURGERY

Age; day of first symptom	Pathology	Notes
50 year old; day 334	Patient's ob/gyn stated findings as bilateral ovarian endometriosis and benign serous adenofibroma of left-ovary	Discharge notes & pathology report requested by Novartis but were not provided. Finding "unrelated" to drug (investigator)
45 year old; day 245	Ovarian cyst diagnosed originally on "Severe Adverse Event Report" but Novartis' staff changed the diagnosis to 'adhesions' after surgery	"no mention of any pathology sent out and no reports were found;" "unrelated" to drug, according to investigator
36 year old; day 306	"3.5 cm thin-walled, partially luteinized follicle cyst and scattered small cysts in the remainder of the R[ight]-ovarian cortex." Possible right ovarian cyst prior to study	Clinical description: "Ovarian tumors"; CT scan reveals "probable ovarian cyst"; pathology report: Ovary cystic and hemorrhagic over 4.5 x 4 cm; large cyst filled with serous fluid; remainder of cortex has scattered small cortical cysts. "unrelated" to drug, according to investigator
37 year old; day 86	Right ovarian cyst believed to have ruptured	"CT scan shows 2.7 cm ovarian [?] cyst on right ovary"; "unlikely" related according to investigator
13 year old; 3 months	Bilateral cysts removed on 3/98. Treatment started 6/98; patient had surgery on 9/98 for right-ovarian cyst (4.0 to 5.0 cm) and found to have cyst and early acute appendicitis	No cyst histology provided; hospital discharge notes requested but not obtained; "unrelated" according to investigator

**APPENDIX 2: SUBJECT GLOBAL ASSESSMENT OF RELIEF BY GENDER
(STUDY B351)³⁴**

	Original Efficacy Definition ¹			New Efficacy Definition ²		
	4 mg	12 mg	Placebo	4 mg	12 mg	Placebo
Males (n=100)						
Response	24.3%	19.4%	18.8%	32.4%	32.3%	34.4%
Gain ³	5.6%	0.60%		-2.0%	-2.1%	
Adjusted p ⁴	1.0	1.0		1.0	1.0	
Females (n=675)						
Response	30.9%	27.2%	22.0%	40.9%	46.9%	32.2%
Gain ³	8.9%	5.2%		8.8%	14.8%	
Adjusted p ⁴	0.082	0.231		0.062	0.004 ⁵	

¹ "considerable or complete relief at least 50% of the time during the last 4 weeks on treatment"

² either above "OR somewhat, considerable, or complete relief for all of the last 4 weeks on treatment"

³ percent difference of response rates between the drug and placebo group (taking into account center effect)

⁴ adjusted for two doses and for multiple comparisons

⁵ statistically significant ($p < 0.05$)

**APPENDIX 3: SUBJECT GLOBAL ASSESSMENT OF RELIEF BY GENDER
(STUDY B301)³⁵**

Males (n=150)	Original Efficacy Definition¹			New Efficacy Definition²		
	4 mg	12 mg	Placebo	4 mg	12 mg	Placebo
Response	34.6%	24.0%	29.2%	44.2%	36.0%	43.8%
Gain ³	5.5%	-5.2%		0.5%	-7.8%	
Adjusted p ⁴	0.54	0.75		0.56	0.56	
Females (n=731)						
Response	26.3%	26.6	18.8%	37.7%	39.0%	27.5%
Gain ³	7.6%	7.9%		10.2%	11.4%	
Adjusted p ⁴	0.039 ⁵	0.039 ⁵		0.013 ⁵	0.012 ⁵	

¹ "considerable or complete relief at least 50% of the time during the last 4 weeks on treatment"

² either above "OR somewhat, considerable, or complete relief for all of the last 4 weeks on treatment"

³ percent difference of response rates between the drug and placebo group (taking into account center effect)

⁴ adjusted for two doses and for multiple comparisons)

⁵ statistically significant ($p < 0.05$)

**APPENDIX 4: SUBJECT GLOBAL ASSESSMENT OF RELIEF BY GENDER
(STUDY B307)³⁶**

	Original Efficacy Definition ¹			New Efficacy Definition ²		
	4 mg	12 mg ³	Placebo	4 mg	12 mg ³	Placebo
Males (n=135)						
Response	15.9%	22.0%	32%	34.1%	39.0%	34.0%
Gain ⁴	-16.1%	-10.1%		0.09%	5.0%	
Adjusted p ⁵	0.29	0.36		0.86	0.86	
Females (n=700)						
Response	27.5%	27.6%	27.2%	40.0%	42.7%	37.5%
Gain ⁴	0.38%	0.43%		1.5%	5.2%	
Adjusted p ⁵	0.98	0.98		0.93	0.57	

¹ "considerable or complete relief at least 50% of the time during the last 4 weeks on treatment"

² either above "OR somewhat, considerable, or complete relief for all of the last 4 weeks on treatment"

³ patients received 4 mg for four weeks and were increased to 12 mg for remaining eight weeks if they had not responded

⁴ percent difference of response rates between the drug and placebo group (taking into account center effect)

⁵ adjusted for two doses and for multiple comparisons

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