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Joan Claybrook, President

August 31, 2000

Jane Henney, M.D.
Director, Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Henney:

Public Citizen, a nationwide consumer organization with about 145,000 members, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately remove from the market the drug alosetron (Lotronex, Glaxo Wellcome), a drug for the treatment of Irritable Bowel Syndrome (IBS) because, according to new information we have just received from the FDA as of August 28, 2000, it has been associated with a total of at least 26 cases of ischemic colitis. Seven of these cases occurred in clinical trials and 19 in the first six months it has been marketed. (Ischemic colitis results from a lack of blood flow to the colon leading to death of bowel tissue.) Four of these have not been publicly announced before and 20 (76%) required hospitalization. Thirty-eight percent of these cases occurred in women aged 50 or younger (including cases among women aged 20, 25, 32, and 33), even though ischemic colitis is extraordinarily rare in patients of this age group. An additional 10 cases that are very suspicious for ischemic colitis have also been reported to FDA.

Moreover, the efficacy of alosetron on the primary outcome measure is limited, with only 10 to 15% of women responding above the approximately 40% of people who respond to placebo alone. Similarly, on a scale of 0 to 4 for abdominal pain/discomfort, alosetron only relieved their symptoms 0.12 to 0.14 more than a placebo. Because IBS is a poorly defined disease, which, although capable of causing significant distress in some individuals, is neither progressive nor life-threatening, the occurrence of serious adverse reactions to Alosetron, such as ischemic colitis sometimes requiring surgery, tips the risk-benefit equation against using the drug.

Ralph Nader, Founder

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Safety

For this part of the petition, we have utilized the data in the FDA Medical Officer Reviews, the transcript of the Gastrointestinal Drugs Advisory Committee Meeting (June 27, 2000), and the FDA Adverse Event Reports through August 28, 2000.

Clinical Trials

i. Ischemic colitis

Ischemic colitis was completely unexpected as an adverse reaction to alosetron. The FDA team leader stated that IBS "is certainly not [normally] associated with ischemic colitis".¹ However, according to the FDA Medical Officer, "With three cases, one in each of the three studies of approximately 300 patients on alosetron . . . , it will be particularly important to be alert for additional cases in the long-term [post-approval] studies."² In contrast to the 3 cases of ischemic colitis in 832 patients (1/277) on alosetron, there were none in 700 placebo patients in the three major clinical trials.³ (A fourth pre-approval case has subsequently been reported by Glaxo.)⁴ Nevertheless, the company misleadingly listed all these cases in the New Drug Application as "unrelated" to the study drug⁵, even though the disease is extremely rare in this age group.

These trials only lasted three months, so the cumulative incidence is likely to grow as more patients remain on the drug for protracted periods of time. (Alosetron cures no one.) Glaxo has continued to conduct clinical trials even after drug approval. Three more cases of ischemic colitis have occurred in these trials, for a total of seven in clinical trials (see Table 1).⁶

¹Hugo Gallo-Torres, M.D., FDA Team Leader, Gastrointestinal Drugs Advisory Committee, June 27, 2000, p.123.

² John Senior, M.D., FDA Medical Safety Review, October 25, 1999; p.37.

³ Ibid; p.17.

⁴ Glaxo Wellcome Briefing Document; FDA Advisory Committee Meeting on alosetron; June 27, 2000, p.13.

⁵ Ibid; pp.24, 29, 36.

⁶ Allen Mangel, M.D., Glaxo Wellcome, Gastrointestinal Drugs Advisory Committee, June 27, 2000, p.40.

Table 1. Ischemic colitis in clinical trials⁷

Age (years)	Alosetron Treatment Days	Hospitalization (days)
33	2	4
41	54	3
48	23	1
61	7	6
20*	2	3
64*	2	None
57*	4	None

*new cases since approval

ii. Constipation

Constipation was the most common pre-approval event and was seen in approximately 30% of treated and 5% of placebo patients. According to the reviewing FDA Medical Officer, "The applicant company, in planning these pivotal trials, had become fully aware of the problem of alosetron-induced constipation . . ."⁸ To reduce problems in their patients, "both protocols included provisions for study drug interruption for 4 days if the patient had no stools for 4 consecutive days . . .". This process could be repeated, if necessary, for another 4 days. If there was still no stool after 8 days, the patient was withdrawn from the study. Data from Studies 3001 and 3002 are given below (see Tables 2 and 3).

Table 2. Cycles of drug withdrawal due to constipation in Study 3001⁹

Cycles of drug withdrawal	Placebo	Alosetron
One cycle	3%	10%
Two cycles	0.9%	2%

Table 3. Cycles of drug withdrawal due to constipation in Study 3001¹⁰

Cycles of drug withdrawal	Placebo	Alosetron
One cycle	2%	9%
Two cycles	0.3%	2%

⁷ Glaxo Wellcome Briefing Document; FDA Advisory Committee Meeting on alosetron; June 27, 2000, pp.13 & 21-22

⁸ John Senior, M.D., FDA Medical Safety Review, October 25, 1999, p.38.

⁹ Ibid; p.32

¹⁰ Ibid; p.39

Post-Approval

i. Ischemic Colitis

Since drug approval in February 2000, the number of cases of ischemic colitis has continued to increase: by the June 1, 2000 cutoff date for the June 26, 2000 Gastrointestinal Drugs Advisory Committee meeting, there were a total of 7 cases from clinical trials and 5 from post-marketing, of which 8 required hospitalization. We have counted 14 more cases (see Table 4) of ischemic colitis (for a total of 26) between June 1 and August 28, 2000 in the FDA Adverse Event Reports, 10 of which required hospitalization. Two of the cases of ischemic colitis occurred in men (for whom the drug is not indicated), an indicator of the increasing problems that often emerge once a drug is marketed and the drug is used outside the controlled setting of the clinical trial. The post-marketing division of FDA looked at the incidence of ischemic colitis and constipation with other drugs used in IBS and found that "this really is a huge signal here".¹¹

Table 4. Cases of ischemic colitis outside of clinical trials, February 28 to August 28, 2000

Month/year	Age/sex	Finding	Outcome
4/18/00	55/M*	Colitis ischemic	Other
4/21/00	59/F	Colitis ischemic	Hospitalization
5/11/00	61/F	Colitis ischemic	Hospitalization
5/15/00	56/F	Colitis ischemic	Hospitalization
5/16/00	50/F*	Colitis ischemic	Other
5/30/00	53/F*	Colitis ischemic	Hospitalization
5/5/00	46/F*	Ischemic colitis	Hospitalization
5/5/00	51/F*	Colitis ischemic	Hospitalization
6/19/00	69/F	Colitis ischemic	Hospitalization
6/21/00	42/F	Colitis ischemic	Other
7/7/00	?/M	Colitis ischemic	Other
7/19/00	62/F	Colitis ischemic	Hospitalization
7/19/00	44/F	Colitis ischemic	Hospitalization
7/19/00	?/M	Colitis ischemic	Hospitalization
7/19/00	82/F	Colitis ischemic	Hospitalization
7/24/00	56/F	Colitis ischemic	Hospitalization
7/26/00	?/F	Colitis ischemic	Hospitalization
8/8/00	25/F	Colitis ischemic	Hospitalization
8/11/00	32/F	Colitis ischemic	Hospitalization

*Post-marketing cases mentioned by Glaxo Wellcome at June 27, 2000 Advisory Committee meeting.

¹¹ Evelyn Rodriguez, M.D., MPH; FDA Post-Marketing Division, Gastrointestinal Drugs Advisory Committee, June 27, 2000, p.148.

The number of ischemic colitis cases is certainly greatly undercounted because 1) many suspected cases only had flexible sigmoidoscopies which would miss the disease when it occurs at the splenic flexure, beyond reach of the sigmoidoscope¹²; and 2) post-marketing surveillance relies on spontaneous reports by physicians, patients and drug companies. Since most adverse event cases are never reported to the FDA, one must multiply these 24 cases by a factor of 10, at a minimum, to estimate the true number of cases of ischemic colitis. FDA has acknowledged that the "huge signal" for ischemic colitis in IBS patients taking Alosetron may still be only a small part of what actually exists: "it is going to be difficult to ascertain all of these cases in automated databases because the . . . codes are non-specific. . . and there would be substantial under-reporting for a diagnosis of constipation".¹³

FDA's Adverse Events Reporting System database contains an additional 10 post-approval cases which were suspicious for ischemic colitis (see Table 5).

Table 5. Post-approval cases suspicious for ischemic colitis, February 28 to August 28, 2000

Month/year	Age/sex	Finding	Outcome
4/12/00	?/F	Intestinal ischemia	Other
4/18/00	44/F	Colitis	Disability
6/7/00	68/F	Colitis	Hospitalization
6/7/00	?/F	Colitis/rectal bleeding	Disability
6/16/00	72/F	Colonic perforation	Hospitalization
6/16/00	76/F	Intestinal ischemia	Hospitalization
7/7/00	39/F	Colonic perforation	Hospitalization
7/12/00	70/F	Colitis/rectal bleeding	Hospitalization
7/19/00	29/F	Colitis Nos	Hospitalization
8/16/00	69/F	Colitis Nos	Hospitalization

¹² Mark Welton, M.D., FDA Consultant, GI Drugs Advisory Committee, June 27, 2000, p.162.

¹³ Evelyn Rodriguez, M.D., MPH; FDA, Gastrointestinal Drugs Advisory Committee, June 27, 2000, p.148

ii. Constipation

There are now six reports of cases of constipation in addition to those occurring in the pivotal clinical trials severe enough to require hospitalization (see Table 6).

Table 6. Constipation cases, February 28 to August 28, 2000¹⁴

Age	Treatment days	Outcome
54*	7	Hospitalization
56*	27	Hospitalization
50	No data	Hospitalization
"70s"	7	Hospitalization
"Adult"	2	Hospitalization
48	7-10	Hospitalization
32	12	No Hospitalization
77	"several"	No Hospitalization

*Cases seen in clinical trials

Efficacy

Glaxo-Wellcome submitted two "pivotal" studies in support of alosetron's efficacy. These are known as Studies 3001 and 3002. We have obtained the alosetron Medical Officer's review,¹⁵ which describes both studies in detail. In addition, we have reviewed a published article based on Study 3002.¹⁶ Both studies were randomized, double-blinded, placebo-controlled studies using the same alosetron dose with over 300 patients in each arm for three months. Both studies excluded "constipation-predominant" IBS patients. After the study was completed, in an unblinded analysis, the remaining patients were divided into diarrhea-predominant and "alternating" patterns (these patients alternated between diarrhea and constipation), although it is clear that these categories overlapped considerably.

Study 3001

The primary efficacy measure in the studies was "adequate relief of IBS pain/discomfort." Patients used a touch-tone dialing system on a daily basis to indicate whether they considered their relief "adequate" or not and to report other symptoms. The primary statistical analysis measured whether patients indicated that they had "adequate" relief in at least two of the four preceding weeks.

¹⁴ Glaxo Wellcome Briefing Document; FDA Advisory Committee Meeting on alosetron; June 27, 2000, p.24-26.

¹⁵ Prizont R. Medical Officer Review (alosetron). Division of Gastrointestinal and Coagulation Drug Products. Food and Drug Administration, November 4, 1999.

¹⁶ Camilleri M, Northcutt AR, Kong S, et al. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. *Lancet* 2000;355:1035-1040.

There was some evidence of alosetron efficacy in this trial. For the full study population, more patients on alosetron (41%) than placebo (26%) had "adequate" relief for all three months of the trial. This is, of course, a highly subjective and rather vague outcome measure. Moreover, the degree of benefit is modest: 85% of patients (100%-[41%-26%] (the difference between the alosetron and the placebo groups)) did not benefit from the effects of receiving the drug.

Furthermore, patients will experience only minimal additional degree of relief from the drug beyond that due to the placebo. The absolute benefit for abdominal pain/discomfort scores at month three for the diarrhea-predominant patients (the only group for which the drug is now indicated) was only 0.12 better on a 0-4 scale for alosetron compared to placebo (see Figure 1). Most (86%) of the apparent change in alosetron abdominal pain/discomfort scores at month three was actually due to a decrease in these scores in the placebo group. On the endpoint of the number of months with >50% pain/discomfort-free days, there was no benefit from the drug. The full study population did have statistically significant improvements in stool consistency and frequency.

Finally, it should be noted that many of the patients in this trial did not really have diarrhea sufficient to meet diagnostic criteria. As the Medical Officer said, "**IBS patients enrolled in this study did not meet the definition of diarrhea, either by applying the stool consistency scores developed by the sponsor, or by applying the diagnostic Rome Criteria for IBS diarrhea.**"¹⁷ (emphasis in original)

Study 3002

Study 3002 had generally similar results to Study 3001. Forty-one percent of all alosetron patients had "adequate" relief for all three months of the trial, compared to 29% on placebo. Eight-eight percent of patients did not benefit from the effects of the drug (100%-[41%-29%]) and the absolute benefit for abdominal pain/discomfort scores for all patients (the copy of the Medical Officer's review we obtained through the Freedom of Information Act did not include separate data for diarrhea-predominant patients) was only 0.14 better for alosetron than placebo on a 0-4 scale after three months (see Figure 2). Most (84%) of the apparent improvement on alosetron was also apparent in the placebo group. As in Study 3001, there was no benefit from the drug on the number of months with >50% pain/discomfort-free days for all patients (the drug appeared to be efficacious for the diarrhea-predominant patients, but was actually harmful to the alternators on this measure). Patients with both the diarrhea-predominant and alternating stool patterns did have statistically significant improvements in stool consistency and frequency.

¹⁷ Prizont R. Medical Officer Review (alosectron). Division of Gastrointestinal and Coagulation Drug Products. Food and Drug Administration, November 4, 1999, p. 30.

As for Study 3001, the Medical Officer questioned whether the diarrhea-predominant patients in Study 3002 really had diarrhea: "Patients considered by investigators to fit the diarrhea-predominant subtype had at baseline ... **stool consistency values that were neither loose nor watery.**"¹⁸ (emphasis in original)

In sum, alosetron appears to be a drug of only limited efficacy. Only a minority of patients respond and the absolute benefits conferred (compared to placebo) are not very significant clinically. These benefits must be weighed against the dangers of the drug and the ill-defined and non-life-threatening nature of IBS.

Conclusions

There is no way to justify using a minimally effective drug that is only palliative for a non-life-threatening condition, and, in the process, putting women at risk of ischemic colitis, which can be life-threatening, and its serious complications which have required intestinal surgery, including colectomy. As use of this drug spreads to less healthy and more poorly monitored populations, and prescribing extends beyond the 3-month duration of the clinical trials, we will surely see a continued increase in the number and severity of adverse events, and almost certainly, fatalities.

We do not believe that the proposed labeling changes will adequately protect patients. FDA's Dr. Evelyn Rodriguez has found through her studies that labeling changes and "Dear Doctor" letters are not particularly helpful: "providers and patients are confused and do not understand after multiple re-labelings what the really important message is".¹⁹ The likelihood is that the "Dear Health Professional" letters and revised labeling will only continue to expose patients to unnecessary serious health hazards.

FDA has also proposed issuing its first Medication Guide for patients taking alosetron. This starts the important Medication Guide program off on the wrong foot, as its first use will be to avoid the banning of a dangerous drug, rather than simply the informing of patients, of its intended use. In this situation, the Medication Guides shift too much responsibility into the hands of patients to promptly diagnose what could be, for them, a serious or life-threatening situation. You will have best protected patients when you assure that this drug is banned.

ENVIRONMENTAL IMPACT STATEMENT

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

¹⁸ Ibid; p. 39.

¹⁹ Ibid; p. 154.

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,



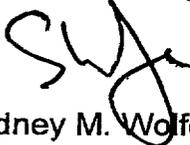
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**Figure 1: Trend in Mean Pain/Discomfort Scores:
Diarrhea-Predominant Patients, Study 3001**

