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SUBJECT: Office of Drug Safety (ODS) POSTMARKETING SAFETY REVIEW
Drug: Alosetron (Lotronex)
Section I: Fatalities, ischemic colitis (IC), and serious complications of constipation (SCC) cases from the Risk Management Plan (RMP); **Section II**: Cases of IC and SCC from Phase IV trials

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EXECUTIVE SUMMARY

This memorandum communicates safety information associated with alosetron (i.e., fatalities, IC and SCC). Alosetron was approved on February 9, 2000 for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS-D); the marketing of alosetron was suspended on November 28, 2000. Alosetron was re-introduced to the market on November 20, 2002 under an RMP with a revised indication for use and a lower starting dose. Under the RMP, use of alosetron is restricted to physicians who enroll in the GlaxoSmithKline (GSK) Lotronex Prescribing Program. The revised indication is for women with severe IBS-D who have chronic IBS symptoms (lasting 6 months or longer) and who have failed conventional therapy. The revised starting dose is 1 mg once a day; after 4 weeks, the dose can be increased to 1 mg twice a day if the dose is well tolerated but does not adequately control IBS symptoms. In addition, the sponsor agreed to conduct several Phase IV studies (e.g., dosing). **All cases discussed in this document refer to adverse event reports submitted through the Adverse Event Reporting System (AERS) under the RMP and Phase IV trials.**

AERS is a passive surveillance system that is subject to under-reporting, normally only 1 to 10% of adverse events are reported to FDA[1,2]. Although AERS is a voluntary reporting system, under the Lotronex RMP and Phase IV clinical trials, enrolled health care professionals/investigators agree to report all serious adverse events as a condition of participation. In addition, reports are received from the Lotronex Patient Follow-Up Survey Program (patient participation in the survey program is voluntary; it is not designed to collect safety information; however, if patients specify an adverse event it is reported to the FDA). GSK has been following up with these patients' physicians whenever possible.

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 under the Lotronex RMP. 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 received under the RMP 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.

AERS has received few serious cases of IC and SCC under the RMP; this could be due to low drug use (possibly due to better patient screening initially), better patient awareness of symptoms and/or patient monitoring (possibly due to better education), and a lower starting dose. The number of adverse events is small. It also appears that all of the parameters of the RMP have been implemented. However, the RMP is in the early stages of implementation, and compliance and impact of each of the RMP components on overall effectiveness have not been evaluated.

Under Phase IV trials, AERS has received 1 case of IC and 1 case of SCC out of a denominator of 767 patients*. Clinical trials have specific protocols that must be followed and established mechanisms to enforce compliance. Even under the strict conditions of clinical trials, we continue to see adverse events of interest associated with alosetron use. It is too early in the postmarketing clinical trials to make a meaningful assessment.

* Denominator data provided by Craig Metz, Ph.D., Regulatory Affairs, GlaxoSmithKline, on March 31, 2004.

Section I: Fatalities, IC, and SCC cases from the Lotronex RMP

BACKGROUND/INTRODUCTION

All cases discussed in this section of the document refer to selected adverse events reported through AERS under the RMP. The cases were received between November 20, 2002 (the re-introduction of alosetron to the marketplace) and February 21, 2004. The sponsor's original cut off date was February 6, 2004, so the February 21 date allows for the sponsor's reports to be received and processed by the agency.

When evaluating spontaneous reports, it is important to keep the following limitations in mind. The main utility of a spontaneous reporting system, such as AERS, is to detect signals of potential drug safety issues that are rare. It should be realized that accumulated case reports cannot be used to calculate incidence or estimates of drug risk for a particular product because under-reporting of adverse events exists. Some of the factors that influence reporting include the length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions. It should also be noted that in some of these cases, the reported clinical data were incomplete, and there is no certainty that these drugs caused the reported reactions. A given reaction may actually have been due to an underlying disease process or to another coincidental factor.

Summary of all death cases

From November 20, 2002 through February 21, 2004, there were a total of 3 deaths in patients receiving alosetron under the RMP; none of the deaths showed an association with alosetron. Causes of death for the 3 patients were listed as acquired immune deficiency syndrome (1), multiple myeloma (1) and respiratory arrest possibly due to pulmonary embolism (1).

Selected Adverse Events

ODS is focusing this review on two areas of special interest, namely IC and SCC. The reports in the IC and SCC categories are mutually exclusive (i.e., there were no reports of patients reporting both IC and SCC).

Four of the reports received through AERS under the RMP were submitted by patients; in general the quality and completeness of the data are not as good as reports received from health care professionals. ODS has included these reports in our analysis because the events could not be ruled out. Note that when GSK receives a report from the Patient Follow-Up Survey Program, they have been attempting to follow up with the patient's physician. Since patient identity may not be known to the sponsor or FDA under the RMP, the patient reports that are included in this section could represent duplicate cases. The absence of supporting documentation does not imply that the patient did not have the event, only that documentation was not obtainable.

Ischemic Colitis: The case definition used by the ODS for IC for epidemiological risk assessment was based on any or a combination of the following: (1) the term "IC" is explicitly used in the AERS report as a possible diagnosis, or (2) any endoscopic or histologic evidence of ischemic change or necrosis. As of February 21, 2004, there were 8 cases of IC in AERS. This number represents unduplicated patient cases, not individual reports.

Description of IC Cases (N = 8)*

Gender: Female (8)
Reporter source: Original report from patient with f/u from physician (2), physician (4), patient (2)
Source: All reports are domestic
Year: 2003 (6), 2004 (2)
Age (years): Median=54, mean=52, range=31 to 65 (6), unk (2)
Indications for use as stated in the report: IBS-D (5), IBS-predominance not specified (2), unk (1)
Daily dose: 1 mg (6), 2 mg (1), unk (1)
Time to onset (days): 4 (1), 13 to 28 (3), 53 (1), 112 (1), 276 (1), unk (1)
Presenting symptoms as stated in the report (not mutually exclusive): Bloody stool: (5)†, abdominal pain (2), nausea (1), unk (2)
Contraindicated conditions as stated in the report: None
Concomitant medications of interest (mutually exclusive): Estrogen (2), sumatriptan (1), beta-blocker (1)
Outcomes: Required hospitalization (3)
Diagnostic certainty (mutually exclusive): Both histologic and endoscopic evidence (4), endoscopic evidence only (2), no documentation provided (2)

* Note that 1 patient with IC (65-year-old female) is being evaluated for rheumatologic disease due to elevated erythrocyte sedimentation rate and C-reactive protein; results are pending.
† This number does not include 1 patient who did not present with bloody stool, but was found to have hemorrhage upon endoscopy.

Serious Complications of Constipation: The case definition used by ODS for SCC epidemiologic risk assessment was constipation or suspected constipation that was associated with an ER visit, hospitalization, or complications, including but not limited to, fecal impaction, bowel obstruction, necrosis, or rupture. As of February 21, 2004, there were 5 cases of SCC in AERS (one patient reporter stated an event

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.

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

(#S3B30048), she was to receive 0.5 mg alosetron tablets, 0 to 2 tablets twice daily. Colonoscopy and biopsy results were consistent with IC; the colonoscopy also noted non-bleeding internal hemorrhoids and diverticulosis. She was not hospitalized. Alosetron treatment was discontinued and she was withdrawn from the study. The patient had no contraindicated conditions or confounding factors; she was not taking concomitant medications known to cause IC.

Serious Complications of Constipation: (Mfr# A0427399A) (2003, domestic) A 61-year-old female developed a partial small bowel obstruction (per x-ray) after taking 0.5 mg of alosetron a day for 10 days to treat IBS-D. Per her study protocol (#S3B30048), she received a variable dose (0 to 2 tablets) of alosetron twice daily as needed. Her symptoms included severe abdominal pain with distention and nausea/vomiting following 4 days without a bowel movement. She was hospitalized; an abdominal x-ray revealed partial small bowel obstruction; an abdominal CT scan showed dilatation of the ascending colon and a stricture of the descending colon. Morphine and promethazine were administered via NG tube. Alosetron was discontinued and the patient was withdrawn from the study. Three days later, a barium enema showed no constricting or obstructive lesions. The patient had no contraindicated conditions or confounding factors; concomitant medications included several laxatives.

OVERALL CONCLUSION

AERS has received few serious cases of IC and SCC under the RMP; this could be due to low drug use (possibly due to better patient screening initially), better patient awareness of symptoms and/or patient monitoring (possibly due to better education), and a lower starting dose. The number of adverse events is small. It also appears that all of the parameters of the RMP have been implemented. However, the RMP is in the early stages of implementation, and compliance and impact of each of the RMP components on overall effectiveness have not been evaluated.

Under Phase IV trials, AERS has received 1 case of IC and 1 case of SCC out of a denominator of 767 patients*. Clinical trials have specific protocols that must be followed and established mechanisms to enforce compliance. Even under the strict conditions of clinical trials, we continue to see adverse events of interest associated with alosetron use. It is too early in the post-marketing clinical trials to make a meaningful assessment.

* Denominator data provided by Craig Metz, Ph.D., Regulatory Affairs, GlaxoSmithKline, on March 31, 2004.

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