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Health Research Group of Public Citizen
FDA Drug Safety and Risk Management Advisory Committee

Adequacy of Lotronex (alosetron) REMS

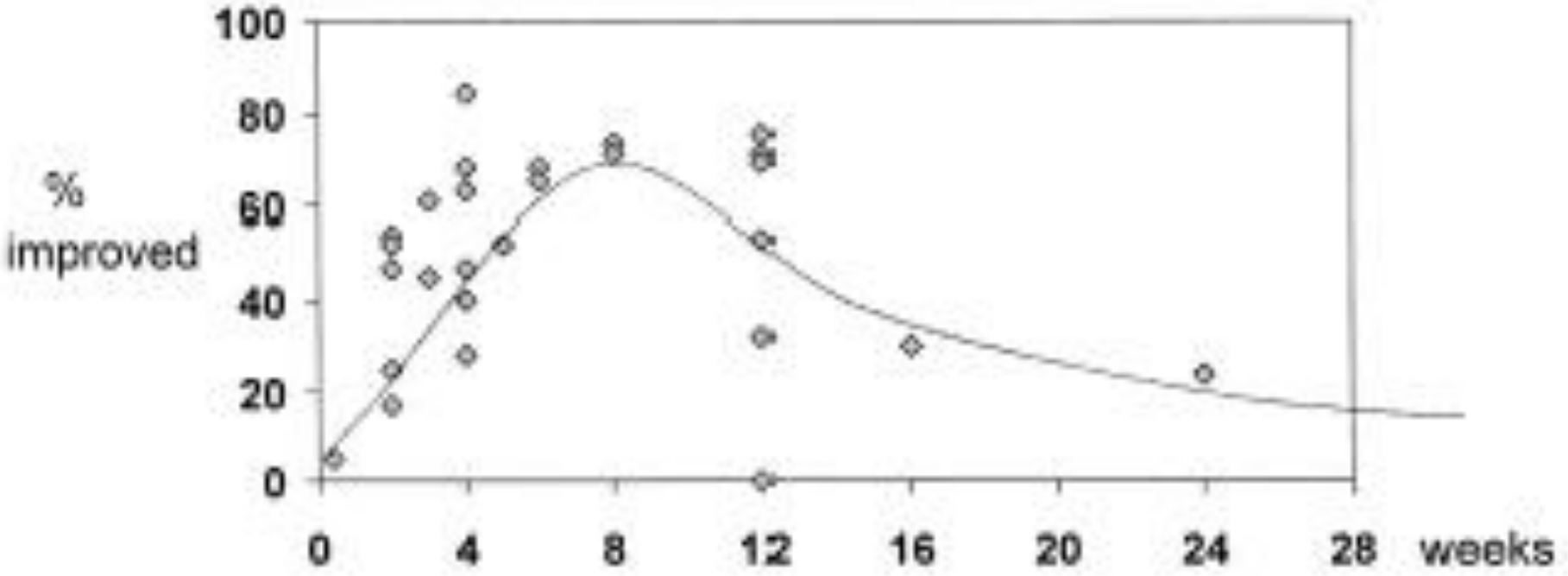
July 10, 2013

(I have no financial conflict of interest)

Introduction to our involvement with alosetron

In August 2000, almost thirteen years ago, we petitioned the FDA to ban alosetron because, in our view, its serious, life-threatening adverse effects outweighed the marginally better-than-placebo effectiveness. At the time of our petition, the FDA was aware of 26 cases of ischemic colitis in people using alosetron. In the major randomized, placebo-controlled clinical trials prior to approval there had been three cases of ischemic colitis in 832 patients (1/277) on alosetron, but none in 700 placebo patients. According to an FDA memo, in one large trial with adequate ascertainment of ischemic colitis, 10 out of 1819 women being treated with alosetron for diarrhea-predominant irritable bowel syndrome (IBS) developed ischemic colitis over the 24-week duration of the trial (S3B30020). There were no cases in the 899 patients in that trial treated with traditional therapy.

Placebo response rate in 27 trials of various treatments for Irritable Bowel Syndrome*



Median placebo response rate was 47% (measured as % improved) with rates as high as 84% and 11 studies had placebo response rates of 60% or greater. The study concluded that this **placebo response rate was approximately three times the size of the difference between placebo and drug response** (median 16%).[1]

*Spiller RC. Problems and challenges in the design of irritable bowel syndrome clinical trials: experience from published trials. Am J Med 1999;107:91s-97s.

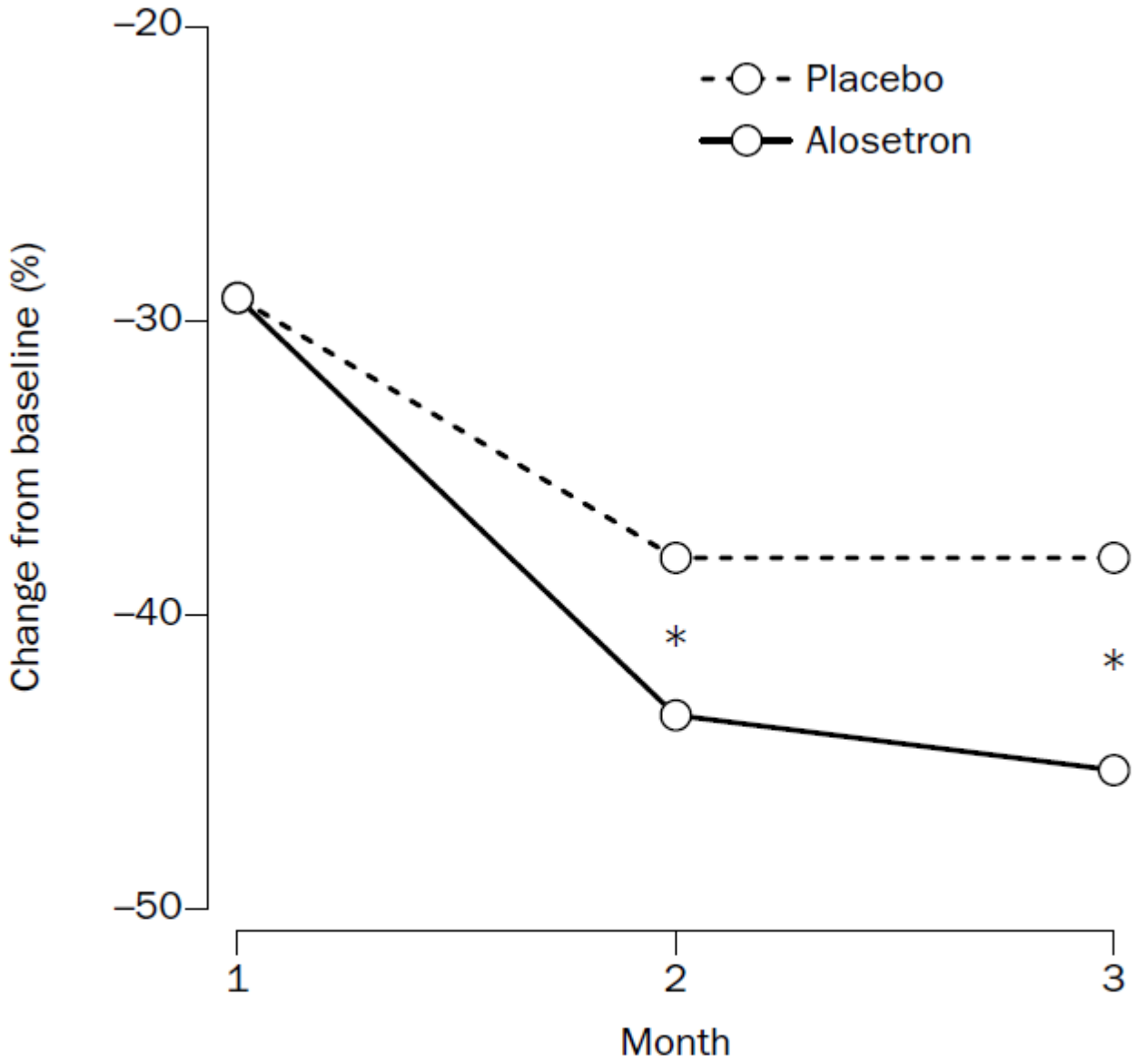


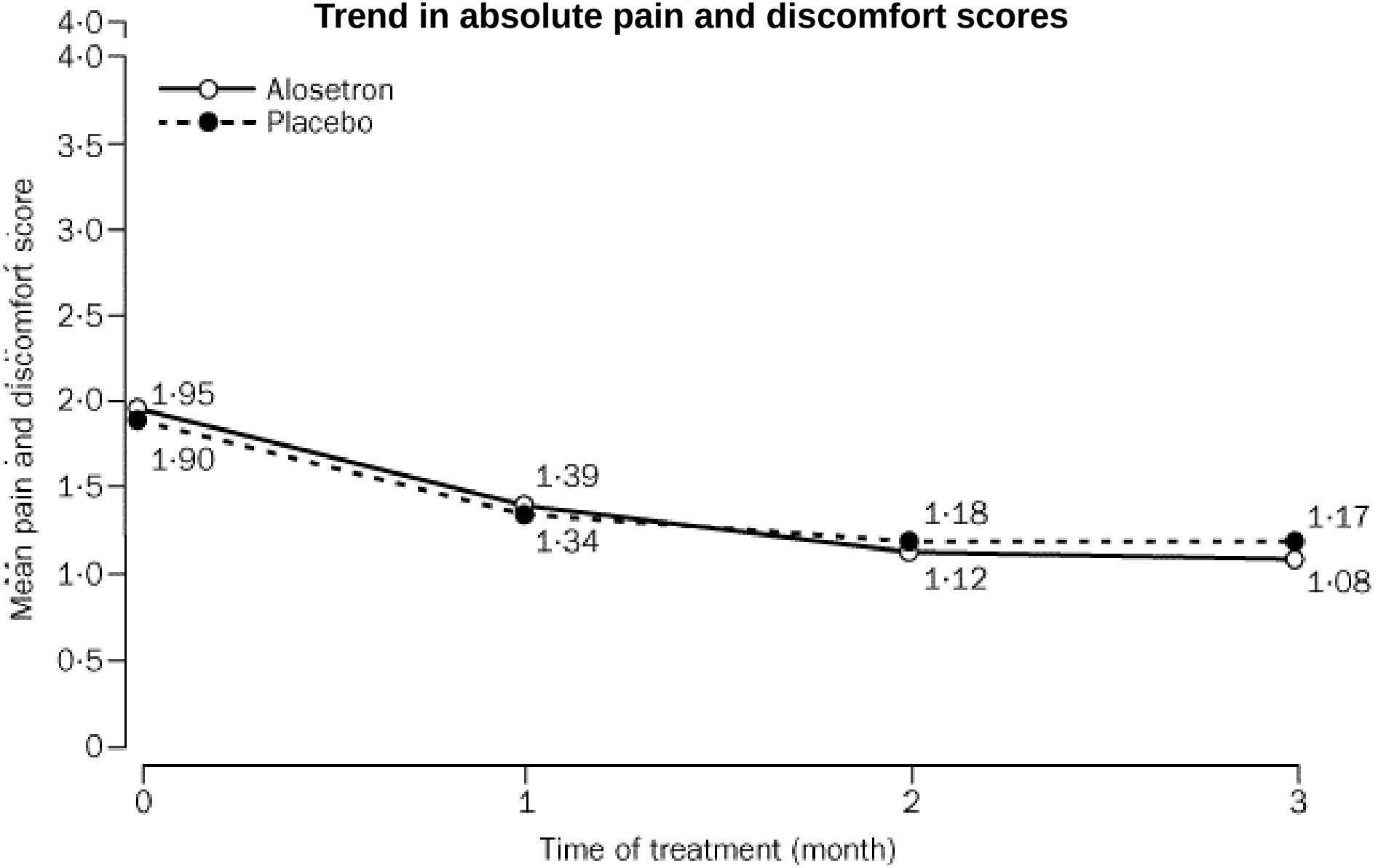
Figure 3: **Change in pain severity scores from baseline by month**

*p<0·05.

GSK-funded study/publication: *Lancet* 2000; 355; 1035–40

GSK RCT Approval Study: Placebo vs 2 mg of alosetron

Trend in absolute pain and discomfort scores



Barbehenn E, Lurie P, and Wolfe SM. Alosetron for irritable bowel syndrome. *Lancet* 2000; 356 (9246):2009-10. (using GSK data)

FDA Office of Post-marketing Drug Risk Assessment (OPDRA) memo: November 16, 2000

" . . . *there are no known risk factors to predict either ischemic colitis or severe constipation*" and that *"Early warning of the dire side effects of this drug is clearly not feasible*" (we are not aware of new information disputing this)

Severe Adverse Event Cases Referable to the GI System (based on 11/16 memo)

*Data from clinical trials plus 36 weeks of post-marketing (through November 10, 2000)

	OUTCOME OF LOTRONEX USE		
Phase of Use	**Ischemic colitis**	**Severe constipation**	**Mesenteric vasculopathy**
Phase III clinical trials	5	4	0
Post-marketing (March 2000 to November 2000)	44	17	3
Total*	49 (30 hosp)	21 (14 hosp)	3

11/16/00 FDA memo (cont'd)

Ischemic colitis is not a class effect (that is, other drugs with a similar structure and function do not cause ischemic colitis): "NO cases of ischemic colitis were identified with other 5-HT3 receptor antagonists, including Zofran (odansetron), Kytril (granisetron), and Anzemet (dolasetron)." (emphasis in original)

Ischemic colitis is not an adverse effect of other drugs used for IBS: "NO cases of ischemic colitis were identified for any other drugs used 'off-label' to treat IBS, including Imodium, Lomotil, Valium, Librium, Levsin, and Levsinex." (emphasis in original)

IBS does not, by itself, cause severe injury: "IBS does not lead to surgery, does not shorten the life span and does not cause death." Therefore, risks acceptable for life-saving drugs are not acceptable for IBS drugs.

Ischemic colitis cannot be predicted: "The warning signs and symptoms of ischemic colitis or colonic ischemia are not always clear, not always typical, and do not always occur." "The sponsor has not identified a subset of women who will respond to Lotronex therapy safely."

Adverse Reactions Reported in ≥1% of Patients With Irritable Bowel Syndrome and More Frequently on LOTRONEX 1 mg Twice Daily Than Placebo (current label)

	Placebo	1 mg twice daily
	n = 2,363	n = 8,328
Constipation	6%	29%
Abd. discomfort pain	4%	7%

History of Incidence of Alosetron-induced Ischemic Colitis: Glaxo Estimates vs. FDA Estimates

Date/Source	Risk Estimate	Risk per 1,000 Person Years
6/99 FDA Medical officer (pre-approval)	1/307 per 12 weeks	14.7/1000
1/00 Glaxo label	1/700 (no time specified)	
3/00 FDA epi	1/218 for 3 months	18.3/1000
12/01 Glaxo	1/700	5.6/1000
3/02 FDA epi	1/182 for 24 weeks	16.9/1000

From my testimony at FDA AC meeting April 23, 2002

Increase in Patients Getting a Lotronex Prescription

Year	2008	2009	2010	2011	2012
# of patients	7789	8455	9724	10,622	10,332
% increase from 2008	----	+ 9%	+ 25%	+ 36%	+ 33%

Source: FDA analyses

Changes in Prescriptions and Sales of Lotronex

Interval	June 2010 thru May 2011	June 2012 thru May 2013	Change
RXs Filled	43,000	46,000	+ 7 %
Sales	$41 million	$59 million	+ 44%

IMS Health Data

From Glaxo Briefing Document for May 2004 FDA Advisory Committee Meeting

"The primary concern at present relates to the low rate of product prescribing given our understanding of the target population size. This may reflect unintended barriers to prescription to the extent that appropriate and needy patients are being under served. *Alternatives designed to redirect or remove some of the unintended barriers from the physician and from the patient are required if Lotronex is to address the significant unmet medical need of appropriate women with severe diarrhea predominant IBS.* Our goal is to work with the FDA to modify the RMP for Lotronex to improve product access for appropriate physicians and patients while continuing to effectively manage risk." (from page 87, GSK Briefing Document)

From FDA Briefing Document page 16

"over the most recent 12 month period for which there are data, 10% of prescriptions dispensed were written by non-enrolled prescribers. Additionally, the pharmacist survey analysis found that only 63% of pharmacists knew not to accept telephone, FAX, or computerized prescriptions for Lotronex. The Committee should discuss potential modifications to the REMS program to address these findings."

From Prometheus Briefing Document for this meeting (PDF page 14)

"Patient access is limited when prescribers chose not to accept the burden of writing a LOTRONEX prescription…. Prometheus would like to further build upon the success of the current REMS program, while making modifications to *reduce the burden*"

From Prometheus Initial Public Offering (IPO) Filed with SEC August 10, 2010

"Limitations on the number of prescriptions written for Lotronex as a result of the prescribing program or concerns over side effects may limit our ability to expand sales of Lotronex and adversely impact our financial position and results of operations……The decreased sales force promotion on diagnostics was a result of increased promotional effort on Lotronex…….. Our sales force actively promotes Lotronex, Entocort EC…… "

Where Do We Go From Here?

Alternatives:

- Make drug available under an IND since the use, with inability to predict harm, is much like an experiment and life-threatening IC continues
- Address two FDA-identified deficiencies in the REMS program: a/ 10% of prescriptions are by non-registered docs and b/ only 63% of pharmacists knew not to accept telephone, FAX, or computerized prescriptions for Lotronex

Further Suggestions

- Change inaccurate wording in patient information part of the REMS (Medication Guide) that now states:

"About 3 out of every 1,000 women who take LOTRONEX over a 6-month period may get a serious problem where blood flow to parts of the large bowel is reduced. This is called ischemic colitis."

This does not comport with FDA's own estimates of ischemic colitis incidence and seriously understates this life-threatening problem.

Prometheus Briefing material: PDF pages 55-56

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Conclusion

With the exception of some drugs used to treat cancer, the frequency and severity of a life-threatening adverse reaction, in this case ischemic colitis in patients using alosetron, is amongst the highest I have seen for any other drug. This risk coupled with the marginal benefit — beyond that seen with a placebo alone — results in a risk-benefit ratio clearly unfavorable for most if not all patients with irritable bowel syndrome. If the DSRM committee and the FDA decide to loosen, rather than strengthen the REMS/ETASU, there will predictably be hundreds more cases of ischemic colitis.