Summary of Serious Adverse GI Events Associated with Alosetron

Scheldon Kress, M.D. Medical Officer CDER HFD-180

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Alosetron, a 5-hydroxytryptamineType 3 (5-HT_3) receptor antagonist, approved February 9, 2000 for treatment of *women with diarrheal type irritable bowel syndrome*, has been associated with several unique and potentially serious adverse events. These **colonopathies** include constipation with life-threatening sequelae and ischemic colitis.

As of May 31, 2000, there have been approximately 130,000 prescriptions dispensed and 12 gastrointestinal serious adverse event (SAE) reports received through AERS (Adverse Event Reporting System). The incidence of post-marketing gastrointestinal SAEs approaches 1 SAE per 11,000 prescriptions. In clinical trials, the rate of reported cases of ischemic colitis was 7 among 6800 patients. This translates into a rate of approximately 1/970 with a 95% confidence interval of (1/480, 1/2500) as calculated by the exact binomial method. Complications associated with constipation in clinical trials were reported in one patient.

Constipation is a frequent dose-related side effect of treatment with alosetron, 25 to 30% of approximately 6800 patients receiving this drug in clinical studies experienced constipation. Approximately 9% of patients in the clinical trials had no stool for 4 consecutive days. This constipation was severe enough to cause approximately 10% of patients taking alosetron to withdraw from clinical studies. Post-marketing reports describe patients taking alosetron who developed severe constipation associated with abdominal pain and rectal bleeding. Several known serious complications of constipation requiring hospitalization (6 cases) have been seen: fecal impaction, intestinal obstruction, ischemic (stercoral - hard feces induced) ulceration, perforation and gangrenous colitis. Some cases have probably been related to the inappropriate use of the drug by constipated patients, e.g., a constipation-prone male IBS patient. Three patients have required intestinal surgery which included a patient with gangrenous colitis who required a total colectomy with ileostomy.

Ischemic colitis has occurred in patients in clinical trials and has been reported after marketing in patients taking alosetron. In patients taking alosetron, this clinical colonopathic syndrome appears to be a new variety of nonthrombotic ischemic colitis. The syndrome consists of abdominal pain (usually crampy and severe), diarrhea, bloody diarrhea and rectal bleeding. Less frequently the syndrome includes nausea, vomiting and bloody constipation. Eight patients with this syndrome required hospitalization and four required out-patient diagnostic endoscopic evaluations. Findings on abdominal computerized tomography scans have included mural thickening of varying degrees of severity occurring in both the small and large bowel. The classic early radiologic signs of ischemic colitis, bowel-wall thickening with "thumbprinting," have not been seen.

Colonoscopic findings have varied from patient to patient and have included patchy areas of friable, ischemic or hyperemic, edematous mucosa with erosions that in later stages became necrotic, ulcerated and hemorrhagic with mucosal sloughing. Histopathological findings have been compatible with the diagnosis of ischemic colitis, and included mild edema of the lamina propria, focal coagulation necrosis of the superficial crypts, and normal architecture and spacing of the deeper crypts. Granulomas were not identified.

To date, prompt discontinuation of alosetron in patients with alosetron-associated ischemic colitis has resulted in return of the mucosa to normal upon endoscopic visualization without progression to life-threatening hemorrhage, necrosis, perforation of the colon, or death. However, long term follow up data from these patients to rule out delayed colonic stenosis and stricture formation are not available.

Three patients, one in clinical trials performed before approval (case #4595), the another two in post-marketing spontaneous reporting (A0119607A; A0120634A), exhibited significant abnormalities of liver function; alosetron may be definitely implicated in one or two cases. Several patients experienced abdominal pain and bloody diarrhea in both the pre- and post-approval clinical trials and the post-marketing spontaneous reporting in which insufficient diagnostic information precluded more-definitive confirmation of suspected diagnosis of alosetron-induced colonopathy.

Several patients on alosetron in both the post-approval clinical trials and from the post-marketing spontaneous reporting presented with abdominal pain and bloody diarrhea and were ultimately diagnosed with inflammatory bowel disease (e.g. ulcerative colitis) or diverticulitis. One patient in the pre-approval clinical trials with a healthy pre-randomization flexible sigmoidoscopy presented with abdominal pain and bloody diarrhea and had severe irregular ulcerations of the left colon that were attributed either to Crohn's colitis or ischemic colitis.

IBS has never been a precise diagnosis, but instead has been a constellation of signs and symptoms meeting a set of diagnostic criteria in the absence of associated laboratory, endoscopic or pathological findings. Prior to the current era of managed care and cost containment, the diagnosis of IBS was one of rigorous and meticulous exclusion. Physicians tested patients extensively to rule out other medical conditions before diagnosing the patient with IBS. Today, physicians and other health care providers may often initiate drug treatment based on a suspected but unproven diagnosis before excluding other more serious disorders. In this setting, patients are more likely to receive inappropriate or delayed treatment of gastrointestinal/colonic lesions unrelated to IBS. As described above, in at least some cases, adverse events occurring in apparent association with alosetron administration turned out to be undetected errors in diagnosis.

Summary of Patients with Alosetron Associated Serious Adverse Events of the GI Tract

	INDs					
	Pre Approval	**Post** Approval	**Post** Marketing	**SAE Totals**	**Hospitalization Totals**	**Surgery Required**
Ischemic Colitis						
	4	3	5	12	8	0
Constipation Complications						
	0	2	5	7	6	3
						1. Gangrenous colitis/ toxic megacolon, bacteremia heart and renal failure transmural ischemia **(Total colectomy with ileostomy)** 2. Perforation sigmoid colon with Abscess **(Surgical repair and antibiotics)** 3.Small Bowel Intestinal Obstruction **(Temporary decompression colostomy)**
Hepatotoxicity						
	1	0	2	3	2	0

As of June 1, 2000

Summary of Patients with Alosetron Associated Serious Adverse Events of the GI Tract

INDs

Pre Approval	Post Approval	Post Marketing	SAE Totals	Hospitalization Totals	Surgery Required
Ischemic Colitis					
4	3	5	12	8	0
2829 7195 15687 34069	72823 ★ 72824 ★ 78134	A117893A ★ A119468A ★ A120828A A120834A A121411A		2829 7195 15687 34069 78134 A120828A A120834A A121411A	
Constipation Complications					
0	2	5	7	6	3
	03773 67694	A117392A A117431A A118883A A119786A A120067A		03773 67694 ☒ A117392A A117431A A118883A ⭘ A120067A ✞	☒ Gangrenous colitis/ toxic megacolon, bacteremia heart and renal failure transmural ischemia (**Total colectomy with ileostomy**) ⭘ Small Bowel Intestinal Obstruction (**Temporary decompression colostomy**) ✞ Perforation sigmoid colon with Abscess (**Surgical repair and antibiotics**)
Hepatotoxicity					
1	0	2	3	2	0
4595		A119607A A120634A		A119607A A120634A	

★ Symptoms severe enough to require diagnostic endoscopy, but not hospitalized.