ADDENDUM

TO

FDA BRIEFING DOCUMENT ON

LOTRONEX & ITS RISK MANAGEMENT PLAN

FOR DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE MEETING
May 5, 2004

Addendum date: 04/28/04

of "bad blockage" without identifying the location of the blockage; this case was excluded from analysis). This number represents unduplicated patient cases, not individual reports. (Note that the reports included in this section did not specifically mention "constipation;" however, they have been included in this case series because constipation may have preceded the complicating event [oftentimes symptoms are not described in detail in MedWatch reports].)

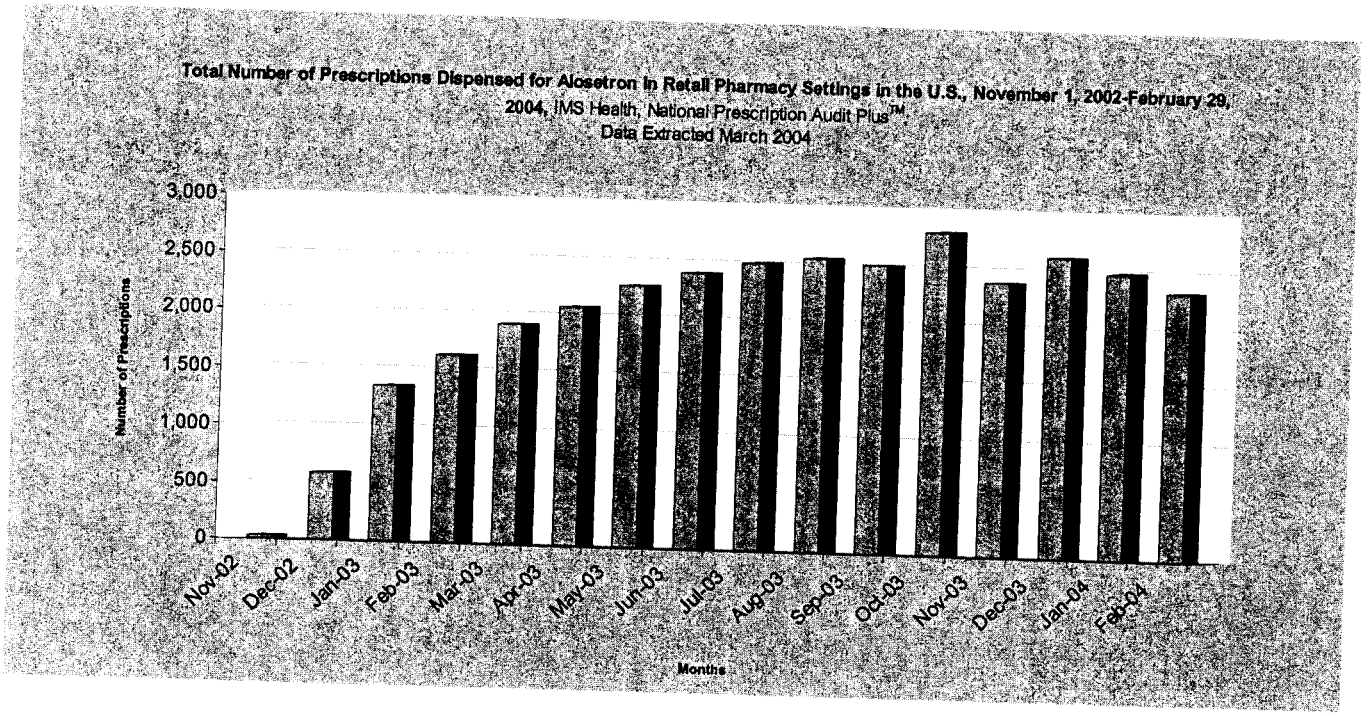
Description of SCC Cases (n = 5)

Gender: Female 5
Reporter source: Original report from patient with f/u from physician (2), nurse (1), patient (2)
Source: Domestic (5)
Year: 2003 (4), 2004 (1)
Age (years): Median=59, mean=56, range=49 to 60 (n = 3), unk (2)
Indications for use as stated in the report: IBS-D (2), unk (3)
Daily dose: 1 mg (2), 4 mg (1), unk (2)
Time to onset (days): 5, 7, 117, 123 (n = 4), unk (1)
Event: Intestinal obstruction (3), fecal impaction (2)
Presenting symptoms as stated in report (not mutually exclusive): Abdominal pain (2), nausea (1), unk (3)
Diagnostic certainty: 2, unk (3)
Contraindicated conditions as stated in the report: None
Outcomes (mutually exclusive): Required hospitalization (2), ER visit (2), required laparoscopy (1)*

* Note that the patient stated that she had an exploratory laparoscopy; upon follow-up, the reporter physician was unable to confirm the procedure. It is not known if she was hospitalized.

Drug Use*

IMS Health (projected data): There were a total of 38,107 alosetron prescriptions dispensed by retail pharmacies (chain, independent, food stores, and mail order) in the U.S from November 1, 2002 through February 29, 2004. The chart below depicts monthly totals of prescriptions dispensed.



Advance PCS: There were a total of 6,420 prescription claims processed by Advance PCS from November 1, 2002 through February 29, 2004 (dispensed in retail pharmacies; note that these data are not projected to represent a national total and do not include non-Advance PCS-reimbursed prescriptions or mail order prescription claims); of those, 592 (9%) were for male patients.

* Drug use data provided by Yoon Kong, Pharm.D. (Drug Utilization Specialist) and Laura Governale, Pharm.D. (Drug Utilization Team Leader), Division of Surveillance, Research and Communication Support, ODS.

DISCUSSION

As of February 21, 2004, there were 3 fatalities (appears to be no association with alosetron), 8 cases of IC, and 5 cases of SCC reported to AERS. Of the IC and SCC cases, there were no deaths, no blood transfusions, and one unconfirmed surgery. Per this case series (IC and SCC cases), it appears that the targeted population has been identified (i.e., all patients were female, none of the patients had contraindicated conditions or confounding factors [as stated in the report], most patients were using the drug for IBS-D). Although in some reports, details about the dosing regimen were not provided, most of the patients were receiving the recommended starting dose of 1 mg per day; this could be another indication that the RMP is working.

A total of 8 out of 13 reports in this case series were initially submitted by patients. Under the Lotronex RMP, health care professionals agree to report all serious adverse events as a condition of participation; however, loopholes in reporting under the RMP could exist. For example, in at least one case, a patient did not make the prescribing physician aware that her adverse event (intestinal obstruction) was treated by a different physician. It also could be that patients think that since they have completed a survey, there is no need to notify their physician or perhaps prescribers are not reporting adverse events to the sponsor or FDA as agreed when they enrolled in the RMP.

The Lotronex MedGuide instructs patients to contact their physicians if they become constipated[3]; however, AERS continues to receive reports of SCC. It is not known if the complication is occurring rapidly or if patients are not contacting their physicians if they become constipated. Self-reported constipation is difficult to define since criteria may be patient specific.

Section II: Postmarketing Safety Review of Cases from Phase IV Trials

BACKGROUND/INTRODUCTION

This section provides a summary of cases of special interest associated with alosetron in patients enrolled in Phase IV trials. Under the Lotronex RMP, the sponsor agreed to conduct several Phase IV studies (e.g., dosing studies). **All cases discussed in this section of the document refer to adverse event reports submitted through AERS involving patients enrolled in Phase IV trials.** The Phase IV studies were initiated after November 20, 2002 (the re-introduction of alosetron to the marketplace). As of February 21, 2004, there have been 1 case of IC and 1 case of SCC reported to AERS (see Section I for case definitions for IC and SCC); this is out of a denominator of 767 patients* enrolled in clinical trials. There were no deaths, no blood transfusions, or surgeries.

Selected Adverse Events

ODS is focusing on two areas of special interest, IC and SCC. The two cases received are discussed below. Note that the report of SCC included in this section did not specifically mention "constipation;" however, it has been included because constipation may have preceded the complicating event (oftentimes symptoms are not described in detail in MedWatch reports).

Ischemic Colitis: FDA# 4046317 (Mfr# A0443267A) (2003, domestic) A 62-year-old female developed lightheadedness, vomiting, bloody diarrhea, abdominal cramping, and fainting with "moments of loss of consciousness" after taking 1 mg of alosetron a day for 6 days to treat IBS-D. Under her study protocol