

GSK Medicine: Alosetron hydrochloride
Study No. WWE114591/WE138
Title: Incidence of colonic ischemia, hospitalized complications of constipation, and bowel surgery in relation to use of alosetron hydrochloride
Rationale: Alosetron hydrochloride, a potent selective 5-hydroxytryptamine ₃ receptor antagonist, was approved in February 2000 in the United States for the treatment of diarrhea-predominant irritable bowel syndrome (IBS) in women. Marketing was suspended in November 2000, after reports of colonic ischemia and serious complications of constipation. We sought to compare the incidence of colonic ischemia, hospitalized complications of constipation, and bowel surgery among alosetron users and a cohort of patients with IBS who did not use alosetron. This information was submitted to the FDA to meet a Phase IV regulatory commitment.
Objectives: (1) To compare the incidence, including relative risks, and examine the risk factors for colonic ischemia, complications of constipation requiring hospitalization, and bowel surgery in patients receiving alosetron and in patients with IBS not receiving alosetron.
Indication: Irritable bowel syndrome
Study Investigators/Centers: Ingenix, Epidemiology Division, Newton, Massachusetts (i3 Drug Safety)
Research Methods:
Data Source(s): The data source was the Ingenix Research Data Mart. Affiliated with a large US health insurer (UnitedHealthcare), the database contains medical, pharmacy, and laboratory results data on all insurance claims for approximately 20 million current and past members from January 1993 through present.
Study Design: Retrospective cohort
Study Population(s): This claims database analysis utilized medical and pharmacy claims on members in 25 US states during the period September 1, 1999 to December 31, 2000. Individuals with IBS, colonic ischemia, or hospitalization for complications of constipation were identified through a multistage process beginning with review of computerized insurance claims, followed by medical records review. Inclusion criterion: Patients were classified as having IBS if any insurance claim had an irritable colon diagnosis code. Exclusion criterion: Patients with diseases whose symptoms could be confused with IBS, including Crohn's disease, ulcerative colitis, colorectal cancer, chronic pancreatitis, pancreatic cancer, liver cirrhosis, celiac disease, other intestinal malabsorption syndromes, and ovarian cancer, were not permitted to enter the IBS group, or were dropped from the IBS group if already in, beginning at the time that they received an exclusionary diagnosis.
Study Exposures, Outcomes: Two distinct IBS cohorts were identified: (1) alosetron users (n=3631) who had a pharmacy dispensing claim for alosetron between March 1, 2000 and December 31, 2000, and (2) IBS patients who had IBS claims during the study period but no alosetron dispensing (n=2480). The alosetron users were initially divided into two groups depending on whether they had a qualifying IBS service between September 1999 and their first alosetron dispensing. Of the 3631 alosetron users, 1464 also had a qualifying IBS service between September 1999 and their initial alosetron dispensing. Because alosetron users with and without IBS claims after September 1999 were essentially identical with respect to age, sex, health plan, month of first alosetron dispensing, and outcome events, the two groups have been treated as a single cohort in all of the analyses that follow. The IBS/no alosetron cohort consisted of 2480 patients drawn from the UnitedHealthcare population who had IBS claims during the study period but had no alosetron dispensing. Up to two comparators were matched, as closely as possible, to each member of the alosetron-IBS cohort by age, sex, health plan, and calendar month. The observation period began on the start date of alosetron therapy and ended with the earliest of the occurrence of a disqualifying diagnosis, disenrollment from UnitedHealthcare, or December 31, 2000. The start date of observation for each IBS/no alosetron patient was that of the corresponding alosetron-IBS patient. Outcomes: Using insurance claims patterns, cohort members with colonic ischemia were identified by a diagnosis of vascular insufficiency of the intestine (International Classification of Diseases, 9th Revision, codes 557, 557.0, 557.1, 557.9) on the same day as a colonoscopy or colectomy or at least one claim for physician services for vascular insufficiency of the intestine within 3 months after a colonoscopy or colectomy. Medical records for these members were reviewed. Further, medical records were reviewed if a cohort member met any of the following conditions within the first 3 days of a hospital admission: (1) the patient had an inpatient physician service for intestinal obstruction or paralytic ileus; (2) the patient had an inpatient physician service for bowel perforation without a procedure code indicating that bowel perforation could be an accidental result from a colonoscopy within the same admission; (3) the

patient had a service code (of any kind) for impaction of colon; and (4) the patient had a constipation diagnosis code of any kind on the same claim as an abdominal procedure. For bowel surgery, claims for therapeutic surgical procedures involving the GI tract including incision, excision, resection, repair, and lysis of adhesions, but not including minor procedures during colonoscopy were identified. A practicing gastroenterologist with clinical research experience reviewed the abstracted records, with copies of notes and discharge summaries, in conjunction with other members of the study team.

Data Analysis Methods: Age, sex, calendar month, frequency of outcome, and average length of follow-up were tabulated at the start of observation for both cohorts. The 10 most common diagnosis codes, procedure codes, and prescription drugs were compared between cohorts in the baseline and observation periods. In the alosetron user cohort, the number of alosetron dispensings was tabulated. Subsequently, counts of colonic ischemia, bowel surgery, and hospitalized complications of constipation were tabulated in categories of age, sex, calendar month, and cohort group. Incidence rates were calculated for each outcome as the number of outcome cases divided by the person time specific to that cohort, age, or gender stratum. Also, 95% CI for the crude incidence rates were calculated using exact methods. Incidence rate ratios and their 95% CI were calculated using the normal approximation and the asymptotic variance of the Poisson regression coefficients.

Limitations: The numbers of patients, whereas substantial, do not permit strong conclusions about rare events. The short-term follow up precludes any conclusion about long-term use. The ascertainment of IBS did not distinguish between diarrhea- and constipation-predominant forms of the disease. Presumably, all or nearly all of the alosetron patients were suffering from diarrhea, whereas some fraction of the comparator cohort had constipation. Some patients may not have had IBS, since all patients with at least one IBS diagnosis were included. The alosetron group was much smaller than the 10,000 person cohort originally planned, and the follow-up time was much shorter, both because the removal of alosetron from the market. As a result, this study cannot rule out risks that the originally planned cohort could have addressed. There were no cases of colonic ischemia identified. We cannot rule out the possibility that some cases occurred but resolved spontaneously with only non-specific symptoms and no diagnostic evaluation. A number of members classified as 'nonalosectron users' for this study may have had exposure to alosetron.

Study Results: After an average follow-up time of 5 months, there were no instances of colonic ischemia in either cohort. Further, the rate ratios comparing bowel surgery and confirmed complications of constipation in alosetron users and IBS patients/no alosetron patients were both compatible with no effect of alosetron on risk, but the limits of the CIs do not rule out potentially relevant differences in risk for the alosetron users and nonusers (see table).

The most frequent diagnoses, prescriptions, and procedures were similar in the two cohorts.

Demographics/Baseline Characteristics	Alosetron (%)	IBS/No Alosetron (%)		
Total N	3631	2480		
Age (yr)				
00-09	12 (0.3)	2 (0.1)		
10-19	119 (3.3)	68 (2.7)		
20-29	477 (13.1)	360 (14.5)		
30-39	788 (21.7)	564 (22.7)		
40-49	1023 (28.2)	698 (28.2)		
50-64	1108 (30.5)	737 (29.7)		
≥65	104 (2.9)	51 (2.1)		
Gender				
Male	500 (13.8)	266 (10.7)		
Female	3131 (86.2)	2214 (89.3)		
Outcomes				
Bowel surgery	19 (0.5)	11 (0.4)		
Complications of constipation	2 (0.1)	1 (0)		
Ischemic colitis	0 (0)	0 (0)		
Outcome Events	Alosetron		IBS/No Alosetron	
	Hospitalized complications of hospitalization (n=2)	Bowel surgery (n=19)	Hospitalized complications of hospitalization (n=1)	Bowel surgery (n=11)

Age (yr)				
00-09	0	0	0	0
10-19	0	0	0	1
20-29	0	1	0	0
30-39	0	7	0	1
40-49	2	2	0	2
50-64	0	9	1	7
≥65	0	0	0	0
Gender				
Male	0	3	0	0
Female	2	16	1	11
Incidence and rate ratios				
Cohort person-year	Bowel surgery	Complications of constipation	Colonic ischemia	
IBS/No alosetron 1081.6 person-yr				
n	11	1	0	
IR*	10.17	0.92	0	
95% CI	5.08-18.20	0.02-5.15	0-3.41†	
Alosetron 1616.9 person-yr				
n	19	2	0	
IR*	11.75	1.24	0	
95% CI	7.08-18.35	0.15-4.47	0-2.28†	
Rate ratio	1.16	1.34	Not applicable	
95% CI	0.52-2.69	0.07-78.94		
* IR = incidence rates/1000 person-yr.				
† One-sided, 97.5% CI.				
Conclusion: Alosetron users did not differ from IBS patients not using alosetron in the incidence of bowel surgery or hospitalized complications of constipation; there were no cases of colonic ischemia. The statistical upper limit of colonic ischemia rates in alosetron users was 2.28/1000 person-yr. Because of the market withdrawal, the size of the cohort and the duration of follow-up were smaller than originally planned; consequently, the statements about the safety of alosetron were necessarily limited				

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