April 18, 2002

VIA OVERNIGHT DELIVERY

[illegible] Thomas H. Perez
United States Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-0001

Re: Notice to the FDA of Twenty-Seven Lotronex Injuries and Opposition to Reintroduction of Alosetron (formerly sold as Lotronex)

Dear Ms. Mackey and Mr. Perez:

This is a submission on behalf of twenty-seven Lotronex-injured patients represented by this firm, all of whom strongly oppose any reintroduction of Alosetron, formerly sold as Lotronex. Our clients have all suffered serious physical injuries as a result of their ingestion of Lotronex and believe that Lotronex's many serious dangers strongly outweigh any and all potential benefits.

This submission in opposition to Lotronex includes complete copies of all available medical and pharmacy records for each of the twenty-seven clients, who are identified by initials and whose injuries are summarized on Exhibit A hereto for your convenience. Their medical and pharmacy records are produced to you pursuant to the Medwatch program and in reliance upon our understanding that you will keep these patients' individual identities and medical records private and confidential. We hope that this submission will be helpful to you in connection with the upcoming meeting on April 23, 2002 in Bethesda, Maryland to "discuss risk management for new drug application 21-107 Lotronex (Alosetron)."

In further opposition to the reintroduction of Lotronex, our clients submit that there is no justification sufficient to justify the reintroduction of Lotronex in light of extremely modest demonstrable benefits and enormous risks of serious injuries and death. Notably, Irritable Bowel Syndrome (IBS) is a common, non-life threatening gastrointestinal disorder. The disorder has poor specificity and is diagnosed after other disorders are excluded. Symptoms of the IBS disorder include abdominal pain or discomfort with diarrhea and/or constipation often accompanied by bloating. While IBS is inconvenient, can involve abdominal pain, often requires frequent bouts of defecation and can have adverse effects on quality of life, IBS is never

life-threatening and has never been associated with ischemic colitis (Camilleri 2001, Kupecz 2000).

Pre-approval clinical trials of Lotronex demonstrated, at best, extremely modest success in treating IBS. Indeed, as well-explained in the Public Citizen Group's August 31, 2000 Petition to Remove Lotronex From the Market, only 10% to 15% of women responded to Lotronex above the 40% who responded to placebo alone. Similarly, Lotronex only relieved symptoms 0.12 to 0.14 more than placebo, according to the abdominal pain/discomfort scores at month three for the diarrhea-predominant patients and on the endpoint of the number of months with more than 50% pain/discomfort-free days, there was no benefit from the drug. These very modest potential benefits are outweighed by an unprecedented number of serious injuries, hospitalizations and deaths resulting from Lotronex-induced ischemic colitis, toxic megacolon, diverticulitis, necrotic bowel, severe constipation, blood clots and other problems, including severe permanent IBS exacerbation.

Of course, Lotronex is only a palliative treatment for those few people who respond and it has no claimed benefit of any kind following cessation of use and, as a result, needs to be taken chronically. However, chronic use is particularly dangerous since the association with ischemic colitis appears to be dose duration dependant.

When Lotronex was first marketed, the product labeling said ischemic colitis had occurred "infrequently" in clinical studies. Only in August, 2000 was the labeling changed and doctors advised that 1 in 700 women taking Lotronex were at risk of ischemic colitis. However, the true risk appears to be that 1 in 218 women who ingested Lotronex for three months would develop ischemic colitis and a dose duration relationship was found, according to FDA epidemiologist Dr. Zili Li, "The longer a woman is on the treatment, the more likely it is she will develop an episode of ischemic colitis." April 2, 2001 memo.

In addition to ischemic colitis, nearly 30 percent of patients in clinical studies experienced mild to severe constipation, which is noteworthy because it and/or abdominal pain were often the only early symptom of ischemic colitis. Unfortunately, constipation and abdominal pain would not normally alert the IBS patient to any drug side effect because these individuals often already suffered from these problems in connection with irritable bowel syndrome. Therefore, there is no reliable way to detect or avoid early signs of Lotronex-induced ischemic colitis. This is all the more problematic because ischemic colitis can and does occur in some patients with just one or two Lotronex doses.

Finally, the experience of our clients reveals another serious Lotronex side effect which has never been discussed and never studied: Lotronex exposure causes significant incidences of severe, permanent exacerbation of the patient's IBS in the form of severe cramping, pain and constipation and/or diarrhea far worse than any IBS problem which existed prior to Lotronex exposure. (See LCHB patient records and injury descriptions for examples). The existence of a serious post-Lotronex IBS exacerbation injury is supported by earlier studies of infectious or idiopathic colitis causing worsening of IBS. Collins, S.M. et al., *The Putative*

Role of Inflammation in the Irritable Bowel Syndrome, Gut, 2001; 49:743-745. This means that Lotronex actually forever worsens the very condition it is supposedly "treating."

Each of the patients that we represent asks the FDA to ensure that no one else ever has to undergo the terrible suffering and injuries that they sustained from Lotronex and, as a result, that Lotronex never be re-introduced under any circumstance because there is no safe and no effective use of the product.

Thank you for your time and consideration.

Very truly yours,

Fabrice N. Vincent

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EXHIBIT A

Summary of LCHB's Lotronex Patient Injuries

	Patient	Records Produced	Brief Description of Injuries Sustained from Lotronex
1.	KA		Lotronex-induced ischemic colitis in 44-year-old female New York resident (40-70 cm of colon affected, not yet treated surgically); permanent IBS exacerbation in the form of severe lower abdominal cramping and diarrhea much worse than any pre-Lotronex IBS.
2.	PA		Lotronex-induced ischemic colitis in 63-year-old female New York resident; severe ongoing exacerbation of IBS in the form of severe and unpredictable cramping significantly worse than any pre-Lotronex IBS.
3.	KB		Acute Lotronex-induced reaction in a 36-year-old woman from Mississippi involving extreme abdominal pain, severe bloating.
4.	CB		37-year-old woman hospitalized in Kentucky for three days with severe Lotronex-induced abdominal pain following ingestion of Lotronex; she now has a permanently bloated stomach.
5.	CB2		Severe Lotronex-induced constipation/colonic inertia in a 39-year-old woman from Illinois whose doctor at one time posited colon removal surgery as a result of Lotronex problems (which she declined to date to undergo); hospitalized with severe constipation for one week.
6.	TC		Lotronex-induced ischemic colitis and severe permanent IBS exacerbation in the form of severe pain and cramping and bleeding, far worse than any pre-Lotronex IBS, rectal fissures, and bleeding in 48-year old female Utah resident.
7.	RD		Lotronex-induced ischemic colitis in a 54-year-old woman from Florida; permanent worsening of IBS and rectal incontinence.
8.	DG		Lotronex-induced ischemic colitis in 43-year-old female from South Carolina, causing her to lose more than 40% of her colon (hemicolectomy); rectal fissures which may still require surgery; permanent disability.
9.	JG		Ischemic colitis and necrotic bowel caused by taking Lotronex in 57-year-old woman from Colorado requiring colon removal surgery (1/3 removed) (right hemicolotomy); multiple serious surgical complications, including pulmonary edema, hypotension and tachycardia, which required two week hospitalization.
10.	AH		Lotronex-induced acute abdominal pain and related temporary disability in Mississippi female.

	Patient	Records Produced	Brief Description of Injuries Sustained from Lotronex
11.	JH		Lotronex-induced ischemic colitis in a 45-year-old nurse from Georgia; permanently disabled; extremely distended abdomen; constant abdominal pain; extreme difficulty defecating; permanent IBS exacerbation far worse than any pre-Lotronex IBS; hypertension, hypoxia, tachycardia, dypsnea and edema.
12.	OJ (de-ceased)		Lotronex-induced bowel obstruction, followed by death in 83-year old female from Alabama.
13.	EK		Lotronex-induced diverticulitis and related colon surgery and surgical complications (infection) (1 foot of colon removed) (sigmoid colectomy) in a 59-year-old woman from Ohio; two weeks hospitalization; permanent worsening of IBS far worse than any pre-Lotronex IBS and typified by pain and constipation alternating with diarrhea .
14.	PK		Lotronex-induced diverticulitis and/or ischemic colitis in a 61-year-old female from California who required colon repair surgery, and a colostomy bag for several months; 18 day hospitalization (plus six further days hospitalization to remove colostomy); increased colon pressure and decreased muscle control causing incontinence.
15.	LK		Lotronex-induced toxic megacolon and pseudomembraneum colitis requiring complete colon removal surgery in a 24-year-old female student from Michigan; has returned to school after a long convalescence but remains severely anemic (will likely require transfusions) and has great difficulty absorbing sufficient nutrition to maintain a healthy weight; re-hospitalized for two weeks in March 2002 for serious post-operative infection and complications (hospitalized for abdominal abscess discovered at incision site during 1 year post-op check up, and then contracted staph infection and pancreatitis.)
16.	LL		Worsened IBS from Lotronex in 29-year-old woman from Oregon who sustained acute illness from Lotronex.
17.	HP		Lotronex-induced severe constipation and hospitalization in young woman from Missouri.
18.	JR		Lotronex-induced severe constipation requiring hospitalization in 47-year-old woman from Georgia; rectal bleeding and recommended future surgery to remove sigmoid colon, partially disabled from work; permanent severe IBS exacerbation in the form of severe chronic constipation requiring regular enemas, far worse than all pre-Lotronex IBS problems.
19.	JR2		Lotronex-induced ischemic colitis and permanent, severe IBS exacerbation in 46-year-old female Idaho resident.

	Patient	Records Produced	Brief Description of Injuries Sustained from Lotronex
20.	SR		Lotronex-induced ischemic colitis and pseudomembranous colitis in 80-year-old female New York resident who also suffered serious secondary complications including yeast sepsis, ARDS, recurrent depression and renal failure; completely disabled and ten month hospitalization/rehabilitation.
21.	MS		Acute adverse reaction to Lotronex in 60-year-old retired California resident; permanent worsening of IBS in the form of severe abdominal pain and chronic constipation far worse than any pre-Lotronex IBS.
22.	PS		Lotronex-induced ischemic colitis in a 51-year-old male from Tennessee and permanent worsening of IBS.
23.	LVD		Lotronex-induced hospitalization for severe constipation and diverticulitis in a 58-year-old female resident of Texas; permanent, severe IBS exacerbation in the form of severe constipation and rectal incontinence — neither of which existed prior to Lotronex.
24.	CW		Lotronex-induced abdominal blood clot which was potentially fatal and required hospitalization and long-term medication in a 55-year-old Florida resident; permanent worsening of IBS in the form of severe constipation and chronic pain far worse than all pre-Lotronex IBS; disabled since 9/00.
25.	TW		Overall worsening of IBS and significant anal stenosis from Lotronex in 35-year-old Michigan resident; ulceration, erythema, marked scarring and inflammatory changes in anal canal; symptomatic recurrent high-grade ileal J-pouch anastomotic stricture due to localized chronic inflammation, requiring surgery.
26.	HW		Lotronex-induced severe IBS exacerbation in 45-year-old woman from Michigan who still experiences recurrent episodes of severe abdominal pain, nausea, fever, and diarrhea much, much worse than all pre-Lotronex IBS problems.
27.	KY		Lotronex-induced hospitalizations for severe constipation and bowel obstructions in 57-year-old male Minnesota resident with pre-existing Crohn's disease requiring NG tube, IVs and two hospitalizations.